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Somatomedin binding proteins in GH deficient children with normal somatomedin.

Somatomedin-C/insulin-like growth factor-I(SM) circulates in plasma bound to a large molecular weight (150K) GH dependent protein complex (SM-BP). There is also a smaller (38K) non-GH dependent protein which binds exogenous radiolabeled SM. Although SM is GH dependent, children with certain nutritional disturbances show a dissociation between GH and SM. SM-BP was studied in 3 children with normal SM (by RIA) and normal growth rate inspite of documented GH deficiency. All are hyperphagic and obese; 2 are status-post craniopharyngioma resection; the third has arrested hydrocephalus. Insulin responses to oral glucose were elevated but prolactin levels were not. [^{125}I] SM (20,000 cpm) was incubated (4°, 16 hrs) with 1 ml of plasma. The mixture was subjected to gel filtration (2.6 X 80 cm, Sephacryl-200, 0.1 M Tris, 5mM EDTA, pH 7.4). Endogenous SM eluted at Ve/Vo of 1.2-1.25 (≈150K). Some [^{125}I] SM also eluted in this region while the major portion eluted at Ve/Vo of 1.5 (≈40K). This pattern of endogenous and [^{125}I] SM was identical to that seen in normal adults and hyposomatotropic children on GH. These results indicate that 150K SM-BP is regulated in parallel with SM in those instances when SM and GH are discordant. Such closely coordinated regulation might be accomplished if SM and SM-BP were synthesized together.

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Role of Somatomedin-C (Sm-C) and Epidermal Growth Factor (EGF) in Fibroblast Growth

Addition of serum to quiescent, density arrested Balb/c 3T3 mouse fibroblasts (MF) results in renewed DNA synthesis after a lag of 12 hours. Similar responses to platelet poor plasma (PPP) occur only if the cells are first rendered "competent" by brief exposure to platelet derived growth factor (PDGF). When PDGF treated MF are incubated in hypopituitary PPP, they become arrested 6 hours prior to the G_1/S boundary; completion of transit through G_1 occurs only after the addition of SM-C ($1x10^{-9}$ M). A combination of EGF and Sm-C can fully replace normal PPP in permitting competent cells to progress through G_1. EGF ($1x10^{-9}$M) plus Sm-C ($1x10^{-10}$M) are required during the first 6 hours, whereas Sm-C alone ($1x10^{-9}$M) is sufficient for completion of G_1. PDGF treated human fibroblasts (HF) differ from MF by their ability to initiate DNA synthesis in response to hypopituitary PPP, although the rate of entry into S is slower than in normal PPP. This difference is attributable to the capability of HF (but not MF) to synthesize Sm-C. Sm-C production is increased additively in response to PDGF and hGH. Conclusions: 1) Sm-C is an obligate requirement for both MF and HF to progress through the G_1 phase of the cell cycle; 2) the apparent independence of HF from the Sm-C requirement can be attributed to their ability to synthesize this peptide, 3) preincubation with hGH normalizes the rate of entry of HF into S in the presence of hypopituitary PPP.

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Epidermal Growth Factor (EGF) in normal children, children with constitutional short stature, and children with growth hormone deficiency.

Urinary EGF was measured using a human placental membrane radioreceptor assay. This assay does not cross-react with insulin growth factor I (IGF I), somatomedin A, fibroblast, or nerve growth factors. Urinary excretion of EGF was measured in normal children (NL), in children with constitutional short stature (Con SS), untreated growth hormone deficient children (GH defic), and in growth hormone deficient children after growth hormone therapy (GH defic post Rx).

	EGF	
	(μg/24 hr±SEM)	(μg/M^2/24 hr±SEM)
NL (n=11)	32.8 ± 5.5	31.2 ± 5.0
Con SS (n=12)	29.6 ± 3.2	35.8 ± 4.1
GH defic (n=5)	13.3 ± 3.1	16.2 ± 3.2
GH defic post Rx (n=5)	32.0 ± 4.9	39.4 ± 6.0

EGF excretion did not differ in NL, GH defic post Rx, or Con SS children. However, it was significantly less in GH defic compared to GH defic post Rx ($p<.02$), NL ($p<.05$), and Con SS ($p<.02$) children. Our finding of diminished EGF excretion in untreated hGH deficiency and an EGF response to hGH therapy is the first demonstration of an alteration in EGF in association with a pathologic disorder in the human. We speculate that EGF may be implicated in hGH biologic activity.

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Fibroblasts from a patient with Leprechaunism are resistant to Epidermal Growth Factor (EGF) as well as Insulin.

Leprechaunism is characterized by severe intrauterine growth retardation and insulin resistance. We have reported (JCEM 48:495, 1979) that Leprechaun fibroblasts have diminished DNA synthesis in response to insulin or serum, despite apparently normal binding of ^{125}I-insulin and ^{125}I-somatomedin-C. The doubling time of Leprechaun fibroblasts is prolonged (96 vs 48 hrs.), suggesting an aberrant growth mechanism(s). To further characterize the defect in this syndrome, we compared the metabolic responses of Leprechaun and normal skin fibroblasts in culture. Stimulation of ^{3}H-glucose uptake was minimal with low insulin (1-10 ng/ml) relative to control cells, but was comparable at higher insulin concentrations (1-10 μg/ml). Insulin-stimulated ^{3}H-aminoisobutyric acid (^{3}H-AIB) uptake by Leprechaun cells was less than normal at all concentrations tested. Defective responses of Leprechaun cells were not limited to insulin, since EGF also had diminished effects on ^{3}H-AIB uptake and DNA synthesis. ^{125}I-EGF binding, however, was normal. Conclusions: 1) In addition to defective responses to insulin, fibroblasts from our patient are resistant to the effects of EGF. 2) Since receptors for these peptides are apparently normal, it is likely that these cells have a post-receptor defect. 3) We speculate that Leprechaun cells have an alteration in a metabolic pathway which is involved in the action of multiple growth factors.

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A pilot newborn screening for congenital adrenal hyperplasia(CAH)due to 21-hydroxylase deficiency at New York Hospital(NYH) and Alaska.

A pilot newborn screening program for CAH was conducted in Alaska using a 3mm disc filter paper elution technique of capillary whole blood for 17-hydroxyprogesterone (17-OHP) by RIA. In a control normal population the highest values of 17-OHP in 4569 consecutive births (ages 2-14 days) was 40 pg/disc and the range of values for 16 newborns with proven CAH was 57-980 pg/disc. Thus all Alaskan newborns with 17-OHP of 57 pg/disc or greater were referred for diagnostic workup and those with 17-OHP of 41-56 pg/disc were recalled for repeat specimen. In 11,177 neonates screened in a 19mo period (7802 Caucasians, 644 Yupik Eskimos, 2731 others) 15 had 17-OHP values greater than 57 pg/disc, of which 3 (including 2 Yupik Eskimos) were proven to have the salt-losing form of CAH. Of the remaining 12, 4 were not available for followup and 8 were distressed premature infants including 2 who died. Of the 21 whose 17-OHP values were 41-56 pg/disc, 14 were proven to be normal, and 7 could not be reached. Thus the neonatal Alaskan screening revealed an incidence of the salt-losing form of CAH of 1:7802 live births in Caucasians and 1:322 live births in Yupik Eskimos. The predicted carrier rate is 1:44 in the Caucasians and 1:9.5 in the Yupik Eskimo. The false positive and recall rates were 0.088% and 0.25%. This study demonstrates the feasibility of a newborn screening program for CAH and indicates the frequency of the salt-losing form of CAH may be greater than previously reported by case assessment methods.

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Pittfalls in the etiological diagnosis of congenital adrenal hyperplasias (CAH) in the neonatal period.

We have studied 9 males (0-34 d.) and 9 females (0-7 d.) affected with either 21-hydroxylase (21OH), 11-hydroxylase (11OH) and 3β-ol dehydrogenase (3β-ol) defects. Plasma levels of 8 steroids (specific RIAs) were studied longitudinally and before treatment. The first 2 days of life levels of 17OH-progesterone (OHP) were elevated (780-18900 ng/dl) in all cases but could not help to localize the enzymatic block : the lowest and highest values were seen in newborns with 21OH, whereas OHP levels ranging between 2000 and 5000 ng/dl were seen in the 3 blocks. A drastic increase in DHA levels (20-30 000 ng/dl), theoretically the marker of 3β-ol defect, was similarly seen in one case of 11-OH at 3 days, in two cases of 21-OH at 2 and 3 days and in the 3β-ol seen at 7 days of life. Supranormal levels and normal temporal pattern of DHAS (rapid postnatal decrease) were seen in all cases. Levels of androstenedione were also markedly elevated at birth in all cases and similar in 11-OH and some cases of 21-OH. Elevation in testosterone was variable and not sex related. In most cases early diagnosis was only ascertained by multiple steroid studies and dynamic studies. Longitudinal studies were also helpful, although the temporal pattern in Δ5 and Δ4 steroids were not parallel during the first week of life. All discrepancies were not found in infants studied later on life (case of most boys). It is suggested that the peculiar steroid pattern seen in the various enzymatic blocks during the first week of life is related to the different morphological and functional evolutions between the fetal and adult zones of the adrenal glands in the neonatal period : predominance in Δ5 production decreasing rapidly as does the fetal adrenal zone.