925 AUTOSOMAL DOMINANT INHERITANCE OF ALOPECIA CONGENITA WITH KERATOSIS PALMO-PLANTARIS. Lytt I. Gardner. Department of Pediatrics, SUNY, Upstate Medical Center, Syracuse, New York.

The syndrome complex of congenital (total) alopecia, keratosis of palms and soles and dystrophy of nails is a rare mutation with an autosomal dominant pattern of inheritance. Only one other report could be found (Stevanovic, *Acta Genet.* 9:127, 1959). In the previously described kindred, as well as in the present one, there was variable expression of the listed traits. In the present kindred there were three individuals with the full syndrome and five with partial or no alopecia, yet exhibiting keratosis of palms and soles and nail dystrophy. The proposita had total alopecia, including absence of eyebrows, eyelashes and sexual hair. She perspired normally and had no dental abnormalities. Nails were ridged and dystrophic, and palms and soles were covered with heavy keratosis having an opalescent orange-pink color. Intelligence was normal. Karyotype on peripheral leucocytes was 46,XX. Banding studies are incomplete.

Similar variability in expression of traits is seen in other vertically inherited syndromes such as pseudo-pseudohypoparathyroidism and Gardner's syndrome, and may represent unequal crossing over with duplication or triplication of loci in subsequent generations. An animal model is represented by the situation at the Bar locus in *Drosophila* (region 16-A of the X-chromosome). Unequal crossing over results in duplication or triplication of region 16-A, with triple-Bar presenting a more abnormal phenotype than double Bar. Whether present banding techniques are sensitive enough to test this hypothesis in man remains to be seen.

926 THE EFFECTS OF MODERATE ALCOHOL CONSUMPTION DURING PREGNANCY ON FETAL GROWTH AND MORPHOGENESIS. James W. Hanson, Ann P. Streissguth, David W. Smith

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Although heavy alcohol consumption during pregnancy has been widely recognized as a serious risk to the exposed fetus, previous studies have not indicated the magnitude of risk which may be associated with consumption of moderate amounts of alcohol. As a part of a larger study of pregnancy and health in 1529 mothers, information on maternal alcohol intake during the month preceding pregnancy and during the first five months of pregnancy, was collected. At the time of delivery, 97 infants born to women who drank an average of one ounce of ethanol or more per day, in the month prior to pregnancy or during the first five months of pregnancy, were selected. For each infant, a control infant whose mother drank a lesser amount of alcohol was selected. Each received a clinical evaluation without knowledge as to maternal drinking history. Of eleven infants judged clinically to show signs compatible with a prenatal effect of alcohol on growth and morphogenesis, nine were found to be from the high risk drinking group. Two of these infants, from the heaviest drinking mothers, had the fetal alcohol syndrome. The other seven infants, who showed lesser alterations of growth and morphogenesis, were born to women who drank moderate amounts of alcohol during the earliest part of pregnancy. Most of these women were found to be "binge" drinkers. These results indicate that moderate levels of alcohol intake during early pregnancy, may result in significant alterations of growth and morphogenesis in the fetus. "Binge" drinking may represent an additional risk factor for the fetus.

927 SMALL MOLECULAR WEIGHT HYDROXYPROLINE-CONTAINING COMPOUNDS IN THE DEVELOPING MOUSE LIMB. Lewis B. Holmes and Robert L. Trelstad, Mass. Gen. Hosp. and Shriners' Burns Institute, Boston, MA.

We have found 3 small molecular weight hydroxyproline (OHP)-containing compounds that are abundant in the developing mouse limb. The amino acid OHP is customarily related to the presence of collagen and elastin, molecules in the extracellular matrix that contain OHP. Cells cannot incorporate free OHP directly into collagen during synthesis; instead OHP is formed by the post-translational hydroxylation of polypeptide-bound proline. In fibroblast cultures (*J. Cell Sci.* 12:217, 1973) most of the labeled OHP made from proline is a free amino acid or in a small polypeptide.

We have cultured developing limbs from day 10 to 14 embryos with C^{14} -proline for 4 hrs. Small and large molecular weight fractions were obtained by chromatography on Sephadex G-25. The amount of C^{14} -OHP was determined on an amino acid analyzer column. Over 80% of the C^{14} -OHP was in the small molecular weight fractions and included trans-4-OHP, cis-4-OHP and trans-3-OHP. These compounds were also produced in the presence of α -dipyridyl, which inhibits the known hydroxylation enzyme. The presence of cis-4-OHP is a surprise as it prevents the formation of a stable collagen helix. This compound has never been isolated from mammalian tissues. Trans-3-OHP is abundant in type IV collagen, the most common source of which is basement membranes. The role (if any) of these 3 small molecular weight OHP compounds in development remains to be elucidated. Supported by NIH Grants HD09689 and HL18714.

928 FURTHER HETEROGENEITY IN LETHAL NEONATAL SHORT-LIMBED DWARFISM. Horton, William A., Rimoin, David L., Hollister, David W., and Lachman, Ralph S. UCLA-Harbor General Hospital, Division of Medical Genetics, Torrance, Calif.

In recent years the extent of the heterogeneity within lethal neonatal short limbed dwarfism has become apparent, with the delineation of numerous distinct syndromes such as thanatophoric dwarfism, achondrogenesis and the short rib polydactyly syndromes. Utilizing a combined clinical, radiologic, histologic and biochemical approach, we have observed further heterogeneity within this group of disorders. For example, we feel we can distinguish at least 3 distinct disorders in what has been called "thanatophoric" dwarfism, by histological and biochemical criteria. One group of patients is recognized by the Kleeblattschädel skull deformity. They differ both radiologically and in the histologic appearance of their growth plates from patients not manifesting this deformity. In this latter group, 2 additional disorders can be distinguished by specific growth plate histopathology and biochemical abnormalities observed on whole chain electrophoresis of collagen isolated from resting cartilage. Similarly, 2 distinct varieties of achondrogenesis can be clearly separated by radiologic and histopathologic criteria. The short rib polydactyly syndromes were originally divided into the Majewski and Saldino-Moonan types on the basis of radiologic criteria. We feel that the latter type can be further subdivided into 2 distinct entities. These studies demonstrate that the true heterogeneity of this group of disorders is only beginning to be appreciated, and that further heterogeneity will likely be found by this multidisciplinary approach.

929 DETERMINANTS OF GROWTH IN PATIENTS WITH VENTRICULAR SEPTAL DEFECT. Robert Levy, Annon Rosenthal, Olli Miettinen and Alexander S. Nadas. Harvard Medical School, Children's Hospital Medical Center, Department of Cardiology and Epidemiology, Boston, Mass.

Growth status was assessed in 1210 patients (pts) with ventricular septal defect (VSD) participating in the Cooperative Study on the Natural History of Congenital Heart Disease. Height (Ht) and weight (Wt) maturation were compared to the new National Center for Health Statistics norms. A total of 793 pts were managed medically; 194 underwent successful surgical repair, and 223 were surgically palliated. Mean follow-up period was 6.4 years (range 4 to 8 years). On initial assessment 77.0% of pts were below normal median Wt ($X^2=495$, $p<.001$) and 67.8% below normal median Ht ($X^2=132$, $p<.001$). Multivariate analysis revealed major significant determinants of Ht at initial assessment and after medical or surgical management to be birth Wt ($t=-6.5$, $p<.001$), pulmonary/systemic pressure ratio ($t=-4.8$, $p<.001$), presence of extracardiac congenital anomalies (ECA) ($t=-3.4$, $p<.001$), and advancing age ($t=+3.3$, $p<.001$). Determinants of Wt were similar to those for Ht except for the additional influence of pulmonary/systemic flow (Qp/Qs) ratio ($t=-4.5$, $p<.001$). Mean Ht increased to the same extent independently of management, but remained subnormal ($t=-8.9$, $p<.001$). By contrast Wt status showed significantly greater gains after repair ($t=+2.5$, $p<.01$) with improvement to normal mean Wt. We conclude that growth in pts with VSD is strongly influenced by intrauterine growth, presence of ECA and hemodynamic abnormalities. Correction of abnormal hemodynamics improves growth if other relevant determinants are favorable.

930 THE MECKEL-GRUBER (MGS)/ULLRICH-FEICHTIGER (UFS) SYNDROME: ANTEMORTEM HORMONAL STUDIES. S.L. Maby, H.L. Villet, M. Degnan, R. Urizar, H.M. Rosenberg, M.L. Cowger, & J.H. Porter. Birth Defects and Kidney Disease Inst., N.Y.S. Dept. of Health and Alb. Med. Col., Dept. Peds., Albany, N.Y.

Controversy exists regarding differentiation of the MGS and UFS. Because of variation in features in MGS, and question of the existence of UFS, a better definition of the hormonal pathophysiology should permit precise delineation. We have studied a neonate with the following anatomic defects: occipital protuberance (increased transillumination), coronal synostosis, low set ears, Brushfield spots, bulbous nose, micrognathia, bilateral hydronephrosis, a 2.5 cm hooded phallus, 10 hypospadias and absent scrotum; a posteriorly displaced anus, loose skin, joint contractures, simian creases, bilateral talipes equinovarus, bilateral duplication of the first toes and absent toenails on digits 3-5/6 on the left. Many of these features are shared by MGS and UFS. Chromosomal analysis was normal, 46,XY.

Endocrinological investigations included thyroid studies: absent epiphyseal centers, T4 1.6, FT4 0.5 ng/dl, TSH > 160 μ U/ml, antithyroid antibodies neg; pituitary-adrenal axis: urinary steroids (mg/da) 17KS < 0.44, 17OH < 0.5, P'triol < 0.2, ACTH-pending; pituitary-gonadal axis: FSH 10.4 mIU/ml, LH 32.6 mIU/ml, testosterone 17 ng/dl; hGH > 50 ng/ml; no abnormalities of Ca/P or glucose homeostasis. These studies demonstrate primary thyroidal, gonadal, and probably adrenal failure. Previous anatomic descriptions of the endocrine abnormalities in these syndromes have implied functional relationships with an inability to define 10 vs 20 hormonal dysfunction.

The morphological abnormalities described here are consistent with UFS and lend support to it being a distinct nosologic entity. As a result of this study end-organ failure should now be included as a diagnostic feature of the UFS. The infant expired before other hormonal studies were completed. Necropsy findings will be discussed.