- 80 *Placental Passage and Fetal Secretion of Aldosterone.* FRANCIS J. BAYARD, ISADORE G. ANCES, ALAN J. TAPPER, VIRGINIA V. WELDON, AVINOAM KOWARSKI and CLAUDE J. MIGEON, Dept. of Ped., The Johns Hopkins Univ. and the Dept. of Obstet. and Gynecol., Univ. of Maryland, Baltimore, Md.

The transplacental passage and production of aldosterone by the mother and fetus were studied near term during a constant infusion of 1,2-³H-aldosterone to 9 mothers at the time of elective cesarean section.

This study showed that there was a transplacental passage of aldosterone. The fetal plasma levels of 1,2-³H-aldosterone, expressed as percentage of the maternal values, ranged from 40.0 to 79.2%. The levels of non-labeled hormone, determined by a double isotope dilution technique, were consistently higher in the fetus than in the mother (mean $\pm$ SD = 17.2 ± 9.5 μ g/100 ml and 3.7 ± 1.4 μ g/100 ml, respectively). Since the specific activities of aldosterone were lower in the fetus than in the mother (6.5 to 23.4%), and if one assumes that equilibrium between maternal and fetal compartments was reached after more than 2 h of constant infusion, it can be concluded that the fetus secretes aldosterone.

The metabolic clearance rate of aldosterone was not modified by pregnancy.

The steroid blood production of the mothers was about twice the non-pregnant values. The relatively small increments might be related to the fact that our subjects were supine for at least 10 h at the time of the study.

- 81 *Effects of Castration and 5-methoxy-N-acetyltryptamine (Melatonin) Upon Luteinizing (LH) and Follicle Stimulating (FSH) Hormones in 21-day Male Rats.* ALLEN W. ROOT and R. DAVID RUSS, Temple Univ. Sch. of Med., and Albert Einstein Med. Center, Philadelphia, Pa.

Male rats, maintained under controlled environmental conditions with 14 h of light daily, were orchietomized or sham-operated on the 21st day and sacrificed on the 42nd day of life. Melatonin (200 μ g) or diluent (2% ethanol) was administered i.p. daily from the 21st through the 41st days of life to groups of intact and castrated animals. Pituitary and serum LH and FSH were measured by double antibody radioimmunoassays. In diluent treated-orchietomized rats the pituitary weight, pituitary LH content and concentration and serum LH and FSH levels were significantly ($p < 0.01$) higher and the pituitary FSH concentration was significantly (< 0.01) lower than in diluent treated intact animals. The administration of melatonin to intact animals was associated with significantly ($p < 0.05$) decreased pituitary LH content and testicular weight, but was without effect upon pituitary FSH content or upon serum LH and FSH concentrations. The administration of melatonin to orchietomized animals was without apparent effect. It is concluded that under the conditions of the present experiment; (1) there is increased secretion of LH and FSH following castration of the juvenile male rat; (2) melatonin may suppress LH synthesis in intact animals; (3) melatonin is unable to suppress LH secretion in castrated 21 day male rats; (4) melatonin does not effect FSH secretion in either intact or orchietomized juvenile rats.

- 82 *Erythrocyte Na Flux in Cushing's Disease.* G. GALL, J. MELBY and R. KLEIN, Boston Univ. Sch. of Med.

This study was designed to establish whether cortisol which increases renal Na retention and K excretion also has the same effect as aldosterone on Na transport across other cell membranes. At last years meetings we reported increased erythrocyte Na flux rates in patients with primary aldosteronism. Since then we demonstrated that these patients have increased Na+K ATPase activity and that aldosterone increases active Na transport *in vitro*. Erythrocyte ghost Na flux, intracellular H₂O, Na, and K, and Na+K dependent ATPase were measured in control subjects and patients with primary hyperaldosteronism and Cushing's disease. Mean $\pm$ SEM are given in the table.

	Active trans	Passive leak	ATPase Na+K Dep.
Control	0.41 ± 0.02	0.21 ± 0.01	0.054 ± 0.004
Aldost	$0.80 \pm 0.15^*$	0.23 ± 0.02	$0.093 \pm 0.008^*$
Cushings	$1.46 \pm 0.20^*$	0.24 ± 0.01	0.126^*

	H ₂ O _i	Na _i	K _i
	Kg RBC		
Control	664 ± 2.47	8.9 ± 0.30	97.2 ± 0.92
Aldost	659 ± 6.90	10.5 ± 0.74	96.5 ± 5.1
Cushings	665	6.5	99.0

* Indicates difference from control was $p < 0.01$.

When 10^{-6} M aldosterone and 10^{-7} M cortisol were added *in vitro* to normal erythrocyte ghosts Na efflux rates increased by 37% and 76%, without change in the passive leak. Thus aldosterone and cortisol had similar effects on Na flux and Na+K dependent ATPase activity, at secretory rates approximately 10^3 greater for cortisol than for aldosterone.

- 83 *The Development and Characterization of Diabetes Mellitus in Cystic Fibrosis.* DOUGLAS S. HOLSCLOW, THEODORE AVRUSKIN, STEWART J. SOELDNER and HARRY SHWACHMAN, Harvard Med. Sch., Children's Hosp. Med. Center, Dept. of Ped. and Med., Boston, Mass.

The association of cystic fibrosis with chemical glucose intolerance and overt diabetes mellitus is becoming increasingly more common. It is not yet clear whether this results from genetic intertwining or pancreatic islet cell destruction or both. 200 children with cystic fibrosis over 7 years of age were screened for glucose intolerance. Factors as sex, age, severity of cystic fibrosis and family history of diabetes mellitus were analyzed. 48 of the 200 were classified as glucose intolerant (1-h blood sugar over 175 mg%). 3-h oral glucose tolerance tests were performed on these 48. Significant impairment of glucose tolerance was demonstrated in 85% (values greater than 97th percentile of normal established by PICKENS *et al.*). No relation was established as to sex, age or ideal body weight. Two and one half years later, these 48 were re-studied. Six had developed overt insulin requiring diabetes mellitus. These were evaluated by blood glucose measurements and serum immunoreactive insulin and growth hormone assays following oral and intravenous glucose, intravenous tolbutamide and intramuscular glucagon tolerance tests. Findings compatible with a severe insulin deficient state were obtained.

- 84 *A Role for Cyclic AMP in the Alpha Adrenergic Inhibition of Insulin Release by Hypoxia.* DAVID BAUM and DANIEL PORTE, Jr., Univ. of Wash. Sch. of Med., Seattle, Wash.

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 $282 \mu\text{g}/24 \text{ h}$ (normal: 91 ± 30.4). In 4 out of 5 patients on the 240 mEq sodium regimen, the mean ASR was $205 \mu\text{g}/24 \text{ h}$ (normal: 35.9 ± 16.1); the 5th patient suppressed moderately to ASR $62 \mu\text{g}/24 \text{ h}$. On the 9 mEq sodium regimen, all 5 patients were able to increase normally to ASR $702 \mu\text{g}/24 \text{ h}$ (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.

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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 GH, 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. MADDIAH, IRAJ REZVANI,