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NEUROFIBROMATOSIS AND CHILDHOOD LEUKEMIA.

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To clarify the suggested link between childhood leukemia and neurofibromatosis (NF), we ascertained 10 previously unreported cases at 6 medical centers including our own, almost doubling the 15 adequately documented cases in the literature. Among these 25, acute lymphoblastic leukemia (ALL) developed in 9 and various forms of myelogenous leukemia (non-ALL) in 16, including 8 with acute myelomonocytic and 4 with juvenile chronic myelogenous leukemia. The ALL:non-ALL ratio of 9:16 is quite different from the predominance of ALL in U.S. whites, 4:1; Down's syndrome, 7:3; and ataxia-telangiectasia, 7:1. By contrast, only non-ALL has been reported in Fanconi's anemia or Bloom's syndrome. Each of these 4 heritable disorders with high risk of leukemia has characteristic though different chromosomal abnormalities, which may be involved in leukemogenesis. In the 25 NF cases cytogenetic studies were rarely made, an opportunity that should not be missed in the future. Variations in the ALL:non-ALL ratio indicate that host factors apparently influence the form of leukemia that develops. To refine further the relation between NF and leukemia, the existing large collaborative oncology groups could provide a) fuller ascertainment of cases with details of physical findings and family histories, b) a denominator for estimating risk, c) cytochemical and immunological clarification of leukemic subtypes, and d) elucidation of possible variant cases excluded from this series (N=15); eg, "transient leukemia" (as in Down's syndrome) seen in 3 children with NF, and "xantholeukemia" seen in 4 others.

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ANDROGEN SECRETION BY A FEMINIZING GRANULOSA CELL TUMOR: Hans H. Bode, Inese Z. Beitins, Christopher Longcope, Dick Hoefnagel, Harvard, Univ. of Mass. and Dartmouth Med. Schools, Dept. of Ped., Mass. Gen. Hosp., Boston

The majority of granulosa cell tumors cause feminization, although in a few women virilization has occurred. MacDonald et al (Obstet. Gynecol. 47:649, 1976) have recently documented that a post-menopausal woman with an androstenedione (A) producing ovarian adenocarcinoma became estrogenized as a result of extraglandular conversion of A to estrogens.

A 4 year old girl with a small right sided granulosa cell tumor presented with rapidly progressing breast enlargement, vaginal bleeding, but without androgen dependent signs of precocity. Pre-operative plasma steroid determinations revealed: estradiol (E₂) 62 pg/ml, estrone (E₁) 12 pg/ml, A 0.1 ng/ml, testosterone (T) 0.02 ng/ml. Serum LH was 0.1 and rose to 1.2 MIU/ml (LER 907) after LHRH while FSH remained suppressed. ACTH stimulation caused no effect, but a single injection of human chorionic gonadotropin resulted in a 20-fold rise in T and A while E₁ and E₂ increments were only 2 to 4-fold. Very high androgen concentrations were also found in right ovarian venous samples (A 94, T 11, E₂ 2.55 and E₁ 0.55 ng/ml). After tumor removal, plasma steroid levels returned to prepubertal values, breast size declined and LHRH caused an exaggerated FSH but normal prepubertal LH response. It is concluded that the absence of virilization in this girl with an androgen secreting granulosa cell tumor resulted from extraglandular conversion of androgens to estrogens.

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MITIGATION OF CRETINISM BY BREAST FEEDING. Hans H. Bode, William J. Vanjonack, John D. Crawford. Harvard Medical School, Shriners Burns Inst., Massachusetts General Hospital, Dept. of Pediatrics, Boston.

An athyreotic infant presented with hypothyroidism at 12 months of age. History, detailed growth data and photographs documented absence of symptoms and maintenance of normal growth (>90%ile) until age 10 months when breast feeding was discontinued. Yet, his bone age was that of a newborn, thus supporting the congenital nature of athyreosis. These observations suggested that breast feeding attenuated hypothyroidism possibly by providing significant quantities of thyroid hormones in the milk. To test this hypothesis we measured T₄, T₃ and reverse T₃ (rT₃), in serial breast milk samples collected from five "La Leche League" volunteers between 96 days prior, to 128 days after delivery. RIA determinations of iodothyronines were preceded by alcohol extraction to correct for variations in protein and lipid content. During pregnancy breast milk T₄ averaged 1.3ug% and fell to 0.8ug% within 3 days postpartum. With delivery there was a highly significant increase in milk T₃ content from 145ng% to 283ng%, levels far exceeding serum T₃ concentration. This postpartum rise in breast milk T₃ was apparently not due to a shift in deiodination of T₄, since rT₃ levels were low and remained unchanged. (5.2-7.2ng%) The rise in milk T₃ postpartum preceded the fall in total protein, albumin and immunoglobulin and the rise in α₂-antitrypsin content. It is concluded that: a) T₃ is secreted selectively by the mammary gland, b) human breast milk contains sufficient thyroid hormone to mitigate congenital hypothyroidism.

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STRESS HORMONES IN DIABETIC KETOACIDOSIS. Erika

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The aim of this study was to define the role of "stress hormones" in the pathogenesis of acute diabetic ketoacidosis. Hourly plasma levels of glucose, growth hormone (GH), cortisol (C) and glucagon (G) and urinary norepinephrine (NE) and epinephrine (E) were measured for the first 24 hours in 20 children, ages 2-21 years who presented on 25 occasions with ketoacidosis of a few hours duration despite their usual insulin therapy.

In 23/25 studies, E excretion was >4 S.D. (in 7 studies >10 S.D.) above the normal mean during the first hour while NE was within or slightly above 2 S.D. of the normal mean in 21. Plasma C was above 25 µg/dl in 16/25 and often remained elevated for several hours. Ten patients with an initial C level >40 µg/dl excreted >1 µg/M² of E (normal <0.3) per hour. The mean admission GH was 13.7 ng/ml (range 1-39.6). It rose sharply after high or low dose insulin injections in 19/25. The mean peak for all patients was 34 ng/ml (range 6.7-160), independent of a fall of glucose. 7/20 cases had glucagon levels >200 pg/ml on admission, 3 of these >1000 pg/ml. No correlation was noted between initial G and any of the other hormones, including E.

The data suggest endogenous E production in response to stress is the trigger event in acute ketoacidosis in insulin-treated juvenile diabetics. High or inappropriate secretion of glucocorticoids, GH and glucagon also is present in many patients with this disorder.

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SICKLE CELL DWARFISM Salvador Castells, Narayanan

Muthukrishnan, Chhaya Chakrabarti, & Susanna Neumann. Dept. of Ped., SUNY, Downstate Med. Ctr., Bklyn., N.Y.

We use the term sickle cell dwarfism to describe a group of children with sickle cell disease suffering from severe growth and pubertal retardation. Three males and 3 females, ranging from 9 to 17 yr., with multiple sickle cell crisis, were found to have a height 5 to 3 SD from mean for black population, markedly retarded bone age, and lack of pubertal development. Pituitary and thyroid functions were evaluated by measuring serum concentrations of T₃, T₄, TSH, LH, FSH, hGH and prolactin (PRL) by immunoassay; adrenal functions by plasma cortisol, urinary 17KS and 17KGS concentrations and ACTH and metyrapone tests; gonadal functions by plasma testosterone and estradiol. hGH was stimulated by insulin induced hypoglycemia and PRL by chlorpromazine and compared to 16 and 9 controls respectively. In 5 children there was no increase in serum hGH after hypoglycemia; in all 6 patients basal serum PRL were lower than controls, but chlorpromazine stimulated serum PRL concentration. Synthetic thyrotropin-releasing factor administered to the only child with hypothyroidism produced a normal increase in serum TSH. All 6 patients had low 17KS and 17KGS; 2 had low basal cortisol levels at 8 a.m. and after hypoglycemia. ACTH produced normal increases in plasma cortisol levels in all 6 patients. Metyrapone failed to stimulate adrenal function in 1 child. Basal FSH and LH were no different from normals. These data suggest that sickle cell dwarfism may be the results of hGH deficiency, isolated or combined with other pituitary hormone deficiencies. Hypothalamic dysfunction may be present.

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EFFECT OF GROWTH HORMONE (GH) ON SOME ACTIVITIES OF LEUKOCYTES AND LYMPHOCYTES (LY) IN CHILDREN. Collipp,

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We have shown in laboratory animals that GH stimulates several mitochondrial processes like protein synthesis, bulk-protein turnover, levels of cytochromes and enzymes, and respiratory activity. We have presently studied respiratory activity (RA) in white cells (WC) and thymidine uptake in LY of children before and after GH therapy. RA (ngm of O₂/mg protein or µg DNA) was measured in WC, prepared by layering whole blood on metrizoate-dextran medium, with a Clark-Oxygen electrode in Krebs-Ringer solution containing glucose. There is significant correlation (r = 0.8) between percent increase in respiration due to GH therapy for 1 month and height gain after 4-8 months of therapy in 18 children. This correlation may have significance in the early prediction of growth-promoting effect during therapy.

LY, isolated by layering whole blood over Lymphoprep, showed an increase in WBC, LY count and rosette forming LY in 11-12 children but showed a decrease in 5-6 children. There is a significant decrease in thymidine uptake by unstimulated LY in all 12 children. Therefore, stimulation index (uptake with stimulation by phytohemagglutinin/uptake without stimulation) increased. These results suggest that GH therapy may reduce basal rate of DNA synthesis in LY.