● 692 ALLOPURINOL (AP) INDUCED OROTIDINURIA (ODNU): A TEST OF HETEROZYGOSITY FOR ORNITHINE TRANSCARBAMYLASE (OTC) DEFICIENCY. Saul Brusilow & David Valle, Johns Hopkins Univ School of Medicine, Dept. of Pediatrics, Baltimore.

In addition to its effects on purine metabolism, AP, via its metabolite, oxipurinol ribonucleotide, inhibits pyrimidine biosynthesis (PB) at the level of orotidine monophosphate decarboxylase. This inhibition results in increased ODNU. Women heterozygous at the OTC locus have 2 populations of hepatocytes; OTC normal and OTC deficient. We hypothesize that, as a consequence of carbamyl phosphate accumulation in the latter cells, PB is chronically increased. Therefore, inhibition of PB by AP should result in an even greater increase in ODNU in OTCH as compared to controls. The AP test includes administration of 300mg of AP followed by four pooled consecutive 6 hr urine collections. Urinary orotidine was measured by reverse phase HPLC after isolation of nucleosides on a boronate affinity column. We studied 11 control women (C) and 12 obligate OTC heterozygotes (OTCH). The mean (±SEM) peak urine orotidine (μmol/mmol creatinine) of C and OTCH was respectively 7.36±0.46 (range 5.7-10.1) and 39.7±7.3. One OTCH fell in the normal range (7.71); other OTCH values ranged from 17.9 to 97.9. Comparison of these results with a protein tolerance test (PTT) administered to the same subjects, shows that the diagnostic sensitivity of the 2 tests are the same and that the same OTCH was negative in both. We conclude that PB is chronically increased in OTCH; and that the AP test identifies OTCH as well as the PTT, eliminates the risk of hyperammonemia, and is more convenient and acceptable.

693 SOUTHEAST ASIA; THE LAND, THE PEOPLE, AND THE CUSTOMS. Chanthan Chea, Kenneth W. Dumars, Bui Loan, Hanh Nguyen. (Spon. by Thos. L. Nelson) University of California, Irvine, College of Medicine, Irvine, California.

War or religious and ethnic differences has historically resulted in forced migrations. These tragic events do not allow time for planning by either those who must flee for their lives or those who want to provide shelter for the persecuted.

The most recent forced migration has resulted in nearly 1 million people migrating to the United States from Vietnam, Laos, and Cambodia. The admixture of these two diverse cultures is, at times tumultous, and has resulted in misunderstanding in both sectors of the population. For reasons of these cultural differences particularly in the provision of health care, this presentation will address those issues of importance for any medical practitioner caring for patients/clients from Vietnam, Cambodia, or Laos. Actually, the perceived problems are not unique to this forced migration, but serve as a model for any situation which requires surmounting cultural barriers. In order to provide equivalent health care to our new citizens, it is believed essential to understand: 1)Heterogeneity of population involved, 2) Cultural, in this instance health beliefs, of the newly arrived population, and 3)method of coping with cultural differences.

An additional presentation will quantify the population differences necessary to provide any special programs for genetic and/or congenital disorders unique to this, as with any, population sub-group.

● 694 MOLECULAR ANALYSIS OF THE STEROIDOGENIC 11β-HYDROXYLASE ENZYME Streamson C Chua, Jr, Maria I New, and Perrin C White Cornell University Medical College, Division of Pediatric Endocrinology, New York, NY.

We have isolated bovine cDNA clones corresponding to a full length mRNA encoding cytochrome P-450 (11βOH), using a short previously described clone (John et al, J Biol Chem 260:5760) and a size-fractionated library enriched for full length 11βOH cDNA. Sequence analysis shows an open reading frame of 1500 nucleotides which contains the highly conserved heme-binding region and shows 40% homology to cytochrome P-450 (SCC) at the amino acid level. The open reading frame contains sequences corresponding to several tryptic peptides of the porcine enzyme (J. Shively, pers comm). Several human cDNA clones have been isolated, the longest of which is 3700 base pairs (bp). Hybridization analysis with human genomic DNA suggests that the gene is present in a single copy and is about 18 kbp. Analysis of genomic DNA from four patients with 11β-hydroxylase deficiency shows no gross deletions or rearrangements within the structural gene. Hybridization to a panel of somatic cell hybrid cell lines indicates that the gene is on a chromosome distinct from the other steroidogenic P-450 genes (which are on Chr 6, 10, and 15).

695 MODERATE CHANGES IN PLASMA PHENYLALANINE CONCENTRATIONS AFFECT BRAIN ELECTRICAL DISCHARGE. Louis J. Elsas, James F. Trotter, Charles M. Epstein, Philip P. Dembure. Emory University, Department of Pediatrics, Division of Medical Genetics, Atlanta, Georgia

We previously demonstrated that large changes in blood phenylalanine (phe) concentrations (500 - 2000 μM) decreased plasma L-DOPA, slowed brain electrical discharge and prolonged performance (Ped. Res. 20:112, 1986). In this study we ask whether moderately elevated plasma phe affects brain function. Six heterozygotes for phenylketonuria (PKU) and 2 normal controls were studied in a crossover, blinded protocol of 4, 2-week intervals. Volunteers ingested a constant diet of 40-50 mg/kg/day phe supplemented either with 100 mg/kg/day phe or placebo. On the last three days of each period the mean power frequency of three electroencephalograms (MPF) were measured. Plasma phe rose in both heterozygotes and controls on ingesting supplemental phe from a mean placebo phe concentration of 99 + 20 to 140 ± 166 μM. The range of changes was from -200 to +400 μM. There was an inverse relationship between changes in plasma phe above 50 μM and changes in the MPF. By regression analysis 100 μM change in plasma phe produced an inverse change of 0.12 CPS in MPF. We conclude that plasma phe concentrations are raised by phe ingestion in both PKU heterozygotes and homozygous normal, and that alterations in brain electrical discharge are induced by intermediate changes in blood phe concentrations supporting a linear rather than threshold relationship to altered brain function.

● 696 CYSTEAMINE EYEDROPS DISSOLVE CORNEAL CRYSTALS IN YOUNG PATIENTS WITH NEPHROPATHIC CYSTINOSIS. W. Gahl, I. Fujikawa, T. Kuwabara, S. Jain, and M.I. Kaiser-Kupfer. Section on Human Biochem. Gen., NICHD; and Clinical Branch, NEI, Bethesda, MD.

In nephropathic cystinosis, corneal cystine crystals are present by one year of age and increase in density with time. The crystals are blamed for the photophobia and corneal erosions which plague older patients. We studied the safety and efficacy of eyedrops containing cysteamine, a cystine-depleting agent, in dissolving corneal crystals. First, cystinotic corneal stromal cells, cultured from a penetrating keratoplasty specimen, were depleted of 82% of their cystine by 1 mM cysteamine within 30 min. Second, rabbits treated for 8h per day for 3 weeks with 50 mM cysteamine eyedrops in a placebo-controlled, masked study exhibited no toxicity. Third, two cystinotic children (<2 years old) received cysteamine eyedrops (10 mM, hourly while awake) in a double-masked, placebo controlled trial. Normal saline was put in the opposite eye. In both children, biomicroscopic examination and slit lamp photography documented: a) Bilateral increase of crystals in the cornea between the start of oral cysteamine and the start of the eyedrop protocol; b) Nearly complete clearing of crystals from the cysteamine-treated corneas after 4-5 months of eyedrops; c) Progression or lack of regression in the corneas not treated with cysteamine. No toxicity was observed, and we are now treating the placebo eyes with cysteamine and enrolling older patients. This represents the first in vivo demonstration of crystal dissolution by cysteamine in cystinosis, and suggests that oral cysteamine, if adequately delivered to target tissues, might dissolve crystals in other cystinotic organs also.

697 NONRENAL COMPLICATIONS OF NEPHROPATHIC CYSTINOSIS AFTER RENAL FAILURE. W.A. Gahl, M.I. Kaiser-Kupfer, and J.K. Fink. Section on Human Biochem. Gen., NICHD, Clinical Branch, NEI, & NINCDS, NIH, Bethesda, MD.

We examined 15 patients with nephropathic cystinosis age 13-27 years. One 15-year-old girl had received peritoneal dialysis for 3 1/2 years; the others each received an initial renal allograft between 7 and 13 years of age. All 15 patients had photophobia and episodes of corneal erosion. These were at times incapacitating in 4 patients; one 13-year-old boy received substantial relief from a penetrating keratoplasty, performed after other treatment modalities failed to offer relief. Five patients had markedly decreased uncorrectable visual acuity, posterior synechiae and crystal deposition on the lens surface. Four had color vision deficits; 3 had elevated dark adaptation. Electroretinography supported these findings. All 15 patients were growth retarded, with mean height age 8.9±3.8 (SD) years less than chronological age. Bone age was also far behind chronological age. Sexual development was delayed, but usually complete by 17 years of age. Hepatic function appeared normal. Nine patients required thyroid replacement. One patient had neurological impairment with bradykinesia, dementia, dysarthria and dysphagia. Six patients, all asymptomatic, had significant cerebral atrophy on CT scan, and two had deep white matter calcifications. Recently, oral cysteamine therapy has been shown to help prevent renal deterioration and improve growth in young children with cystinosis. The extensive nonrenal involvement in longstanding cystinosis suggests that this cystine-depleting agent should be considered as therapy for post-transplant patients as well.