●1254 GLUCOCORTICOID-INDUCED PHOSPHOLIPASE A_2-INHIBITORY PROTEINS (PLIP) MEDIATE GLUCOCORTICOID TERATOGENICITY IN VITRO. Allen S. Goldman, Chhanda Gupta, Richard Herold, and Ronald Piddington. The Children's Hospital of Philadelphia and The Departments of Pediatrics and Dental Medicine, University of Pennsylvania, Philadelphia, PA

Our recent work has suggested that anti-inflammatory glucocorticoids produce cleft palate in mice by the same biochemical pathway as utilized in their anti-inflammatory action. This pathway includes a glucocorticoid receptor mediated induction of phospholipase A_2-inhibitory proteins (PLIP) which inhibit the release of the prostaglandin precursor fatty acid, arachidonic acid, from membrane phospholipids at the level of phospholipase A_2, which in turn leads to a subsequent inhibition of prostaglandin production. In this report we have prepared and partially purified such PLIPs of molecular weight about 55,000, 40,000, 28,000, and 15,000 from A/J mouse thymus and from 12-day embryonic B10.A palates. Sufficient quantities of calf thymus PLIP and of the 15,000 molecular weight mouse thymus and palate PLIPs were prepared and tested as inhibitors of programmed cell death in the medial edge epithelium of single mouse embryonic palatal shelves in culture. This event is completely prevented by the inclusion of nanomolar quantities of cortisone in the culture medium. All the proteins tested prevent the loss of the medial edge epithelium and thus produce the teratogenic effects of glucocorticoids in the palatal culture model. This teratogenic action of both PLIP and glucocorticoids is reversed by arachidonic acid, the precursor of prostaglandins suggesting that PLIP mediates the effects of glucocorticoids by inhibiting phospholipase A_2 (PLA_2).

1255 ACHONDROPLASIA AND OBSTRUCTIVE SLEEP APNEA:CORRECTION OF APNEA AND SLEEP ENTRAINED GROWTH HORMONE RELEASE BY TRACHEOSTOMY. S. Goldstein, RHK Wu, M. Thorpy, R. Shprintzen, R. Marion, A. Sher, P. Saenger, Dept. Peds., Sleep-Wake Disorders Unit and Craniofacial Ctr., A. Einstein Coll. Med., Bronx, New York.

Obstructive sleep apnea (OSA) may occur in patients with achondroplasia. Since the bulk of growth hormone (GH) is secreted in relation to slow wave (non REM) sleep, disordered sleep may interfere with GH release and subsequent growth. To examine the relationship between sleep apnea and growth we studied a 9 yr old achondroplastic dwarf with growth failure (>-3SD on achondroplasia growth curve) and OSA. Polysomnography with q 20 min. sampling for sleep entrained GH was performed before and 4 mos. after therapeutic tracheostomy (T).

	growth velocity (cm/yr)	apneic episodes (per hr)	% slow wave sleep	GH secret. episodes (during sleep)	Total GH secret. (during sleep)
before T	3	105	none	1	24μg
after T	5.3	none	25.6	2	73μg
nl for age	5	none	13-30	2-3	54-122μg

Thus correction of sleep apnea normalized sleep stages in this patient and led to significantly increased sleep entrained growth hormone secretion resulting in normalization of growth rate. Caloric intake was unchanged before and after tracheostomy. Conclusion:The results suggest that OSA in achondroplasia may further impair growth in these youngsters. Deficient sleep entrained secretion of GH is reversible by therapeutic tracheostomy.

1256 BILATERAL NEOPLASTIC KIDNEY DISEASE, PULMONARY CYSTIC DISEASE, AND FETAL MACROSOMIA: A SPECTRUM OF DEVELOPMENTAL ABNORMALITIES. John M. Graham, Jr., William Boyle, Jeffrey Troxell, Gary J. Cullity, J. Bruce Beckwith (Spon. by Robert Z. Klein), Dartmouth-Hitchcock Medical Center, Hanover, NH, Princess Margaret Hospital for Children, Perth, Australia, Children's Orthopedic Hospital and Medical Center, Seattle, WA.

Three similar cases of bilateral neoplastic disease of the kidney were associated with congenital pulmonary cystic disease and fetal macrosomia. These cases are compared to several in the literature. We suggest that these three cases represent a spectrum of abnormal morphogenesis that affects both the kidney and the lung. Case 1 had bilateral multilocular cysts of the kidney in association with hamartomatous pulmonary cysts, This case is compared with Case 2 who had bilateral multilocular renal cysts, with one area of mesoblastic nephroma and multiple pulmonary cysts. These cases are compared to Case 3 who demonstrated markedly hyperplastic renomegaly with medullary dysplasia (similar to what is seen in the Beckwith-Wiedemann syndrome) in association with classical bilateral cystic adenomatoid malformation of the lungs. All three cases were overgrown at birth, and we suggest that these cases illustrate similarities in the development of kidneys and lungs. Embryologically the kidney and lung begin their development around the same time. During the 5th week of gestation, the ureteric bud invades the unsegmented mesoderm that becomes the metanephric system, and the lung bud invades the splanchnic mesoderm which provides the stimulus for its growth. The predominant pattern of a congenital kidney or lung neoplasm may reflect the timing of a prenatal neoplastic event.

1257 FOLATE SUPPLEMENTATION DOES NOT PREVENT NEURAL TUBE DEFECTS INDUCED BY ALCOHOL OR HEAT. John M. Graham, Jr., Vergil H. Ferm, William Layton, Departments of Maternal and Child Health and of Anatomy, Dartmouth Medical School, Hanover, NH, 03756.

Recent studies suggest that either maternal binge drinking or maternal hyperthermia might be one cause for neural tube defects. Timed pregnant golden hamsters were exposed to a double dose of ethanol on the morning of the 8th day of gestation (the day of neural tube closure in this species), and a 44 percent incidence of neural tube defects was observed). Similar defects could be engendered by treating the animals with varying periods of heat in a water-jacketed incubator at 39.5 degrees centigrade on the morning of Day 8. A 50-minute heat exposure resulted in a 35 percent incidence of neural tube defects, and a shorter exposure (44 minutes) resulted in a 23 percent incidence, while a longer exposure (56 minutes) resulted in a 68 percent incidence. We attempted to explore the hypothesis that maternal vitamin supplementation with folate may be effective in reducing the incidence of neural tube defects. Osmotic pumps filled with either folate or saline were placed subcutaneously in pregnant hamsters on the 6th day of gestation. Despite significantly increased maternal folate levels prior to providing a teratogenic insult with either a double dose of alcohol 4 hours apart or 50 minutes of heat in water-jacketed incubator, no significant protection from neural tube defects was afforded by supplementing the mother with folate. We question whether preconceptual vitamin supplementation may promote careful pregnancy planning which includes avoidance of known teratogens.

●1258 VITAMIN A TERATOGENESIS IN A SENSITIVE GENETIC BACKGROUND. John M. Graham, Jr., Eileen F. Rawnsley, Kathleen K. Sulik (Spon. by Robert Z. Klein), Department of Maternal and Child Health, Dartmouth Medical School, Hanover, NH, 03756 and Department of Anatomy, University of North Carolina, Chapel Hill, NC, 27514.

The critical event in lip formation is the convergence of the facial prominences. A variety of teratogens are known to interfere with later stages of facial prominence formation, and certain inbred mouse strains are known to be more susceptible to such teratogenic effects. Recently, we observed an otherwise normal child with severe bilateral cleft lip and palate. The mother took 50,000 iu of Vitamin A (one 25,000 iu Aquasol capsule bid) for 20 days between the 3rd and 6th week after conception, and the father had a unilateral cleft lip. To test the hypothesis that this may represent a teratogenic effect in combination with a sensitive genetic background, vitamin A was administered to A/J mice and 2 other inbred strains just prior to normal lip closure. A/J, IIWh, and SWFr mice were given 200 iu per gram vitamin A (retinyl palmitate) by gastric lavage at either 9:00 a.m. or 1:00 p.m. on day 9 (equivalent to 26-30 days gestation in the human). The frequency of cleft lip observed was not significantly different from the spontaneous frequency in the A/J strain, but there was a marked increase in the frequency and severity of cleft palate. Other inbred strains were not affected by cleft lip, and there was a less dramatic increase in the incidence of cleft palate in those strains. We conclude that the genetic background of the parents may be an important factor in evaluating risks for teratogenetic outcomes.

†1259 GONADAL DYSGENESIS AND GONADOBLASTOMA IN CRYPTOPHTHALMOS SYNDROME. Frank Greenberg, Bruce Keenan, Viamny De Yanis and Milton J. Finegold (Spon. by Arthur L. Beaudet). Baylor College of Medicine, Departments of Pediatrics and Pathology, Houston.

Cryptophthalmos syndrome is a presumed autosomal recessively inherited complex of malformations including fusion of the eyelids, microphthalmia, projection of the hair on the lateral forehead, notching of the alae nasi, cardiac defects, and genital abnormalities. Bilateral inguinal masses were noted in a phenotypic female with features of the cryptophthalmos syndrome. Peripheral blood chromosome analyses revealed 46,XX, in 41 cells. Serum testosterone and androstenedione which were both less than 25 ng/dl, rose to the adult female range after HCG administration. Frozen section of the biopsied right mass revealed numerous primary oocytes and some follicular development. Microscopic examination of the left mass revealed numerous primary follicles, some with prominent granulosa cells and multiple oocytes. Some follicles were distorted with evidence of gonadoblastoma in situ. There were also numerous accessory tubules of Wolffian origin appended to the ovary. Gonadoblastoma arising from dysgenetic gonads, not previously reported in this syndrome, rarely occurs in the absence of a Y chromosome containing cell line. In our patient, there was no additional evidence of Y chromosomal mosaicism nor Y-specific DNA. The presence of this tumor in our patient tends to contradict the prevailing Y chromosomal theory of the etiology of gonadoblastoma, but may support a recent hypothesis based on dysfunction of gonadal maturational process.