4A N.E. HYPOTHYROIDISM COLLABORATIVE (read by R. Z. KLEIN, Dartmouth Med. Sch. Hanover, N.H.) Neonatal Thyroid Screening: Effects on IQ

63 infants with hypothyroidism diagnosed on neonatal screening and treated at age 25±15 days before clinical manifestations had Stanford-Binet IQ measurements at 3 or 4 years of age. 21 had ectopic radioactive uptake, 12 eutopic (with increased uptake in 6) and 17 had no uptake. The mean IQ at 3 or 4 years for 18 normal siblings and 39 euthyroid children who had low T4 but normal TSH concentrations on screening was 106±15. That of the 63 infants was 106±16 with normal distribution. The IQs of an additional 4 infants with sufficient manifestations to be diagnosed clinically on the day of birth were 110, 50, 64, and 76. The last had an euthyroid twin with an 80 IQ. The only factor that influenced the IQ scores of the 63 infants treated with thyroxine before clinical diagnostic manifestations was inadequate treatment in the first year of life. This was defined as a decrease in T4 to less than 8mcg/dl with simultaneous elevation of TSH on at least two occasions. The normal mean and distribution of IQs in the 63 infants demonstrate that mental retardation is a result of thyroid deficiency and not a concomitant and that whatever protects the child from developing clinical signs of hypothyroidism in utero also protects against mental retardation.

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Processing of pro-opiocortin in Cushing tumors.

Recent work in several laboratories has proven that ACTH, LPH-endorphin, and another peptide of 103 amino acids (the N-terminal fragment) all derive from a single polypeptide, pro-opiocortin. Recently we showed that the pro-opiocortin produced by a pituitary tumor from a patient with Nelson syndrome was indistinguishable from the pro-opiocortin produced by an ectopic ACTH-producing tumor, suggesting both eutopic and ectopic ACTH arise from the same gene (Proc. Natl. Acad. Sci. 77: 5211, 1980). We have now analyzed tissue from a tumor producing Cushing disease. Two-dimensional (2-D) gel electrophoresis of proteins synthesized and labeled in vitro with [^{35}S] methionine and [^{3}H] glucosamine indicates that pro-opiocortin is processed by the same scheme in Cushing tumors as in Nelson tumors and mouse AtT-20 cells. The 35 kilodalton pro-opiocortin is first glycosylated, then the βLPH moiety is cleaved off, followed by cleavage of the ACTH moiety, leaving the glycosylated N-terminal fragment. No further cleavage of the N-terminal fragment was detected. Electrophoresis of tryptic peptides of pro-opiocortin labeled with [^{35}S] methionine and [^{3}H] glucosamine confirms the conclusion from the 2-D gels that the single glycosylation site of human pro-opiocortin lies in the N-terminal fragment.

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Diagnostic value and regulation of plasma arginine vasopressin (AVP) in childhood.

AVP, measured by radioimmunoassay, was studied in relation to plasma and urine osmolality (Posm and Uosm) in 90 controls (0-15 yrs), in 19 polyuric children, and in 48 patients with various medical problems. In controls AVP was significantly elevated in the first week of life (14.6± 6.5 pg/ml,M±SD), while AVP did not change with age in older children (3.1±2.0 pg/ml). In adults slightly lower AVP levels were found (2.1±1.5 pg/ml). After 14-18 hrs of water deprivation in clinical trials serving as controls AVP increased (5.3±2.7 pg/ml), but no correlation between Posm and AVP was observed. In complete or partial central diabetes insipidus (n:7) AVP was undetectable or an inadequate rise after dehydration was found. AVP was highly elevated (>10 pg/ml) and Uosm was low in renal diabetes insipidus (n:2) and in tubular disorders (n:10). Extrarenal fluid loss, e.g. in gastroenteritis (n:7) and burns (n:4), resulted in an increase of AVP and Uosm. In cardiovascular shock, sepsis, and severe stress (n:18) AVP was raised although no disturbance of water balance was apparent. Conclusions: 1) Measurement of AVP in combination with Posm and Uosm is of diagnostic value in the differentiation of polyuric states. 2) Nonosmotic factors play an important role in the regulation of AVP in childhood.

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Involvement of Nerve Growth Factor in Neuroendocrine Regulation.

Nerve Growth Factor (NGF), a poly-peptide which is essential for development and maintenance of peripheral sympathetic and sensory neurons, has been investigated for its effects on the hypothalamo-pituitary adrenocortical axis (HPA). Intravenous injection of NGF in rats is followed by a prolonged elevation of plasma-ACTH, beta-lipotropin, beta-endorphin and corticosterone. In contrast to the acute intensive drinking response, this endocrine effect is independent from the renin contaminant of the standard 2.5 S NGF-preparation. This is supported by the fact, that intraventricular captopril (a potent inhibitor of the angiotensin converting enzyme) abolished the drinking response, but did not block the stimulation of the HPA-axis. In addition a renin-free NGF, prepared by isoelectric focussing, stimulated ACTH-release, but failed to induce thirst.

In vitro incubation of NGF with dispersed anterior pituitary cells did not result in an enhanced ACTH-secretion, suggesting that NGF acts either at the hypothalamic level or has a specific peripheral action. However, it is still uncertain, whether the effect of NGF on the HPA-axis is direct or indirect.

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Prepubertal Children Secrete LH in a Pulsatile Manner.

Pulsatile secretion of LH has not been demonstrated previously in children with a bone age (BA) of <9 yrs. To determine the gonadotropin secretory pattern during childhood, 16 prepubertal children were studied in the CRC. Ten children (Group A) had BA's 4.5-9.5 yrs. ($\bar{x}$=7.5y) and six children (Group B) had BA's of 10-11.5y ($\bar{x}$=10.3y). Six patients were endocrinologically normal, 9 had isolated growth hormone deficiency and 1 had gonadal dysgenesis. Blood samples were obtained every 20 min. between 1000-1800h and 2200-0600h. LH and FSH were measured by RIA ($\bar{x}$ sensitivities: LH 0.65; FSH 1.1 mIU/ml). Mean nocturnal LH and FSH values were significantly greater than daytime means in 6/10 & 3/10 Group A children, respectively; in Group B, 4/6 & 1/6 children had augmented $\bar{x}$ LH and FSH values during the night. Five Group A (youngest BA=4.5y) and 3 Group B children had significant LH pulses during sleep; four Group A and 2 Group B children had LH pulses during the day. In children with discernible LH pulses, frequency was similar between groups at night (Group A 1.7 pulses/4 hr; Group B 1.8 pulses/4 hr), but apparently greater in Group B during the day (A 1.2 pulses/4h; B 2.3 pulses/4h). Nocturnal pulse amplitude was also greater in Group B than in A (A 1.9±0.2; B 2.5±0.3 mIU/ml). These data demonstrate that pulsatile secretion of LH occurs in some children well before a BA of 9y. Furthermore, LH pulse frequency in prepubertal children is similar to that previously reported by us in early pubertal children (Ped. Res., 15:157, 1981). Grants HD12306, HD13111, and 5M01RR42

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Persistant induction of catechol-estrogen forming enzyme in brain and in liver, by prenatally administered phenobarbital

Catechol estrogens (CE) are formed by hydroxylation of estrogens by a P540 dependent microsomal enzyme which is most active in liver and brain. In liver this is a major degradative pathway and the half-life of the CE formed is extremely short. In the brain however CE may have specific neuroendocrine effects since they have been reported to react with specific CE receptors in pituitary and brain and to compete for dopamine receptors in pituitary. They also may inhibit both synthesis and metabolism of catecholamine neurotransmitters. In the immature male rat and in the female, but not in the mature male, the liver but not the brain enzyme is inducible by phenobarbital (PB). We injected pregnant female rats with PB on days 18 and 19 of gestation and measured estrogen 2-hydroxylase activity in the brain and liver of offspring. Liver enzyme showed a diphasic response to this prenatal treatment with a 80% decrease in enzyme specific activity on days 1 and 2, and a 100% increase in enzyme activity persisting from days 5-21. Brain enzyme levels were significantly increased (↑50%) by this treatment from days 7-21. This prolonged induction of a liver microsomal enzyme differs from that seen in young animals where enzyme activity returns to normal by one week after treatment with PB. This is also the first report of induction of a brain microsomal cytochrome P450 with PB. Since PB is often used during pregnancy for seizure disorders and for pre-eclampsia, this may be of clinical relevance.