759 HERITABILITY OF SODIUM REABSORPTION CAPACITY IN AN EXOCRINE GLAND OF THE RAT. Thomas W. Seale, Barbara H. Farber, Marinus Flux and Owen M. Rennert. Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

In cystic fibrosis (CF) patients Na reabsorption from the primary secretions of exocrine glands is markedly reduced. Because the ducts of rat salivary glands have Na reabsorptive activity levels second only to the kidney tubule and can be inhibited by a component of CF exocrine secretions, they provide a good system for studying factors which alter ion transport in exocrine glands. We found that male rats (n=10) from two different Sprague-Dawley lines (designated OU and SI) produced parotid salivas with intrinsically different Na contents (e.g. 90 vs 30 mEq/L) when induced to salivate with pilocarpine. Serum Na levels were indistinguishable from one another. Crosses between OU and SI lines produced F_1 males (n=12) with parotid Na levels which were intermediate to either parent. Reciprocal crosses gave identical results, i.e. the relative activity of the ductal Na transport system was controlled by a single pair of incompletely dominant autosomal alleles. Reserpine-induced inhibition behaved as a simple dominant. Three daily doses of reserpine had no effect on the Na content of F_1 progeny or the SI line but elevated the Na content of the OU line. Backcrosses of F_1 progeny to each parent line produced males (n=10) with phenotypes of the F_1 hybrid and the appropriate parental type, again, consistent with a single gene autosomal recessive mode of inheritance of the low Na transport capacity phenotype. This gene appears to control a component of the ductal Na transport system which is sensitive to the humoral inhibitor induced by reserpine administration.

760 DIFFERENCES IN PAROTID SALIVA SODIUM LEVELS AND RESERPINE-RESPONSIVENESS BETWEEN RAT LINES. Thomas W. Seale, Barbara H. Farber, and Owen M. Rennert. Department of Pediatrics, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

The mechanism underlying the inhibition of Na reabsorption from exocrine secretions in cystic fibrosis (CF) is not known. In the animal CF phenocopy of Martinez, chronic reserpine (RS) administration to rats causes histological and physiological changes in exocrine glands similar to those in CF. To examine the effect of chemical sympathectomy on Na transport, we studied the onset of inhibition of Na reaborption from parotid saliva in male Sprague-Dawley (SD) rats given i.p. RS (0.5 mg/kg) daily. Saliva stimulated by i.p. pilocarpine was collected by cannulating the parotid duct. A single RS dose caused a marked increase in Na content within 24 hr in rats from our colony (OU). Na content increased linearly with the duration of RS administration. Saliva of SD rats from Sasco Inc. (SI) contained much less Na than that of OU rats at all saliva flow rates below 70 ul/min/g gland wet weight. RS administered to SI rats caused no demonstrable increase in saliva Na content until the 4th day. Na increased only to levels seen in untreated OU rats. These results indicate that both the intrinsic activity and the susceptibility to inhibition of the ductal Na transport system of exocrine glands show specific differences. Such differences complicate the use of uncharacterized rat strains for the bioassay of CF factors but may provide valuable insights into the biological regulation of Na transport in the exocrine gland duct.

761 MULTIPLE SIBLING MENTAL RETARDATION AND THE IMPACT OF THE FRAGILE X CHROMOSOME. LAWRENCE R. SHAPIRO MURRAY D. KUHR, AND PATRICK L. WILMOT. New York Medical College, Westchester County Medical Center, Departments of Pediatrics and Pathology, Valhalla, and Letchworth Village Developmental Center, Genetics Laboratory, Thiells, New York.

Mental retardation in two or more siblings with two normal parents represents an area about which little is known and is a difficult problem with regard to accurate diagnosis, elucidation of genetic mechanisms, and genetic counseling.

Sixty-one families with two or more mentally retarded siblings with two normal parents were ascertained from a large institution for the mentally retarded and a clinical genetics service. Investigation included pedigree analyses, physical examination, biochemical/metabolic analyses and chromosome analyses. A specific diagnosis and/or genetic mechanism was found in only 25% (15/61) of the families.

Of the sixty-one families, 22 had affected males only, of which two had definite X-linked recessive mental retardation. When chromosome analysis utilizing Medium 199 was done, an Xq27 fragile site was found in 36% (8/22) of the families with affected males only, including one of the known X-linked recessive families. Thus, the ability to detect the Xq27 fragile site resulted in an increase to 36% (22/61) of definite diagnoses for all families.

Multiple sibling mental retardation represents a major clinical problem for which the detection of the Xq27 fragile site has an important impact.

● **762** GENETIC COMPLEMENTATION ANALYSIS IN FIBROBLASTS FROM GYRATE ATROPHY (GA) AND THE SYNDROME OF HYPERORNITHINEMIA, HYPERAMMONEMIA AND HOMOCITRULLINURIA (HHH). Vivian E. Shih, Roseann Mandell, Lee B. Jacoby and Eliot L.Berson. Neurology Service and Genetics Unit, Mass. General Hosp.,Berman-Gund Lab., Harvard Med. Sch., Boston.

Hyperornithinemia is a finding in GA (B_6-responsive and non-responsive variants) due to ornithine transaminase (OKT) deficiency and in HHH, in which all known enzymes in ornithine metabolism are normal and the primary metabolic defect is not defined. Fibroblasts from GA and HHH when incubated for 6 hrs. with ^{14}C-ornithine and ^{3}H-leucine failed to incorporate ^{14}C into protein, resulting in low $^{14}C/^3H$ ratios (0.006-0.017; control $0.239 \pm .046$). The GA B_6-responsive variant was able to incorporate ^{14}C into protein at a reduced rate (ratio of 0.097). Following PEG 1000 mediated cell fusion $^{14}C/^3H$ incorporation was measured in heterokaryons. Each of 3 GA B_6-nonresponsive lines was hybridized with the GA B_6-responsive line. Lines of both GA variants were fused with 2 HHH lines. No complementation was observed between any of the GA B_6-nonresponsive lines and the GA B_6-responsive line, but both GA variant lines complemented the HHH lines. These data suggest that the B_6-responsive and -nonresponsive variants of GA are due to non-complementing mutations in the same structural gene. The complementation between GA cells and HHH cells supports other biochemical and clinical data that the mechanisms of hyperornithinemia are distinct in these two disorders.

● **763** EVIDENCE FOR TWO GENES ENCODING HUMAN ARGINASE. E.B. Spector, S.C.H. Rice, and S.D. Cederbaum; U. of California, Los Angeles; Depts. of Psych. and Peds.

Patients missing liver arginase retain considerable capacity to synthesize urea. The mechanism by which this occurs is unknown and previous biochemical and immunologic studies did not distinguish a one from a two-locus model.

A kidney biopsy was obtained from M.U., an 11-year-old boy with arginase deficiency. The kidney had a specific activity of 1.34 µmol/30min/mg protein as compared to 0.35-0.87 µmol/30min/mg protein in control biopsy and autopsy kidney. When tested with rabbit anti-human liver arginase (RAHLA), the M.U. kidney demonstrated a line of identity with normal human liver and kidney. RAHLA did not precipitate kidney arginase in M.U., but did precipitate 50% of normal kidney and 100% of normal liver arginase. Precipitation-inhibition experiments demonstrated an antigenic but enzymatically inactive protein in M.U. kidney that cross-reacted with liver arginase.

The data support the existence of two arginase genes in man, one expressed in liver (AI) and two in kidney (AI and AII). AI codes for enzyme active in normal liver and kidney, but not in M.U. kidney. M.U. has an inactive AI protein as demonstrated by precipitation-inhibition. AII is expressed in normal kidney and in M.U. kidney. AII probably arose as a result of gene duplication and appears to be inducible as demonstrated by the high specific activity of arginase in M.U. kidney. The presence of a second arginase gene expressed in kidney explains the ability of arginase-deficient patients to synthesize urea.

764 LEUKOCYTE CHROMOSOMES FROM PARENTS OF CYTOGENETICALLY ABNORMAL OFFSPRING. Richard Stallard, Nancy R. Haney, Patricia A. Frank, Patty Styron, and Richard C. Juberg. Wright St. Univ. Sch. of Med., and Children's Med. Cnt., Dayton, OH

Hypermodal spreads are less frequent than hypomodals in routine chromosomal preparations. Hypomodals are probably artifacts resulting from preparative technique. However, hypermodals may signify mosaicism or a tendency to misdivision.

Our materials were 435 leukocyte cultures of cells from phenotypically abnormal or normal subjects studied during 38 months in a diagnostic laboratory. Most preparations were G-banded, and 2 or more observers analyzed deviations from modality.

There were no apparent temporal or sequential patterns to appearance among 14,710 spreads of 27 hypermodals (frequency = 1/545): 9 spreads with a single additional autosome; 2 with +7, 2 with isochromosome 11q, 2 with a fragment, 3 with +21, 3 with +Y, and 4 with +X; and 2 spreads each with 2 extra chromosomes.

The frequency of hypermodals was 1/156 among 30 parents of 16 aneuploid offspring: 10 with +21, 2 with +18, 1 with +13, 1 with XXY, 1 with XXX, and 1 with XXXXY. Comparisons showed: (1) a frequency of 1/681 among the remaining 405 subjects ($P < 0.001$ by χ_1^2); (2) a frequency of 1/810 among 50 similarly aged parents ($0.02 > P > 0.01$ by χ_1^2). Moreover, the addition of an X or Y occurred in 0.86 of the hypermodals among the parents of aneuploid progeny in contrast to the remaining group, in which the frequency of X or Y hypermodality was 0.05.

These parents of aneuploids showing significant mitotic misdivision *in vitro*, may tend to meiotic nondisjunction *in vivo*.