● **401** THYROID FUNCTION IN CHILDREN TREATED FOR HODGKINS DISEASE (HD). Robert B. Devney, Charles A. Sklar, Tae W. Kim, Mark E. Nesbit, Norma K.C. Ramsay. Univ. of MN Hosp., Dept. of Pediatrics and Ther. Rad., Minneapolis, MN

Thyroid function in 29 children with HD was followed a minimum of 24 months following diagnosis. Age of the patients (pts.) ranged from 4-16 yrs. (median=13 yrs.). 26/29 pts. had lymphangiography. 5/29 received only combination chemotherapy. 24/29 received 2800 to 5000 rads of radiation to the mantle, mediastinum or neck. 10/24 had combination chemotherapy subsequent to irradiation. T_4 RIA, TSH, T_3 uptake were measured at regular intervals. 0/5 pts. treated with only chemotherapy demonstrated any abnormal thyroid function. 14/24 pts. receiving radiation subsequently had elevated TSH (TSH>6.0 uU/ml) and low T_4 index (T_4 index <5.0). 8/24 had normal T_4 index but elevated TSH (range 8.8 to 22, median=14 uU/ml). 2/24 had normal TSH and T_4 index. 11/14 children with abnormal TSH and T_4 index were treated with thyroid replacement. 3/14 with abnormal T_4 index and TSH were not treated; two returned to normal 49 and 55 mo. after radiation. Of the 8 pts. with normal T_4 index but abnormal TSH 1 was treated with thyroid replacement and 7/8 were not treated. TSH returned to normal in 3 untreated pts. 32 to 88 mos. after radiation. One pt. was clinically hyperthyroid with elevated T_4 (23.6 mcg/dl) 6 mo. after radiation but eventually developed severe hypothyroidism (T_4=0.3 mcg/dl and TSH=202 uU/ml). 92% of children in our series developed evidence of thyroid dysfunction following radiation therapy for HD. All children with HD treated in such a manner should have thyroid function monitored closely.

402 GROWTH HORMONE EFFECTS ON ERYTHROCYTE INSULIN BINDING M. Joycelyn Elders, Victoria Herzberg, Donald E. Hill, J. Mark Boughter, Linda Harris, Heinrich K. Schedewie, Univ. Arkansas for Medical Sciences, Dept. of Pediatrics, Little Rock, Arkansas.

Growth hormone (GH) deficiency is associated with increased body fat, increased insulin sensitivity, and relative insulinopenia, suggesting possible interaction of GH and insulin receptor binding (IRB). We have measured erythrocyte IRB in 15 growth hormone deficient (GHD) children, ages 2-13 years, before treatment, after short-term high-dose GH (2 mg bid x 7 days), and long-term maintenance GH therapy (2 mg tiw x 2-12 mos). IRB was measured after fasting (16 hrs) and feeding (4 hrs). Fasting IRB in GHD patients, control children, and adults were 8.2±2.4, 7.4±2.4, and 8.2±2.3%, respectively. Corresponding concentrations of serum glucose were 78, 88, 82 mg/dl, those of insulin 12.2±3.4, 17.3±3.4, 11.2±2.8 uU/ml. There was no significant change in IRB in GHD with feeding vs fasting or short-term high-dose (7.3±2.9%) or long-term maintenance GH therapy (7.0±3.1%). GH increased (<2 ng/dl to 22±4.3 ng/dl) and somatomedin (0.36±.20 to 1.3±.35 U/ml). An inverse correlation was noted between IRB, fasting insulin concentrations, and body weight:height ratios. Patients with high fasting insulin (>20 uU/ml) and low height:weight ratios had very low IRB (3.1±1.2%). IRB after GH treatment increased in patients in whom therapy was associated with an increase in body weight:height ratios. These data suggest IRB may be related to body fat stores rather than circulating GH concentration or somatomedin activity.

403 CEREBRAL RNA AND PROTEIN SYNTHESIS IN NEONATAL SHEEP BRAIN: EFFECTS OF FETAL THYROIDECTOMY. Eric J. Essman, Jahangir Ayromlooi, Walter B. Essman, Denise Desiderio, Queens College of the C.U.N.Y., Flushing, N.Y. and Dept of Obstetrics & Gynecology, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York.

Cerebral structural and metabolic changes have been associated with reduced fetal and perinatal thyroid function in several species. In the present study several indices of neuronal function were assessed in lambs who were thyroidectomized at 64-67 days of gestational age. RNA synthesis measured by the rate of C^{14} orotic acid incorporation into nuclear RNA from six samples each of several brain regions did not differ for the cerebral cortex of hypothyroid (T_4=4.1 ± 1.2 µg/ml TSH=37.5 ± 10.1 ng/ml) as compared with euthyroid (T_4=9.2 ± 1.4; TSH=3.1 ± 1.2) lambs; mitochrondrial RNA synthesis was significantly reduced in the thalamus and hypothalamus (12%; p <.02) and in the cerebellar cortex (18%; p <.02) of hypothyroid animals. Protein synthesis, measured by incorporation of C^{14} leucine into synaptosomal protein, was significantly reduced in the hypothyroid lambs; in presynaptic nerve endings from the cerebral cortex (32%; p<.01), thalamus and hypothalamus (17%, p<.02) and cerebellar cortex (53%; p<.01). The cellular and synaptic changes attending perinatal hypothyroidism are reflected in regional changes in the synthesis of macromolecules relevant to effective cerebral functions.

404 ADRENERGIC AND DOPAMINERGIC RECEPTORS IN GLOMERULI(G) AND CORTICAL TUBULES(T). Robin E Felder, Juan C Pelayo, Melvin Blecher, Philip L Calcagno, Gilbert M Eisner & Pedro A Jose. Depts of Peds, Biochem, Physiol & Biophys. Georgetown University Medical Center, Washington, D.C.

Alpha adrenoceptors(AAC), beta adrenoceptors(BAC) and dopamine receptors(DR) were characterized in isolated rat G & T. Specific binding(SB) was the difference between binding of the ligand alone and in the presence of an excess (100 µM) of a specific competitor. The pairs used were ^{3}H-WB4101 and ℓ-norepinephrine (AAC), ^{3}H-dihydroalprenolol and ℓ-propranolol(BAC) and ^{3}H-haloperidol and ℓ-flupenthixol(DR). SB was rapid, reversible, linear to protein concentration and stereospecific. The potency of agonists and antagonists in competition studies was consistent for the specific receptor being studied. Apparent dissociation constant (K_d) and receptor occupancy (R_o) were calculated from Scatchard plots. The results (mean±SEM) are tabulated:

Tissue		AAC (n=6)	BAC (n=9)	DR (n=6)
G	K_d+	1.86±0.60	186±23.65	6.98±1.51*
	R_o++	0.23±0.09	2.99±0.42*	0.42±0.10*
T	K_d	1.18±0.18	179±19.24	30.70±7.29
	R_o	0.23±0.07	1.26±0.12	1.20±0.49

* p< 0.05 G vs T + nM ++ pmol/mg protein

For AAC, R_o and K_d were similar in G and T. For BAR, R_o was higher in G than in T but K_{ds} were similar. For DR, R_o & K_d were higher in G than in T. These studies give the first evidence for specific DR in rat kidney. The presence of specific catecholamine receptors in G may explain the ability of adrenergic and dopaminergic agents to influence glomerular ultrafiltration.

405 SCREENING FOR DIABETES MELLITUS IN CHILDREN WITH IMPAIRED GLUCOSE TOLERANCE. Pavel Fort, Fima Lifshitz, Robert Brody.Cornell University Medical College, and North Shore University Hospital, Dept. of Peds,Manhasset, N.Y.

The estimation of the validity of the maximum insulin stimulation test (MIST) and oral glucose tolerance test(OGTT) as predictive screening procedures for the development of overt diabetes mellitus(DM) was studied.Thirty children with various degrees of asymptomatic impaired glucose tolerance(IGT)were administered MIST(p.o.glucose;i.v.glucagon and tolbutamide)and OGTT on 2 consecutive days following an overnight fast.Insulin response during both tests was validated by the development of DM during a period of up to 5½ yrs.MIST appeared to be a better prognostic indicator of the chance to develop DM:3 non-obese subjects with poor MIST insulin response(glucose/insulin ratio>4)developed DM. However,one child who was on Orinase at the time of studies,had a good MIST insulin release and developed DM.All other patients had a good MIST insulin response and did not progress to DM.The predictive value for development of DM with a poor MIST insulin response was 75%.The predictive value for non-development of DM with a good MIST insulin response was 96.2%.In contrast,OGTT elicited poor insulin responses in 9 of 30 children;only 3 of them progressed to DM.The predictive value for development of DM with a poor OGTT insulin response at 1 hr was 33.3% and the predictive value for non-development of DM with a good OGTT insulin release was 100%.Thus, in a high risk population of children with IGT the ability to release insulin during MIST may be a better prognostic indicator of the chance to develop DM,whereas OGTT may be more useful in assessing the decreased risk of DM.

● **406** ACTH INSENSITIVITY: A NEW RECEPTOR DEFECT DETECTED BY THEOPHYLLINE STIMULATION. Mitchell E. Geffner, Barbara M. Lippe, Solomon A. Kaplan. UCLA School of Medicine, UCLA Hospital and Clinics, Department of Pediatrics, Los Angeles.

A 2 y/o male was evaluated for hypoglycemia and hyperpigmentation. Studies confirming the diagnosis of ACTH insensitivity were as follows: {cortisol=C, aldosterone (ng/dl)=A, renin (ng/ml)=R, ACTH (pg/ml)=ACTH}: (1) Cortrosyn stimulation: ACTH =2000; C undetectable at 0' and 30'. (2) Upright posture + furosemide: ACTH=2000; A=4.0 at 0', 48.2 at 60'; R=60 at 0', 195 at 60'. (3) Cortrosyn stimulation + high-dose dexamethasone + supine position: ACTH=130; C undetectable at 0' and 30'; A=9.0 at 0', 23.7 at 30'; R=48 at 0', 59 at 30'. Thus ACTH failed to induce glucocorticoid production by the zona fasciculata and reticularis (ZFZR) whereas mineralocorticoid or zona glomerulosa (ZG) response to physiologic stimuli of upright posture and salt-water depletion was preserved. ZG responsiveness to ACTH was also clearly shown for the first time. In an attempt to demonstrate the secretory potential of ZFZR, bypassing the initial interaction of ACTH with the cell, we administered IV theophylline, a cAMP phosphodiesterase inhibitor. After a 120' infusion C rose from undetectable to 7.5 µg/dl.

The defect in this form of ACTH insensitivity appears to be failure to generate intracellular cAMP either because of lack of ACTH receptor binding or impaired coupling of the ACTH-receptor complex with adenylate cyclase. When cAMP levels are increased by a mechanism that circumvents the receptor-adenylate cyclase complex, C production is stimulated.