

can also be found between primary and metastatic tumor; an alteration possibly due to treatment.

- 76 *Apparent Saturation of Diphenylhydantoin Metabolism in Children.* LORNE K. GARRETTSON and OK KYUNG KIM, Dept. of Ped., State Univ. of N.Y. at Buffalo, Buffalo, NY (introduced by W.J. Rahill).

Many patients show an unexpectedly great increase in serum concentration of diphenylhydantoin (DPH) following moderate increases of dose. Published studies of DPH serum levels [LOESER, *Neurol.* 11: 424, 1961 and REMMER *et al.*, *D.M.W.* 94: 1265, 1969] show patterns of increase and decline which are not compatible with a metabolic rate that is a sum of first order processes.

In two girls, ages 10 and 11, who showed signs of DPH toxicity on oral dose of 10.3 and 5.5 mg/kg/d, serum and urine DPH concentration and urinary concentration of total hydroxylated metabolite of DPH (HPPH) were measured using published methods. In the first case, total daily HPPH excretion was 119.5, 195.6, 133.4 and 198.4 mg on days 1 through 4 after cessation of therapy. On the first 3 days there were small losses due to incontinence. During the same period, serum DPH declined from 43.8 to 11.8 mg/l forming an apparent straight line on linear coordinates. Total daily urine DPH fell from 7.4 to 4.9 mg. In the second case, total HPPH values on days one through 5 after therapy ceased were 115.2, 131.3, 143, 111.9 and 73 mg with significant losses only on day 1. Serum declined from 47.6 to 25.2 mg/l. Total daily excretion of DPH varied with urinary output. U/P ratio remained constant. Nearly constant metabolite production at the time of declining high serum levels of DPH in both, and an apparent zero order serum decay in one case, suggests saturation of DPH metabolism. Above the saturating dose, serum levels would rise excessively following any increment in dose. (NIH 5-M01-RR-77 and UHF of WNY CL-6-CH-69.)

- 77 *Experimental Congenital Lipoid Adrenal Hyperplasia: Prevention of Defects Produced by Aminoglutethimide.* ALLEN S. GOLDMAN, Children's Hosp. of Philadelphia, Philadelphia, Pa.

Aminoglutethimide, a selective inhibitor of cholesterol desmolase, produces in rats the fetal adrenal and testicular defects and hypospadias in male fetuses characteristic of the human disease postulated to be due to a genetic defect in this enzyme, but unlike the disease, virilizes female fetuses. The effects of testosterone (1 mg/kg) and corticosterone (10 mg/kg) administered to pregnant rats treated with aminoglutethimide (100 mg/kg) from days 13 to 20 were studied. In the mothers, testosterone did not significantly affect the marked adrenal enlargement or increase of adrenal size and cholesterol content, but corticosterone reduced the increase in adrenal size and cholesterol content produced by this drug. Testosterone prevented the aminoglutethimide-induced production of hypospadias and the increase of testicular cholesterol content. Corticosterone reduced fetal adrenal enlargement, increase in fetal adrenal cholesterol content, and the increase of the anourethral distance in female fetuses produced by aminoglutethimide. These experiments provide evidence that the production of hypospadias by this drug is due to inhibition of fetal testicular cholesterol desmolase, and that the production of the paradoxical virilization of females by aminoglutethimide is due to androgens of aerenal origin.

- 78 *The Metabolism of Androgens by Human Fibroblasts.* THOMAS MOSHANG, JR., ALFRED M. BONGIOVANNI and WALTER R. EBERLEIN, The Univ. of Pennsylvania Sch. of Med., The Children's Hosp. of Philadelphia, Pa.

In vitro studies have demonstrated that testosterone (T) is converted to dihydrotestosterone (DHT) by skin and male accessory organs, and it has been postulated that DHT may be the intracellular biologic androgen of the target organ. In order to study androgen metabolism at the cellular level, fibroblasts cultured from human skin were incubated with radioisotopically labeled steroids in a NADH generating system. Both intact cells and subcellular fractions were studied. The metabolites were separated by paper chromatography and identified by reverse isotopic dilution. DHT was found to be a major metabolite. Etiocholanolone was not found to be a metabolite, indicating no 5 β reduction of ring A. Thus, the fibroblasts metabolized T and androstenedione (Δ 4) in a manner similar to skin and male accessory organs. Preliminary data indicate that fibroblasts cultured from males and females formed comparable amounts of DHT in the same incubation time. However, there appeared to be a more rapid metabolism of T by female fibroblasts through the 17-oxo pathway to Δ 4 and androsterone. The cytoplasmic fraction obtained after homogenization of fibroblasts and centrifugation at 800 g metabolized T to DHT, Δ 4, androstanediol and androsterone. Fibroblasts offer a model for the study of cellular metabolism of androgens and will be useful in elucidating the causes of end organ resistance to androgens.

- 79 *Pseudoaldosteronism (Liddle's Syndrome): Evidence for Increased Cell Membrane Permeability to Na⁺.* HAROLD J. HELBOCK and JOHN W. REYNOLDS, Univ. of Minnesota, Dept. of Ped., Minneapolis, Minn.

A 10-month boy was found to have pseudoaldosteronism (Ps. Ald.) characterized by hypertension (178/116), alkalosis (HCO₃⁻ 35 mEq/l, pH-7.50), hypokalemia (3.0 mEq/l) and very low aldosterone secretion rates (ARS) (0.9-5.8 μ g/d). The hypertension and hypokalemic alkalosis were worsened by salt-loading and unchanged by treatment with spironolactone and dexamethasone. Treatment with triamterene, plus severe Na⁺ restriction (<2 mEq/d) for 12 days, led to normal b.p., and serum electrolytes, and an elevation of the ASR (60 μ g/d). Long-term therapy has been successful with triamterene, hydrochlorothiazide and moderate salt restriction. Because triamterene is a specific therapy for Ps. Ald. and because it reduces epithelial surface Na⁺ permeability of isolated frog skin, an increased permeability to Na⁺ of the luminal membrane of distal renal tubular cells is postulated in Ps. Ald. On no therapy, the patient's RBC Na⁺ uptake was increased (2.6 μ Eq/c.c. cells/h) compared to controls (1.9 μ Eq/c.c. cells/h, p < 0.01), and RBC [Na⁺] was 15.7 mEq/l (controls - 10.1 \pm 1 mEq/l, p < 0.01). After 2 weeks of severe Na⁺ restriction and triamterene therapy, RBC Na⁺ uptake was 2.35 μ Eq/c.c. cells/h (significant decrease, p < 0.01) and RBC [Na⁺] was 11.9 mEq/l. Thus, RBC's show the increased Na⁺ permeability and increased [Na⁺] postulated for the distal tubular cells, in which the increased [Na⁺] would stimulate the Na⁺-K⁺ exchange pump leading to Na⁺ retention and K⁺ excretion.