1183 GLUTATHIONE IS DEFICIENT IN HEREDITARY TYROSINEMIA.

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Extensive metabolic and enzymatic studies in a patient with hereditary hepatorenal tyrosinemia demonstrated for the first time a deficiency of red cell and hepatic glutathione (GSH). Markedly decreased hepatic fumarylacetoacetate hydrolase activity was measured in this patient (1-16% of normal). The activity of enzymes not involved in tyrosine metabolism were also measured in liver tissue. Assay of mixed function oxidase activity demonstrated low levels of arylhydrocarbon hydroxylase and 7-ethoxycoumarindeethylase. This depression of mixed function oxidase activity may result in a decreased detoxification capacity of the liver. Delta-amino levulinic acid dehydratase (ALAD) activity was undetectable. Succinyl acetone (4,6 dioxoheptanoic acid), an abnormal metabolic product secondary to the fumaryl-acetoacetate hydrolase deficiency, was measurable in serum and urine. Succinyl acetone was demonstrated to inhibit ALAD in vitro, as did the urine, plasma and red cell lysates of the patient. The decreased GSH observed in this condition may play a role in the hepatic pathology and increased malignant potential in this disorder. Therefore, the decrease in GSH demonstrated in our patient suggests the possibility of a new mode of therapy.

● 1184 PERSISTANCE OF THE DEFECT IN RENAL BRUSH-BORDER MEMBRANE PHOSPHATE TRANSPORT IN 1α,25-$(OH)_2$ VITAMIN D_3 (1,25-$(OH)_2D_3$)-TREATED X-LINKED HYPOPHOSPHATEMIA.

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We studied the effect of 1,25$(OH)_2D_3$ on phosphate (Pi) homeostasis in the Hyp mouse, a homologue of X-linked hypophosphatemia in man. 1,25$(OH)_2D_3$ (83 pg/g·day, infused subcut. x 10 days) produced significant hypercalcemia in normal mice (11.34±0.07 vs 10.14±0.15 mg/dl, $p < 0.001$) and a rise in fractional excretion index of Ca (FEI_{Ca}) (0.037±0.007 vs 0.005±0.001, $p < 0.001$), without significant alteration of serum Pi (8.94±0.46 vs 8.36±0.23 mg/dl, NS), $FEIp_i$ (0.21±0.02 vs 0.19±0.03, NS) or Na^+-stimulated Pi transport by purified renal brush-border membrane vesicles (BBMV) (844±32 vs 764±41 pmoles/mg protein·15s, NS). At this dose, 1,25$(OH)_2D_3$ had no observable effect in Hyp littermates. At 415 pg/g·day, Hyp mice experienced an increase in serum Ca (11.25 ±0.44 vs 9.64±0.06 mg/dl, $p < 0.001$), FEI_{Ca} (0.013±0.003 vs 0.005± 0.001, $p < 0.005$) and serum Pi (7.70±0.29 vs 4.35±0.15 mg/dl, p <0.001) but no change in $FEIp_i$ (0.40±0.05 vs 0.45±0.05, NS) and no enhancement of Na^+-stimulated Pi transport by renal BBMV (385±23 vs 359±50 pmoles/mg protein·15s, NS). We conclude that 1,25$(OH)_2D_3$ does not correct the renal BBM transport defect in Hyp mice, at the supraphysiologic dose that improves Pi homeostasis. On the other hand, 1,25$(OH)_2D_3$ enhances ($p < 0.02$) intestinal absorption of Pi in the Hyp mouse, thus explaining its effect on Pi homeostasis in the mutant phenotype of mouse and man.

1185 PHARMACOKINETICS AND BIOAVAILABILITY OF A SUSTAINED-RELEASE THEOPHYLLINE PREPARATION (THEODUR) IN CYSTIC FIBROSIS (CF). Scott B. Valet, Robert H. Schwartz, and John G. Brooks, University of Rochester, School of Medicine and Dentistry. Dept. Ped. Rochester, New York.

Theophylline (theoph.) improves lung function in some CF patients. Pharmacokinetics and bioavailability of oral theoph. are not defined for these patients. We studied the elimination of theoph. after IV Aminophylline, and absorption of sustained-release oral theoph. (Theodur) in 10 CF patients (age 10-48 yrs). Each received a bolus of aminophylline (4 mg/kg anhydrous theoph.) and 10 plasma theophs. levels were measured over 8 hrs. Elimination half-life ($T_{½}$), total body clearance (Cl), volume of distribution (V_d) and area under the concentration curve (AUC_{iv}) were determined. Two days later each patient received Theodur (7.47-11.42 mg/kg anhydrous theoph.) and 13 plasma theoph. levels were obtained over 24 hrs. AUC_{po} was determined. Fraction of the dose absorbed (bioavailability) was calculated ($F=AUC_{po}/AUC_{iv}$ corrected for dosages). Mean $T_{½}$±1 SD=4.45±1.58 hrs. (range 2.61-7.30). Mean Cl=87.9± 31.6 ml/kg/hr (45.6-162.2). Mean V_d=505.8±40.7 ml/kg (424.6-572.2). Values are similar to published data for non-CF patients. Mean F= 0.86±0.26 (0.45-1.29), in contrast to complete absorption of Theodur reported for non-CF patients. One patient did not develop detectable levels until 20 hrs. after receiving Theodur but rapidly absorbed 96% of oral liquid theoph.

There is no consistent abnormality of theoph. distribution or elimination in CF patients. Large interindividual differences in elimination exist as in other patient groups. Absorption of Theodur is delayed or impaired in some CF patients.

1186 CALCIOTROPIC HORMONE RESPONSES IN NEONATAL HYPOMAGNESEMIA

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Calciotropic hormone responses in neonatal hypomagnesemia have not been reported. A 3 wk old term female infant developed hypomagnesemia (serum Mg 1.2-1.5 mg/dl) and hypocalcemia (lowest serum calcium 4.1 mg%) over 2 wks. Serum parathyroid hormone (PTH) was 29µl-Eq/ml (normal ≤57µl-Eq/ml) and inappropriately low for the severe degree of hypocalcemia. PTH response to Mg infusion was evaluated by infusing 6 mg/kg of Mg as 50% Mg So_4 IV over 1 hr. Serum PTH rose gradually from 54 µlEq/ml to 63, 63, 61 and 129µl Eq/ml at 1/2, 1, 2, and 6 hrs. Urinary cyclic AMP excretion rose from 1.75-5.0 nmole/mg creatinine before Mg to 7.8, 11.6, 3.4, 6.3, 8.5 n mole/mg creatinine over the next 6 hrs. Incremental doses of synthetic bovine PTH (1-34 fragment) resulted in responses in serum Ca at 6 hrs; ΔCa (change in Ca relative to controls) at 15 units/ kg of PTH was 0.9 mg/dl, at 20 units/Kg 0.7 mg/dl, at 30 units/kg 1.5 mg/dl and at 35 units/kg 1.1 mg/dl. Serum calcitonin concentration was <10pg/ml (normal <107pg/ml). Rapid infusion of 5 mg/kg of Ca as 10% Ca gluconate resulted in a prompt calcitonin response from <10 pg/ml to 77, 26 and 48 pg/ml at +1,+3 and + 5 min. Thus in neonatal hypomagnesemia, magnesium infusion resulted in increased circulating PTH; end organ responses to PTH appeared to be intact; and calcium infusion elicited a prompt calcitonin response. We speculate that part of the etiology of hypocalcemia in neonatal hypomagnesemia is related to inappropriately low PTH levels which can be corrected with magnesium.

1187 A CASE OF PARTIAL, FUNCTIONAL GLUCOSE-6-PHOSPHATASE DEFICIENCY.

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A 4 month old boy presented with recurrent fever, poor growth, and hepatomegaly. Evaluation revealed elevated uric acid (17 mg/dl), cholesterol (291 mg/dl), triglycerides (634 mg/dl) and serum transaminase (SGOT=469 IU/L). Blood glucose (BG) was low (27 mg/dl) and lactate (L) high (6.5 mM) after a 5 hour fast. Glucagon (0.03 mg/kg) given 2 hours post prandial resulted in little rise in BG (93 to 100 mg/dl), and further elevation of L (2.5 to 4.3 mM). Galactose (1 gm/kg IV) and fructose (1 gm/kg p.o.) also caused little rise in BG and further elevation of L.

Liver biopsy revealed 4.5% glycogen content with normal enzyme activities for glycogenolysis and gluconeogenesis. Glucose-6-phosphatase activity was normal in an aqueous homogenate (5.5 umol/gm/min), but had a latency of 78% in a sucrose homogenate (normal < 10%, suggesting a defect in membrane transport of glucose-6-phosphate.

Feeding a glucose-containing formula every 4 hours for the next year resulted in good growth and development, but little reduction in plasma uric acid or triglycerides, and no improvement in plasma L or fasting tolerance. He had intermittent hypernatremia with low urinary osmolality.

The suggested defect is a partial deficiency of the transport component for glucose-6-phosphatase located on the microsomal membrane. Complete deficiency results in the clinical picture of von Gierke's disease. The defect in this patient is less severe, but requires attention to avoid hypoglycemia and poor growth.

1188 THYROID FUNCTION IN NEONATES OF DIABETIC MOTHERS.

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Infants born to diabetic mothers have decreased activity of many metabolic pathways which might be regulated by thyroid hormone. This study was designed to define thyroid function in neonates born to diabetic mothers. Serum TSH, T4, and T3 levels were measured in 19 term infants of diabetic mothers and in 7 normal term babies at 2,12,24, and 72 hrs. of age, as well as in maternal and cord sera. Mean TSH levels did not differ between diabetic and normal mothers or infants. Results are expressed as mean ± SEM.

	T4 (µg/dl)			T3 (ng/dl)		
	normal		diabetic	normal		diabetic
Mat	13.2±1.2	**	9.4±0.7	227±15	***	147±13
Cord	11.9±1.0		10.2±0.7	104±34	*	57± 5
2 hr	16.5±0.9		14.0±0.9	344±46	**	212±24
12 hr	20.3±3.0	*	15.2±0.8	309±61		216±20
24 hr	18.8±3.0		17.4±0.5	313±65	*	221±13
72 hr	18.1±1.4		16.9±1.2	235±19		184±17

*p<0.05 **p<0.02 ***p<0.005

Maternal T4 and T3 levels are decreased at delivery in diabetics as compared to normals. Neonates of diabetics have significantly decreased serum levels of T3, suggesting decreased gland secretion or peripheral synthesis. These data lead to the speculation that decreased thyroid hormone levels may explain some metabolic alterations seen in neonates born to diabetic mothers.