Regulation of insulin release at low O_2 tensions is important to hypoxic children because of their increased reliance upon carbohydrate metabolism for energy production. We have found immunoreactive insulin (IRI) release inhibited by alpha adrenergic receptor stimulation in hypoxic puppies. Since cyclic AMP mediated insulin release is thought to relate the adrenergic receptor and its physiologic response, the effects of cyclic AMP elevation on IRI levels at low O_2 tensions were studied. Hypoxic puppies were given an analogue of cyclic AMP, dibutyryl cyclic AMP (DCAMP), to test the effects of exogenous cyclic AMP elevation and theophylline, a phosphodiesterase inhibitor, to test the effects of endogenous elevation of cyclic AMP.

In air breathing puppies ($PaO_2 > 75$ mm Hg), either DCAMP *or* theophylline infusion resulted in sustained elevations of plasma IRI and glucose. With 75 min of hypoxia alone (PaO_2 25–35 mm Hg), plasma IRI remained at baseline levels despite the development of marked hyperglycemia. In contrast, puppies receiving DCAMP or theophylline after 30 min of hypoxia were found to have significantly higher IRI levels than did the hypoxic control group ($p < 0.05$). The IRI levels reached with DCAMP or theophylline appeared related to the concomitant glucose levels.

These observations suggest alpha adrenergic inhibition of insulin release in hypoxia is the result of reduced cyclic AMP levels.

85 *Aldosterone Metabolism in Cystic Fibrosis (CF).* ARTEMIS P. SIMOPOULOS, ALLEN LAPEY, THOMAS F. BOAT, PAUL A. DI SANT'AGNESE and FREDERICK C. BARTTER, NIH, Bethesda, Md.

CF patients show inability to retain salt through sweat leading to serious and at times, fatal complications through cardio-vascular collapse. Aldosterone-renin system metabolism has never been accurately determined in this disorder.

Five CF patients, 13 to 21 years of age, were studied on an air-conditioned metabolic unit on constant dietary regimens with 9,109, and 240 mEq/24 h sodium intake for 8-day periods. During each 8-day period of different sodium balance, aldosterone secretion rate (ASR) and plasma renin activity were measured; the latter in both the supine and upright position.

All patients were in good sodium metabolic balance and renal electrolyte conservation was normal. On the 109 mEq sodium regimen, the mean ASR was 282 μg/24 h (normal: 91 ± 30.4). In 4 out of 5 patients on the 240 mEq sodium regimen, the mean ASR was 205 μg/24 h (normal: 35.9 ± 16.1); the 5th patient suppressed moderately to ASR 62 μg/24 h. On the 9 mEq sodium regimen, all 5 patients were able to increase normally to ASR 702 μg/24 h (normal mean: 639 ± 441). Plasma renin values were somewhat elevated on the different sodium intakes, but rose normally with the upright posture.

Conclusions: In 5 CF patients, ASR and renin values were slightly elevated, but responded normally to decreased oral sodium intake and postural changes. ASR did not suppress as expected on the high sodium intake. This state of slight hyperaldosteronism secondary to increased renin release is probably due to adaptation to frequent excessive sodium losses via the sweat and consequent extracellular volume changes.

86 *Maturation of Hypothalamic-pituitary Control of Thyroid Function in the Human Fetus.* CALVIN J. HOBEL and DELBERT A. FISHER, UCLA Sch. of Med., Harbor Gen. Hosp., Torrance, Calif., Depts. of Ped. and Obstet.-Gynecol.

The human fetal thyroid is capable of concentrating iodine and synthesizing hormone by 12 weeks. Fetal thyroxine (T_4) production is thyrotropin (TSH) dependent and the fetal pituitary contains TSH by 10–12 weeks. Little is known, however, about maturation of neuroendocrine control of fetal thyroid function. Serum T_4, free T_4 (FT_4) and/or immunoreactive TSH were measured in paired maternal and cord blood specimens obtained at the time of therapeutic abortion or premature delivery of 35 pregnancies 11 to 34 weeks in duration and 17 pregnancies at term. Fetal pituitary were obtained when possible for determination of TSH content. Maternal T_4 and TSH did not change between 11 and 40 weeks but the mean FT_4 between 11 and 18 weeks was higher than the value at term. Fetal T_4, FT_4 and TSH were low between 11 and 18 weeks. TSH and T_4 increased abruptly between 18 and 22 weeks and, with FT_4, increased progressively thereafter to term. Fetal pituitary TSH content also increased abruptly between 18 and 22 weeks. There was no correlation between maternal and fetal serum T_4, FT_4 or TSH values. The data indicate that a) the fetal pituitary thyroid system functions autonomously of the maternal system; b) rapid maturation of the fetal hypothalamic-pituitary control occurs between 18 and 22 weeks; c) fetal T_4 secretion increases progressively between 24 weeks and term.

87 *Short Stature and Growth Hormone Deficiency Due to Histiocytosis X.* M. E. LAHEY, F. M. KENNY and A. L. DRASH, Dept. of Ped., Univ. of Utah Med. Center and The Children's Hosp., Univ. of Pittsburgh Sch. of Med.

Diabetes insipidus (DI) is a common complication of histiocytosis X. Anterior pituitary function has not been previously systematically studied. Both anterior and posterior pituitary function has been evaluated in 11 children with histiocytosis. The following methods were used. Insulin hypoglycemia and arginine infusion for HGH, serum PBI, T_4, and ^{131}I uptake for thyroid function, and metyrapone stimulation for adrenal function. Concentrating ability was used as an index of vasopressin release. Gonadotropin was assessed by physical examination only. In 6 patients, only vasopressin and growth hormone (GH) response was studied. In 5 thyroid and adrenocortical evaluation was also obtained. Of the 11 children, 4 were of normal height for age, while 7 were below the 3rd percentile. Those children with normal height all had normal GH response. Two of them had DI with normal thyroid and adrenal function. Of the 7 children with retardation of linear growth, 6 were found to be GH deficient. The 1 child with normal GH had a strong family history of short stature. Five had DI and all were GH deficient. Thyroid studies were normal in 2 and adrenal studies in 3 of these. One child had histiocytosis of the thyroid gland with goiter and hypothyroidism. In 3 children of adolescent age with short stature, GH deficiency and DI, puberty was delayed. This study documents that histiocytosis may involve the anterior and/or posterior pituitary. An adequate clinical evaluation should include study of the anterior pituitary.

88 *Distribution of ^3H-acetyl Growth Hormone (^3H-HGH) in the Subcellular Fractions of Rat Liver.* VADDANAHALLY T. MADDAIAH, IRAJ REZVANI,

SHANG Y. CHEN and PLATON J. COLLIPP, Dept. of Ped., Meadowbrook Hosp., East Meadow, NY.

To understand the early molecular events that lead to some of the effects of growth hormone on liver, a dose of ^{3}H-HGH (18×10^6 cpm, 60 μg) was given i.v. to hypophysectomized rats. After the injection, livers were homogenized and fractionated by centrifugation. Specific activity (cpm/mg protein) and total radioactivity expressed as percent of that in the homogenate were estimated (table). ^{3}H-HGH in the homogenate was estimated by precipitation with TCA, and with Na_2SO_4 as ^{3}H-HGH antibody complex with and without unlabeled hormone. Up to 10 min most radioactivity was protein bound and ^{3}H-HGH in the homogenate was antigenically similar to the injected dose. In contrast, when ^{3}H-HGH was added *in vitro* before homogenization most radioactivity (77%) appeared in the cytoplasm and the rest distributed almost equally among the other fractions. These results indicate (1) the early rapid uptake by the particulate fractions may be of functional significance and the important initial binding sites may be mitochondria and microsomes; (2) the movement of ^{3}H-GH in liver cell may be from the microsomal and mitochondrial fractions into cytoplasm; (3) after 10 min ^{3}H-HGH is degraded or deacetylated.

Fraction	2 min	5 min
Homogenate	1517 (100%)	2816 (100%)
Crude nuclear	866 (18.3%)	1232 (11.2%)
Mitochondrial	1638 (22.5%)	5043 (41.0%)
Microsomal	4776 (41.9%)	5841 (29.2%)
Cytoplasmic	1464 (27.5%)	2177 (23.2%)
Fraction	10 min	20 min
Homogenate	3246 (100%)	3901 (100%)
Crude nuclear	1707 (13.3%)	2042 (13.8%)
Mitochondrial	6308 (29.9%)	4622 (21.8%)
Microsomal	4754 (15.3%)	2954 (8.5%)
Cytoplasmic	3294 (23.5%)	7186 (46.1%)
Fraction	40 min	
Homogenate	1997 (100%)	
Crude nuclear	845 (13.5%)	
Mitochondrial	1442 (16.1%)	
Microsomal	1302 (7.9%)	
Cytoplasmic	4665 (65.3%)	

89 *Partial 3β-hydroxysteroid Dehydrogenase (3β-HSD) and 21-hydroxylase Deficiencies in a Family With Congenital Adrenal Hyperplasia, With Evidence for Increasing 3β-HSD Activities with Age.* FREDERIC M. KENNY, JOHN W. REYNOLDS and ORVILLE C. GREEN, Univ. of Pittsburgh, Univ. of Minnesota and Northwestern Univ., Depts. of Ped.

In this family, two affected boys have perineal hypospadias and bifid scrotum, and two affected girls have slight clitoral enlargement with otherwise normal genitalia. All are mild 'salt-losers' with spontaneous crises occurring late (3 months and 2 years) in the boys. The girls had negative Na+ balance only when stressed by salt deprivation at ages 2 months and 4 years. All had elevated 17-ketosteroid excretion when diagnosed and, in the 2 youngest, urinary DHA > androsterone. Cortisol production and/or 17-OH-corticosteroid excretions were normal. Steroid excretion patterns showed an increase of 3β-HSD activity with increased age, but with a persisting high excretion of Δ^5-pregnanetriol (Δ^5-p'triol). At 2 months, one girl excreted per 24 h: pregnanetriol (p'triol)-0.23 mg, Δ^5-p'triol-1.2 mg, 17α-OH-pregnenolone-2.6 mg, 16α-OH-pregnenolone-8.2 mg, 16α-OH-DHA-5.4 mg, DHA-0.5 mg. Her sister, at age 10 years, during withdrawal of cortisone therapy, excreted per 24 h: p'triol-24 mg, Δ^5-p'triol-14 mg, DHA-1.2 mg, no 16α-OH-pregnenolone or 16α-OH-DHA. We conclude that these cases have partial 3β-HSD deficiencies, on the basis of the inadequate fetal virilization and persistent post-natal excretion of large amounts of Δ^5-p'triol; and partial 21-hydroxylase deficiencies, on the basis of the high p'triol excretions. The low post-natal excretion of DHA, relative to Δ^5-p'triol and 17α-OH-pregnenolone, may be due to a late fetal appearance of the 3β-HSD for DHA or may be due to an underactivity of the 17–20 desmolase (side-chain splitting) enzyme.

90 *Sulfonylureas Amplify Cyclic 3',5' AMP Mediated Hormone Action.* HANS H. BODE, BARBARA M. HARLEY, ALLEN M. SPIEGEL and JOHN D. CRAWFORD, Harvard Med. Sch., Massachusetts Gen. Hosp., Children's Service and Shriners Burns Inst., Boston, Mass.

The reports that the sulfonylurea compounds have a vasopressin-like action in some patients with diabetes insipidus (DI) and MAHONEY and GOODMAN's observations of benefit in one patient with hypodipsia led us to a trial in three children with both deficiencies. Hitherto extraordinarily difficult management problems, these children have shown restoration of homeostatically appropriate thirst and facultative urinary concentrating ability during chlorpropamide (CPM) treatment.

Observations to provide insight into the mechanism of these clinical effects were as follows: much as in total diabetes mellitus, the sulfonylureas were without benefit in total vasopressin lack (Brattleboro rats) and in clinical nephrogenic DI Sulfonylureas, while inactive alone, augmented vasopressin stimulated water flux across toad bladder. Water flux induced by cyclic 3',5' AMP was not increased suggesting the compounds act neither by augmenting the influence of second messenger nor by phosphodiesterase inhibition. CPM treatment increased and prolonged parathyroid hormone provoked urinary excretion of cyclic 3',5' AMP in two patients with pseudohypoparathyroidism much as it extended and intensified antidiuresis due to exogenous vasopressin in water loaded normals.

The observations support the hypothesis that sulfonylureas act by amplifying the cyclic 3',5' AMP signal generated by hormones at their specific target tissues, possibly including CNS, where second messenger concentrations are high. If correct, the amplifier hypothesis implies extended applicability of sulfonylueras and their congeners in restoring homeostasis in states of attenuated endocrine secretion.

91 *Adverse Effects of Large Doses of Medroxyprogesterone Acetate (MPA) in Idiopathic Isosexual Precocity.* ROBERT A. RIGHMAN, LOUIS E. UNDERWOOD, FRANK S. FRENCH and JUDSON J. VAN WYK, Univ. of North Carolina Sch. of Med., Dept. of Ped., Chapel Hill.

Three girls and one boy with isosexual precocity were treated with large intramuscular doses of MPA, 200–300 mg *q.* 7–10 d., in an attempt to control the rapid advancement of skeletal maturation. Although secondary sexual development regressed, all four developed signs suggestive of corticoid excess. These included rapid weight gain, mild hypertension, plethoric