907 CEREBRAL METABOLIC EFFECTS OF NEONATAL HYPOGLYCEMIA AND ANOXIA.

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To ascertain cerebral metabolic responses to hypoglycemia with superimposed hypoxia, newborn rats were given regular insulin (30 u/kg s.c.). Animals were observed for up to 2 hrs with no ill effects, inspite of blood glucose concentrations of 0.75 mM/l. When exposed to 100% N_2 at 37°C, these animals survive only 1/10 as long as littermate controls with normal blood glucose levels (4.7 mM/l). Treatment of hypoglycemic rats with glucose (25 mM/kg s.c.) 30 min prior to N_2 exposure prevented the anoxic vulnerability. Glycolytic intermediates & high-energy phosphate reserves (mM/kg w.w.) in brains of control (C) hypoglycemic (H) & hypoglycemic-glucose treated (H-G) animals breathing air were:

	Glycogen	Glucose	Lactate	P-Cr	ATP	ADP	
C	4.77	1.88	0.87	2.70	2.65	0.29	*p<0.05 } vs. C
H	2.88+	0.16+	0.59*	2.11*	2.61	0.26	+p<0.001 } vs. C
H-G	2.91+	1.56	0.60*	2.63	2.54	0.28	

The cerebral metabolic rate (CMR) was not altered by hypoglycemia & averaged 2.32 mM~P/kg/min. Following 2.5 min of N_2 exposure, the cerebral energy stores ATP & P-Cr in hypoglycemic rats were lower by 24 & 51%, respectively, compared to normoglycemic animals subjected to the same degree of anoxia. Thus, reduced anoxic resistance of hypoglycemic neonates is not primarily a function of lower brain glycogen levels or altered CMR. Endogenous cerebral glucose stores combined with continued circulating glucose (cerebrovascular perfusion) appears critical for maintaining perinatal hypoxic survival.

908 LIPOPROTEIN FRACTIONS IN CHILDREN WITH LOW AND HIGH TOTAL SERUM CHOLESTEROL.

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The serum cholesterol (SC) determined by single measurement in 2,421 children aged 6-18 years did not differ among those aged 6-11, decreased with ages 12-15, and increased with ages 16-18. Cholesterol in low-density lipoprotein (LDL) paralleled the SC trend (Fig. 1). The increase of SC from lower-decile to higher-decile children was due mostly to increase of the LDL fraction (Fig. 2)--a fact important in study of SC determinants, whether environmental or genetic. In search for "major genes" affecting SC, associations of marker gene distributions with quantitative differences in LDL should be sought, because relationships with LDL may be stronger than relationships with SC or with other fractions. Also, levels of LDL and high-density lipoprotein may be factors in atherogenesis and should be studied further.

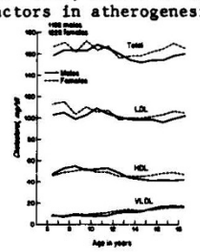

Fig. 1

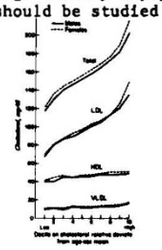

Fig. 2

909 SPECIFIC RADIOASSAY OF 24,25 DIHYDROXYVITAMIN D ($24,25(OH)_2D$) IN SERA OF NEWBORNS, CHILDREN AND ADOLESCENTS.

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To further evaluate vitamin D metabolism in children, serum concentrations of $24,25(OH)_2D$, a metabolite produced by the renal 25OHD-24 hydroxylase system, were measured by a competitive radioassay utilizing normal rat serum as binding protein, ^3H-25OHD as tracer and reference $24,25(OH)_2D_3$ as standard. Biosynthesized ^3H-$24,25(OH)_2D_3$ was used to monitor recoveries. The $24,25(OH)_2D$ and 25OHD from serum lipid extracts were isolated by chromatography on 24 X 0.5 cm columns of Sephadex LH20. Mean (±S.D.) serum $24,25(OH)_2D$ in children (age 2-17 yrs, N=20) was significantly ($p < .01$) higher (3.3±1.3 ng/ml) than in newborns (N=14, 1.87±0.6 ng/ml). Mean radioassayable serum 25OHD was also significantly ($p < .01$) higher (31.3±11 ng/ml) in children than in newborns (14.4±3.4 ng/ml). No significant difference in serum concentrations of $24,25(OH)_2D$ was found between term (N=7) and preterm (N=7) neonates (2.0±0.5 vs 1.7±0.7 ng/ml) nor between prepubertal (N=9) and pubertal (N=11) children (3.8±1.4 vs 2.9±1.1 ng/ml). A significant positive correlation ($r=0.87$, $p < .01$) was found between serum 25OHD and 24,25OHD concentrations in children. However, no such relationship was found among newborns. Conclusions: 1) Radioassay of $24,25(OH)_2D$ will provide further data concerning the specific metabolism of vitamin D in normal and abnormal subjects; 2) Synthesis of $24,25(OH)_2D$ in neonates is apparently independent of the levels of its precursor, 25OHD; 3) Utilization of column chromatography is essential for measurement of absolute levels of $24,25(OH)_2D$ and 25OHD.

910 GLYCOHEMOGLOBIN (HbA_{Ic}): A PROGNOSTICATOR OF BIRTH WEIGHT IN INFANTS OF DIABETIC MOTHERS.

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Hemoglobins A_{Ia-c} (fast Hb), minor variants of HbA, are elevated in diabetes mellitus. Recent studies indicate a relationship of fast Hb's, especially HbA_{Ic} (glycosylated form) to hyperglycemia. A_{Ic} is most manifest in aged erythrocytes. Since infant oversize has been attributed to maternal hyperglycemia and fetal hyperinsulinemia, the relationship of hemoglobin HbA_{Ic} was examined relative to birth weight (actual and relative to gestational age) and maternal glucose tolerance. Fast Hb's were measured by the Amberlite IRC cation exchange technique. Control women (6), gestational diabetics (K_t 1.13%/min) (8), and insulin dependent women (8) were studied in their 3rd trimester. When corrected for gestational age, birth wts. correlated ($p<0.001$) in a linear regression with both fast Hb ($r = 0.69$, $n = 18$) and HbA_{Ic} ($r = 0.67$, $n = 14$). Two women with advanced diabetic vascular disease had smaller infants relative to gestational age and were excluded because of possible placental insufficiency. K_t correlated in a significant manner ($p<0.05$) only with HbA_{Ic} for a linear regression ($r = 0.59$, $n = 15$). Third trimester glycohemoglobin determination in maternal diabetes is a good indicator of infant size relative to gestational age. Furthermore, it has potential as a screening test of gestational diabetes in the 3rd trimester and the immediate postpartum when maternal carbohydrate intolerance may have reverted to normal.

911 CROTONASE DEFICIENCY: DEMONSTRATION OF A DEFECT IN β-OXIDATION IN MAN.

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A patient who presented with severe acidosis (CO_2, 4 meq/L) without hypoglycemia was found to have 1 mM crotonic acid in his serum. During an elective 20 hr fast, β-OH butyrate and acetoacetate rose to 5.3 mM and 1.9 mM. Serum alanine and glucose fell to 137 μM and 57 mg/dl. Crotonic acid rose from undetectable levels to 160 μM at 20 hrs but continued to rise after the fast was terminated to 700 μM by 34 hrs. β-OH butyric acid is not converted to crotonic acid by the methods used. The elevation of crotonic acid appears highly specific as no crotonic acid could be demonstrated in other severely acidotic patients (diabetes, propionic acidemia, ketotic hypoglycemia).

Metabolic studies were carried out in isolated leukocytes. Total crotonase activity was >3 S.D. below normal (.125 vs .319±.051 OD_{280}/min/mg). Tiglyl CoA enoyl hydrase, β-OH butyryl CoA dehydrogenase, and oxidation of branched chain amino acids were normal. Lysine oxidation (which requires crotonase) was 36% of normal. Palmitate oxidation was <25% of age matched controls but only 10-25% reduced from adult controls. Butyrate oxidation was 40% of age matched controls but only slightly reduced from adult values. In fibroblasts butyrate oxidation was 41% of control values.

This child exhibits a partial defect in β-oxidation. These studies also suggest that the enoyl hydrases for branch chain amino acid metabolism may be distinct from crotonase.

912 IMMOBILIZATION HYPERCALCEMIA AFTER SINGLE LIMB FRACTURES IN CHILDREN & ADOLESCENTS.

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Immobilization hypercalcemia has been uncommonly documented in children. In 1975 we began a systematic surveillance of immobilized children by analyzing urinary calcium/creatinine ratios and concentrations of ionized calcium (Ca++) and phosphate in serum. 6 out of 10 children developed immobilization hypercalcemia after a single limb fracture of a weight bearing bone. Their ages ranged from 4 3/12 to 15 8/12 years. The Ca++ in serum ranged from 4.88mg/dl to 6.44mg/dl (normal range = 4.37mg/dl to 4.79mg/dl). Hypercalciuria, defined as a urinary Ca/creatinine ratio ≥ 0.40, was noted in all 6 patients. This represents an early warning of impending hypercalcemia. Urinary levels of hydroxyproline ranged from 170mg/24h to 225mg/24h (normal mean = 63.7mg/24h). Concentrations in urine of cyclic-AMP and serum levels of both parathyroid hormone and 25-hydroxyvitamin D were within normal range. 2 patients with Ca++ in serum ≥ 6.00mg/dl were treated with salmon calcitonin. The combination of salmon calcitonin therapy, and as rapid mobilization as possible, produced prompt resolution of the biochemical abnormalities.

These data indicate that: 1) Immobilization hypercalcemia commonly occurs in both children and adolescents; 2) Single limb fracture of a weight bearing bone is sufficient to produce it;and 3) Frequent measurements of 24h urine collections for calcium/creatinine ratios represents a reliable laboratory method for monitoring such patients.