● **823** 3-METHYLGLUTACONYL-CoA HYDRATASE DEFICIENCY: TWO DIFFERENT CLINICAL AND ENZYMATIC PHENOTYPES IN 3-METHYLGLUTACONIC ACIDURIA. K.M. Gibson, L. Sweetman, W.L. Nyhan, K. Narisawa, K. Roth, W. Lehnert, B. Robinson, M. Duran, S.K. Wadman. Department of Pediatrics, University of California, San Diego, La Jolla, CA 92093

3-Methylglutaconic aciduria has been described in 7 patients in whom urinary excretion of 3-methylglutaconic (3-MGC) and 3-methylglutaric (3-MGR) acids were elevated. In two siblings the only manifestation was speech retardation. Combined excretion of 3-MGC and 3-MGR was 520-940 mmol/mol creatinine (normal less than 6). The other patients had a picture of severe neurologic degeneration and profound mental retardation. Combined excretion of 3-MGC and 3-MGR ranged from a low of 40 to 800 mmol/mol creatinine. The activity of 3-methylglutaconyl-CoA (3-MG-CoA) hydratase in fibroblast lysates derived from the siblings with speech retardation was less than 3% of the control level. In contrast the activity of this enzyme was normal in three patients with the other clinical phenotype. We have postulated that the excretion of 3-MGC and 3-MGR in the patients with neurological abnormality is a secondary accumulation in response to another primary defect not only because of the normal activity of the enzyme but because they also excrete large quantities of citric acid cycle intermediates. We conclude that the mild clinical presentation of the siblings we have studied is the clinical picture of 3-MG-CoA hydratase deficiency. These observations indicate that neither the presence of nor the level of excretion of 3-MGC and 3-MGR correlates with 3-MG-CoA hydratase deficiency.

824 RESPIRATORY COMPROMISE AS A MAJOR CAUSE OF MORBIDITY AND MORTALITY IN HUNTER SYNDROME. M.A. Greenstein, H.M. Saal, A.J. Gainey, and R.M. Greenstein. University of Connecticut Health Center, Department of Pediatrics. (Sponsored by Mark Ballow).

Eleven patients with Hunter Syndrome (MPS II) have been followed at the University of Connecticut, of which 10 have been placed on a monthly leukocyte transfusion protocol. Positive effects of the transfusions have included softening of the skin and hair with resolution of nodular skin lesions and diarrhea. We have also noted marked subjective improvement of joint discomfort in those individuals who are able to communicate. No significant improvement of macroglossia, organomegaly, skeletal, cardiovascular or pulmonary changes have been noted.

Previously, it was felt that mortality in Hunter syndrome was frequently secondary to cardiovascular complications. Our recent experience with 11 patients has shown that the major morbidity is related to respiratory disease, especially with regard to upper airway compromise. Because of the unusual tracheal cartilage conformation which develops in these individuals, tracheostomy has been necessary in 5/11 patients including 2/3 individuals with the mild form of Hunter syndrome. Tracheostomy is a complex procedure in these patients requiring non-standard techniques and appliances. These findings suggest that pulmonary abnormalities may be the primary cause of mortality in Hunter Syndrome. We are also considering that this change in the locus of morbidity may be due to the delay of cardiovascular decompensation secondary to the leukocyte transfusions.

825 REPRODUCTIVE OUTCOME IN COUPLES WITH PREVIOUS PREGNANCY WASTAGE. Sue Hahm, David Chitayat, Gay Sachs and Harold M. Nitowsky. Albert Einstein College of Medicine, Bronx, New York 10461.

A follow up study was carried out of the reproductive experience of 62 couples who had been evaluated earlier at our Genetic Center because of a history of pregnancy wastage (i.e. 2 or more spontaneous abortions (SA)) and no liveborn children. Of 57 couples who had normal peripheral blood chromosome findings, 45 (79%) had subsequent normal liveborn infants, although 14 also had one or more additional SA. In a comparison of couples with 2 (n=29) or 3 or more (n=28) previous SA, the latter had a less favorable outlook for a liveborn infant (93.1% vs 64.3% $p < 0.02$) and also a greater likelihood of no further pregnancies (6.9% vs 25.0% p=n.s.). Among 5 couples with an abnormal karyotype in one member of the pair, only 1 had a normal liveborn child, 1 had an additional SA, and 2 had no recognizable pregnancies despite attempts at conception. Thus, there is a high expectation of favorable pregnancy outcome after 2 SA and a less favorable pregnancy outlook with 3 or more SA among couples with normal karyotype and no previous live births. The reproductive outlook appears to be poor in couples with a structural chromosome rearrangement.

● **826** GENETIC HETEROGENEITY IN ARTHROGRYPOSIS (MULTIPLE CONGENITAL CONTRACTURES). Judith G. Hall, Department of Medical Genetics, University of British Columbia, Vancouver, B.C.

Congenital contractures are commonly present at birth. A single contracture occurs in at least 1 in 200 births. Multiple congenital contractures (Arthrogryposis) occur in about 1 in 4,000 births. A study of multiple congenital contractures was undertaken among 350 patients diagnosed as having Arthrogryposis in order to distinguish genetic heterogeneity. These patients were identified from orthopedic and pediatric hospitals as unknown diagnostic entities. Three clinical subdivisions were utilized: 1) individuals with primarily limb involvement, 2) individuals with limb involvement plus other anomalies, 3) individuals with limb involvement plus central nervous system abnormalities. A differential diagnosis and empiric recurrence risk was established on the basis of these 3 categories. Within each category, a large number of specific entities were recognized and determined to be genetic versus non-genetic. Of the total study group, 80 or 23% were found to have single gene basis, 9 or 3% a chromosomal basis, and 5 or 1% a multifactorial basis. Thus, 27% of the total study group had a genetic basis. Twenty-two or 6% had a recognizable environmental etiology. One hundred and sixty-four or 47% were recognized diagnoses which had no recurrence risk or genetic basis, and 70 or 20% could not be identified as having a specific syndrome. The recurrence risk to patients within the unknown group was approximately 5%. The population incidence of Arthrogryposis during the 5-year period in Washington state was 1 in 4,000 births.

827 EVIDENCE THAT BRONCHIAL REACTIVITY MAY BE INHERITED Russell J. Hopp, Robert G. Townley. Sponsored by James T. Cassidy. Creighton University School of Medicine, Department of Pediatrics, Omaha, Nebraska

Different genetic mechanisms have been proposed to explain the presence of asthma in families. A methacholine (M) inhalation challenge identifies non-specific bronchial reactivity. It may be possible to determine whether the M response is a marker that can be utilized in genetic studies.

Subjects were selected from normal (NF) and asthma (AF) families enrolled in a Natural History of Asthma study. Subjects were included in the analysis if they did not have asthma, allergic disease or a recent respiratory infection. The M studies were performed by standard procedures (JACI 64:569,1979), and expressed as the area under the best-fitting parabola of the dose response curve. One-hundred eighty-four subjects from AF and 128 from NF were included. A frequency plot of age-corrected M responses showed a bimodal distribution of normals from AF while normals from NF had an unimodal distribution.

Twenty-four non-asthmatic parent pairs of normal children from NF and 20 non-asthmatic parent pairs of asthmatics were included in a separate M response frequency plot. The M response of parents of asthmatics had a bimodal pattern, while the distribution of responses of parents of normal children was unimodal.

These results show that the methacholine response can measure non-specific bronchial reactivity without the presence of clinical asthma and that a familial component exists which may be transmitted from one generation to the next.

● **828** ABNORMAL CARTILAGE COLLAGENS IN ACHONDROGENESIS II William A Horton, Mirta A Machado, Jean W Chou, David R Eyre. Univ of Texas Health Science Center, Dept of Pediatrics, Houston and Harvard Medical School, Dept of Biochemistry, Boston.

Achondrogenesis II is an inherited disorder of endochondral bone growth characterized clinically by severe (lethal) dwarfism and pathologically by the production of reduced amounts of cartilage matrix. To further define its pathogenesis, we studied growth plate tissue from 4 patients by a combination of microscopic and biochemical methods. Immunostaining of undecalificied Spurr embedded sections with a battery of collagen antibodies revealed that the major collagen of the resting cartilage matrix was type I rather than the expected type II (cartilage) collagen which was much reduced in amount. Analysis of resting cartilage collagens by SDS-PAGE and size exclusion HPLC mapping of cyanogen bromide peptides confirmed that collagen I was the major collagen and failed to detect collagen II. The results suggest at least two possibilities. First, there may be a defect in the structural gene for collagen II which interferes with the synthesis and/or secretion of the protein in an analagous fashion to that which occurs for collagen I in the osteogenesis imperfecta syndromes. Alternatively, the secretion of collagen I may reflect prematurity and/or abnormal regulation of the normal "switch" from collagen II to collagen I synthesis that occurs during later stages of growth plate chondrocyte differentiation. In any event the observations indicate that growth plate collagen production is disturbed in the disorder.