505 "METABOLIC PORTOSYSTEMIC SHUNTS" IN ORNITHINE TRANSCARBAMYLASE DEFICIENCY? Allen M. Glasgow (Spon. by Wellington Hung). Dept. Endo. & Metab. Children's Hospital National Medical Center, Washington, D. C.

Females with ornithine transcarbamylase (OTC) deficiency, an X-linked disorder, are mosaic in that they have hepatocytes with almost no enzyme activity and hepatocytes with normal enzyme activity. The normal and abnormal cells occur in clusters since cells in an area tend to be the progeny of the same parent cell. Marked variation in OTC was found in small liver biopsies from a female with OTC deficiency, probably because the samples included clusters of normal or abnormal cells. OTC activity was measured in 10 approx. 5 mg specimens of liver from a single surgical biopsy from a 7 year old girl with OTC def. (two experiments and control autopsy liver (three experiments). The OTC activity in the patient varied 10-40 fold in the two experiments with a coefficient of variation of 76 and 97 percent (control 20,21 and 26 percent). Thus OTC activity in a small biopsy in females with OTC def. may not be representative of the entire liver. The OTC activity in several bits of liver from our patient was very low suggesting that clusters of abnormal cells may often involve a major portion of a hepatic lobule. If so, blood passing through these areas would in effect be passing through a "metabolic shunt". These shunts may, in part, account for the hyperammonemia in this disorder. The notion that an X-linked disorder can produce disease in heterozygotes by affecting small functional units could apply to other disorders such as nephrogenic diabetes insipidus or vitamin D dependent rickets.

506 HYPERAMMONEMIA WITH PARTIAL CARBAMYL PHOSPHATE SYNTHASE (CPS) DEFICIENCY RESPONSIVE TO ARGININE THERAPY. Allen M. Glasgow, Sheldon Orloff, Anil Mukherjee, E. Jean Butler, and Joseph D. Schulman. Children's Hospital, Washington, D.C., and NICHD, NIH, Bethesda, MD.

The six week old son of a first cousin marriage presented with hyperammonemia, transient acidosis, hepatosplenomegaly, failure to thrive, and seizures. Quantitative plasma and urine amino acids, including lysine clearance, were normal, orotic acid excretion was not increased, and no organic acid abnormalities were evident by GLC-mass spectroscopic analysis. Notably, during periods when the patient was placed on a diet containing 1 gm/kg /day protein intake, arginine supplementation (100 mgm/kg/day) consistently and significantly lowered plasma ammonia (on arginine, 82 µgm% ± 3, S.E.; off arginine, 113 ± 8; $p<.01$). The mean value for plasma ammonia during periods on a 2gm/kg/day protein diet without arginine (80 ± 17) was lower than on 1 gm/kg/day protein ($p=0.1$). Liver biopsy was examined by light and electron microscopy. Enzymes of the urea cycle were assayed by Dr. P. J. Snodgrass, revealing a partial deficiency of CPS (0.49 µmol/mg prot/hr; normal neonatal mean 1.13, range 0.81-1.41), assayed in the presence of excess N-acetylglutamate. Since arginine activates glutamate N-acetylase and N-acetylglutamate produced by this reaction is a cofactor for CPS, we postulate that arginine, supplied as such or through moderate amounts of dietary protein, lowered plasma ammonia in our patient by stimulating residual CPS activity.

507 CYSTIC FIBROSIS: EVIDENCE OF RELATIONSHIP BETWEEN SEX OF THE CARRIER AND SEX RATIO OF ITS OFFSPRING. F. Gloria-Bottini, M. Antonelli, S. Quattrucci, G. Iovenitti, L. Mastroianni, E. Cardi, and E. Bottini (Spon. by C. D. Cook). Dept. of Genetics, Univ. of Camerino and Dept. of Pediatrics, Univ. of Rome.

It has been suggested that carriers of the cystic fibrosis (CF) gene may have a larger family size and that the concentration of NaCl in the cervical mucus of heterozygous females might be more favorable to the survival and motility of spermatozoa. Moreover, an excess of males in sibships of affected individuals has been observed. We investigated the relationship between CF carrier parent and the sex ratio in the offspring. The data obtained on 100 CF family groups and 405 control families are tabulated below:

	M/F Sex Ratio
Sibships of CF patients	1.22
Offspring of grandparents of CF patients	1.11
Offspring of grandparents of controls	1.04
Offspring of aunts of CF patients	1.21
Offspring of uncles of CF patients	0.87

The results are compatible with the hypothesis that the female carrier is responsible for the excess of males in CF families. Therefore, the elucidation of the physical-chemical characteristics of the genital secretions of the female carriers seem to be important. One may further speculate that the factors influencing sex ratio also influence the equilibrium frequencies of the CF gene in any given population.

508 CLEFT PALATE: A MOLECULAR MECHANISM LINKED TO THE H-2 LOCUS. Allen S. Goldman, Masuyuki Katsumata*, Sumner J. Yaffe, and David L. Gasser*. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104

Genetically different inbred strains of mice have markedly varying susceptibilities to the production of cleft palate by a standard dosage regimen of corticoids at the critical period of palatal organogenesis. This susceptibility to corticoid-induced cleft palate has recently been shown to be regulated by genes in or near the H-2 locus. In order to determine whether susceptibility to cortisone-induced cleft palate may be mediated by genetic differences in a cytosolic corticoid receptor protein, fetal palatal anlagen were obtained by microdissection of the upper and lower fetal jaws on day 11 of gestation 1 hour after maternal injection of 5 µCi (1,2,6,7-^{3}H)-cortisol. Cytosols of maternal palates and fetal jaws of five inbred strains and of the congenic strains B10, and B10-A which has the genetic background of B10, but the $H\text{-}2^a$ allele of the most sensitive strain, A/J, were prepared. The total level of cytosolic protein binders of ^{3}H-cortisol in maternal and fetal palates on day 11 of gestation correlates with susceptibility to cleft palate and the H-2 genotype. After microelectrofocusing, only one maternal and fetal palatal cytosol binder for ^{3}H-cortisol (pI 6.9-7.0) is found to correlate with susceptibility to cleft palate and the H-2 genotype. Thus, a gene product in or near the H-2 locus appears to be the glucocorticoid receptor whose level must be elevated for a cleft palate to occur. This is the only malformation that has been associated so far with the H-2 locus. This mechanism may be applicable to other teratogens as well.

509 A VARIANT OF CARNOSINEMIA WITH NORMAL SERUM CARNOSINASE ACTIVITY IN AN INFANT. Edward F. Gordon, Jr., J. Thomas Coulombe, Stephen J. Sepe and Harvey L. Levy. State Lab. Inst., Mass. Dept. Public Health, Harvard Med. Sch. and Mass. Gen. Hosp., Boston.

An infant was discovered by routine newborn urine screening at age 4 weeks to have carnosinuria, the first such infant in 539,950 screened newborns. Further evaluation revealed persistent carnosinuria and detectable plasma carnosine. He had remained well on a normal diet to age 20 months. Studies were performed on the infant and his parents when he was age 18 months. Following the ingestion of L-carnosine (100 mg/kg) the infant accumulated carnosine in plasma (1.0 mg/dl) and during the first 12 hours excreted 4.3% of the ingested load in the form of carnosine and only 0.2% in the form of β-alanine. Carnosine was undetectable in plasma from the parents and each parent excreted 0.5 - 2.5% of the ingested carnosine in the form of carnosine and 0.4 - 0.8% in the form of β-alanine. Serum carnosinase activity in the infant was 0.64 µmoles/22 hr/ml serum (U) (age-matched controls 0.52 - 1.40). Starch block electrophoresis of serum carnosinase from the infant and his parents revealed a banding pattern identical to one another and to controls. It is probable that the carnosine metabolic defect in this infant is due to a deficiency in liver carnosinase. Thus, serum and organ carnosinase may represent different enzymes.

510 ENZYME MANIPULATION: EVALUATION OF ORAL $ZnSO_4$ SUPPLEMENTATION IN MANNOSIDOSIS TYPE II. Gregory A. Grabowski, Linda L. Walling, Justus U. Ikonne, Leonhard S. Wolfe and Robert J. Desnick. University of Minnesota, Dept. of Pediatrics, Genetics and Cell Biology and The Dight Institute for Human Genetics, Minneapolis, MN 55455.

Mannosidosis types I and II (M I/II) have been differentiated by phenotypic (Pediat.Res. 10:985,1976) and now by enzymatic characterization. M I/II variants both showed residual acidic (pH 4.4) α-mannosidase (αM) activity (1-3% of normal (N)), which was cryolabile; intriguingly, decreased neutral (pH 6.0) αM was consistently found in WBC (<25% of N) but not in fibroblasts or plasma. Thermal inactivation (55°C, pH 4.4 and pH 6.0) revealed differential αM stabilities in M I/II fibroblasts; different K_m values were found only at pH 4.4. Zn^{++} and Co^{++} stimulated the residual αM in M I/II plasma and WBC. $ZnSO_4$ (0.3mM) incubated in the media of cultured M I/II fibroblasts stimulated residual αM >200% of untreated controls after 2d. These *in vitro* studies suggested that oral $ZnSO_4$ supplementation may increase substrate catabolism *in vivo*. Four sibs of consanguineous parents with M II participated in a 6 mo controlled (2 treated; 2 untreated) study. The αM activities were unchanged in plasma, WBC and tears in either group. Urinary mannose-rich oligosaccharides appeared to decrease in treated patients. These results indicate 1) genetic heterogeneity of M, 2) a molecular interrelationship among the isozymes, 3) enzyme manipulation by Zn^{++} *in vitro*, and finally 4) Zn^{++} supplementation in M II may stimulate residual tissue αM and increase substrate catabolism.