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FETAL HYDANTOIN SYNDROME: SUSCEPTIBILITY TO PHENYTOIN-INDUCED CLEFT (LIP) AND PALATE LINKED TO H-2 LOCUS IN MICE. Allen S. Goldman, Masuyuki Katsumata*, and David L. Gasser*. Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104

The human fetal hydantoin syndrome includes cleft (lip) palate. Phenytoin also produces cleft (lip) palate in A/J mice which is sensitive to cortisone-induced cleft palate. Recently, we have shown that the strain differences in susceptibility to cortisone-induced cleft palate in mice can be explained in terms of variation in levels of fetal palatal glucocorticoid receptors, which in turn are regulated by H-2 linked gene(s). Thus, we have tested the hypothesis that phenytoin may have similar genetic differences in susceptibility to the production of this defect in mice as does cortisone. Phenytoin was administered at 50 mgs/kg from the 11-14 days of gestation in the strains A/J ($H\text{-}2^a$), B10 ($H\text{-}2^b$), and B10.A (having $H\text{-}2^a$ but otherwise 99.5% of genetic background of B10). Susceptibility to phenytoin-induced cleft palate is high in A/J (43.8% of offspring) and B10.A (32.9%) but low in B10 (1.6%). Therefore, a gene controlling phenytoin-induced cleft palate is also located in or near the H-2 locus. These results give the first evidence of a genetic control mechanism (by a gene in or near the H-2 locus) for susceptibility to a congenital malformation (cleft palate) to a xenobiotic (phenytoin).

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ASSOCIATION OF CHROMOSOME ABNORMALITIES WITH FETAL DILANTIN SYNDROME. Frank Greenberg, Hope H. Punnett, Mildred L. Kistenmacher and Angelo M. DiGeorge, St. Christopher's Hospital for Children and Department of Pediatrics, Temple University School of Medicine, Philadelphia, Pa.

The Fetal Dilantin Syndrome (FDS) is a clinical entity of recognizable congenital defects associated with maternal exposure to Dilantin, either alone or with other anticonvulsant medications. We have recently investigated four patients with FDS. Two of these patients had coexistent chromosomal abnormalities, Klinefelter syndrome and a 14/21 translocation respectively. In addition to the typical findings of FDS, both had defects not usually associated with the syndrome. There was one previous patient described who had coexistent Turner syndrome and FDS by Chen, et. al. (Birth defects: Original Article Series XIII (3B) : 237-8, 1977). Patients with FDS should be karyotyped, especially if atypical clinical findings are present.

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## 915

ACETAZOLAMIDE-INDUCED FORELIMB MALFORMATION. Lewis B. Holmes and Robert L. Trelstad, Harvard Medical School, Mass. Gen. Hosp., Children's Service and Department of Pathology, Boston.

Acetazolamide sodium, a diuretic in man due to inhibition of carbonic anhydrase, produces postaxial forelimb deformities in mice when administered in utero on days 9 or 10 of gestation. The deformities are much more common on the right side. We have evaluated the pattern of mesenchyme cell aggregation and cartilage formation in day 11½ to 12½ forelimbs of C57BL/6J embryos, a strain known to be susceptible to this teratogen (Teratology 11:37, 1975). In d. 11½ forelimbs, in which aggregation of mesenchyme is normally not visible, there was no limb deformity and no necrosis of tissue. By d. 12 there is absence of the postaxial aggregates of either digits 4 and 5 or the ulna or both in the forelimbs, primarily the right. The remaining aggregates showed normal patterns of cell polarity, as determined by staining the Golgi apparatus with silver nitrate and determining the orientation of the stained mesenchyme cells toward the center of the aggregate. The mechanism of action of acetazolamide is not known. These studies suggest that it interferes with early mesenchyme cell aggregation in a restricted anatomic region presumably by interrupting the normal process of cell-to-cell adhesion.

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FAMILIAL PARTIAL TRISOMY OF THE LONG ARM OF CHROMOSOME 16. Geoffrey Kurland, Norman J. Lewiston, Raymond Hintz and Howard Cann. Stanford University School of Medicine, Department of Pediatrics, Stanford, CA.

A 2 year old Mexican girl with psychomotor retardation, short stature, recurrent pneumonia and purulent otitis media, submucous cleft palate, unilateral choanal stenosis, bifid uvula, and short 5th fingers was evaluated cytogenetically. Trypsin-Giemsa banding revealed 46,XX,12p+, the additional material on chromosome 12 consisting of a dark and light band. Her normal mother and a sister each carry a 12p+ chromosome similar to that of the proband and one chromosome 16 deficient for the segment q22→qter, indicating a balanced translocation: 46,XX,t(12;16)(p13;q22). The proband inherited the maternal 12p+ chromosome and normal chromosome 16. Her karyotype is 46,XX,der12,t(12;16)(p13;q22)mat. She is trisomic for the segment of 16q22→16qter and may be monosomic for the segment 12p13. Although she has had recurrent infections, all immunologic studies including tonsillar biopsy have been normal. Her father and another sister have normal karyotypes. A male half sibling with dysmorphic features died in infancy of pneumonia.

The parents conceived a male child with the same unbalanced translocation as the proband. He has the anatomic defects of his sister plus low set ears, transverse palmar creases, rib and sternal anomalies, ambiguous genitalia and anal atresia. Endocrinologic evaluation has revealed elevated gonadotropins in this child and the proband. These patients show a clinical syndrome which may be distinctive for trisomy of the segment 16q22→16qter and possible monosomy of 12p13.

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IS DISPROPORTIONATE VENTRICULAR SEPTAL THICKENING A RELIABLE MARKER OF HYPERTROPHIC CARDIOMYOPATHY IN INFANTS? Barry J. Maron, Jesse E. Edwards, Stephen E. Epstein, National Heart, Lung, and Blood Institute, Bethesda Md.

Disproportionate septal thickening (DST) (septal-free wall thickness ratio $\geq$1.3) is the most characteristic anatomic feature of hypertrophic cardiomyopathy (HCM). To assess prevalence of DST in infants with congenital heart diseases, and to determine whether septal-free wall ratio $\geq$1.3 should be utilized as the diagnostic criteria of DST in infancy (when absolute wall thicknesses are small), 129 patients <2 yrs old were studied at necropsy. DST was present in 33 (25%) of 129 patients; in these patients septal-free wall ratios ranged from 1.3-2.5 but were $\leq$1.7 in 32. DST was not common in patients with any particular cardiac malformation. Of note, if a septal-free wall ratio $\geq$1.5 was used as the criteria for DST, only 7% of patients were abnormal. In only 3 of 33 patients with septal-free wall ratio $\geq$1.3 was marked disorganization of septal myocardium, characteristic of HCM, present. Hence: 1) DST is common in infants with congenital heart diseases studied at necropsy; 2) the vast majority of such patients with septal-free wall ratios of $\geq$1.3 do not have typical necropsy findings of HCM, since disorganization of septal myocardium is rarely present; and 3) septal-free wall ratio $\geq$1.3 alone is not reliable in identifying associated HCM in infants with congenital heart disease, especially if marked absolute septal thickening or disorganization of septal myocardium are absent.

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SELECTIVE PARENCHYMAL GROWTH RETARDATION IN EXPERIMENTAL OLIGOHYDRAMNIOS. A.C.Moessinger, J. Bassi, G. Ballantyne, L.S.James and W.A.Blanc. Depts. of Ped. & Path., Columbia Univ., Coll. of P & S, N.Y., N.Y.

Puncture of the fetal membranes was performed on rat fetuses during the last third of gestation; the puncture was considered adequate when withdrawal of the needle was followed by continued leakage of amniotic fluid. All animals (n=54) were allowed to develop until term and were delivered abdominally, the littermates serving as controls (n=84). Weights and measurements of the fetus, placenta and various organs were recorded. Total lung DNA, RNA and protein were determined in 14 treated and control animals. The length of the umbilical cord was markedly reduced in the experimental group, ($p<0.001$). Lung weight and lung/body ratio were lower in the treated animals, ($P<0.001$). Total lung DNA was significantly less in the treated animals, confirming lung hypoplasia. RNA/DNA and protein/DNA ratios were not affected, indicating that cell size remained constant. The pathogenetic mechanism leading to hypoplasia appears different from that observed in models of utero-placental insufficiency since the brain/liver ratio was not affected. The same pattern of selective parenchymal growth retardation was noted in 7 newborn infants with documented oligohydramnios. In addition, congenital deformities resembling those seen in infants born after prolonged oligohydramnios were noted in the treated animals. This model should prove useful to clarify the pathogenesis of the oligohydramnios syndrome and lung hypoplasia, and to study the kinetics of lung catch-up growth.