

bone cells contain a variety of acid hydrolyses, the chemical bases for other chondrodystrophies may be related to the altered activity of one or more of these enzymes.

Decrease and inhibition of liver phosphorylase (LP) after fructose:

An experimental model for the study of hereditary fructose intolerance (HFI). JEAN HOLOWACH THURSTON and ELIZABETH M. JONES (Intr. by Philip R. Dodge). *Wash. Univ. Sch. of Med., St. Louis, Mo.*

It has been postulated that inhibition of LP plays a significant role in the fructose-induced hypoglycemia of HFI. To test this hypothesis weanling mice were injected i.p. with 30 m-moles/kg of fructose or saline of equal osmolality. Although liver glucose levels did not fall the findings are relevant to the understanding of the pathophysiology of HFI. 20 min after fructose injection, fructose and fructose-1-P (F-1-P) levels were  $21.4 \pm 2.9$  and  $10.6 \pm 0.9$  m-moles/kg respectively. ATP and Pi were reduced 50%, to 1.36 m-moles/kg and 2.07 m-moles/kg,  $p = 0.001$ . At the same time LP was reduced 48% ( $p = 0.002$ ). This finding suggests a shift to the inactive form of the enzyme. To mimic the *in vivo* situation LP in normal liver homogenate was measured in the presence of the concentrations of Pi and F-1-P found after fructose injection. The activity of the enzyme was reduced 88% by these additions (from 5.9 to 0.74  $\mu$ -moles/g min,  $p = 0.001$ ). Therefore, it appears that *in vivo* the activity of liver phosphorylase is reduced by two mechanisms, a conversion of the active to the inactive form, and an inhibition of the remaining active enzyme by the elevated F-1-P and reduced Pi levels.

X-linked hypophosphatemic rickets: A PTH-insensitive transport defect responsive to phosphate. F. GLORIEUX, C. ARNAUD, C. CLOW, H. GOLDMAN, T. READE and C. SCRIVER. *McGill Univ.-Montreal Children's Hosp. Res. Inst., Montreal, Que., Can.; and Mayo Clinic, Rochester, Minn.*

Six children (2F, 4M) have been treated up to 6 years with a phosphate supplement by mouth 5 times daily (1-4g Pi/d). This regime required 27 home visits/pt/year but yielded a serum Pi conc. of  $3.75 \pm 0.8$  mg% for the group. This in turn achieved: 1) complete healing of rickets in all; 2) satisfactory bone density; 3) marked catch-up growth in 5 of 6 patients. Serum PTH was normal in 4 previously untreated patients (mean = 35  $\mu$ l Eq/ml, normal <40), but was raised during phosphate treatment (mean = 150  $\mu$ l Eq/ml; 6 patients, 11 determinations). Secondary hyperparathyroidism with bone signs and hyperaminoaciduria occurred in 3 patients, reduction of phosphate and use of vitamin D<sub>2</sub> (50-100,000 u/d) suppressed parathyroid hyperactivity. Net tubular reabsorption of phosphate studied intensively in one patient was constantly saturated at 39-50  $\mu$ moles/100 ml GFR (normal <90) over a serum Pi range from 1.5 to 7.3 mg%, and at endogenous serum PTH concs. varying between 28 and 490  $\mu$ l Eq/ml. A primary renal disorder of phosphate reabsorption, which is insensitive to PTH and can be offset by dietary phosphate supplements, is proposed for this X-linked trait.

A new inherited defect of isoleucine catabolism. R. DAUM, E. DELVIN, H. GOLDMAN, P. LAMM, O. MAMER and C. SCRIVER. *McGill Univ.-Montreal Children's Hosp. Research Institute, Montreal, Que., Can.*

Known inborn errors of metabolism affect 4 different enzymes in the oxidation of isoleucine to succinate. A new disease involves a fifth enzyme responsible for the formation of propionate from

$\alpha$ -methylacetoacetate. This compound and its precursor,  $\alpha$ -methyl- $\beta$ -hydroxybutyrate, are not present in significant amounts in body fluids of normal persons. Large amounts were identified by GC and mass spectrometry, at all times in the urine of a boy who experienced 3 episodes of transient but profound metabolic acidosis. Their concentration increased greatly during acute febrile illness and specifically after L-isoleucine loading. Butanone was present on these occasions while levels of amino acids and propionate were normal. The parents and one of two sibs of the proband constantly excrete modest amounts of the two organic acids, and the latter were increased by isoleucine loading in contrast to the normal response. *In vitro* oxidation of isoleucine-<sup>14</sup>C by cultured skin fibroblasts incubated at 37C was 40 percent of normal in the proband; there was no further inhibition after 24 hour incubation at 40C. The study of this mutant phenotype confirms that later stages of isoleucine catabolism are analogous to oxidation of straight-chain fatty acids.

High pyridoxine diet in the rat: Implications for clinical megavitamin therapy. GERALD GAULL, PHYLLIS COHEN, KARMELA SCHNEIDMAN, FREDDA GINSBERG-FELLNER, JOHN STURMAN and JEROME KNITTLE. (Int. by Philip Glade). *N. Y. Inst. Basic Res. Ment. Retard. and Dept. of Ped., Mt. Sinai Hospital Sch. of Med. of City Univ. of N. Y., N. Y.*

Megavitamin therapy has found increased clinical application. Although the toxicity of fat soluble vitamins is well established, little has been learned of the actions and fate of massive doses of the water soluble vitamins. Current interest in the use of vitamin B<sub>6</sub> in the treatment of homocystinuria due to cystathionine synthase deficiency prompted us to explore its mode of action and metabolic side effects in the rat. Large amounts of pyridoxine in the diet had no effect on appetite but resulted in a 20% increase in body weight and 40% in liver weight of pair-fed controls. The fat/protein ratio and the percentage of each in liver was unchanged despite the increased liver weight. The weights of brain, pancreas and kidney were unaffected. There appeared to be an increase in peritoneal fat, however, the epididymal fat pads were significantly smaller in the high-pyridoxine group because of smaller cell size. Concentrations of free amino acids were unchanged as were the activities of cystathionine synthase and cystathionase. Incorporation of <sup>35</sup>S from both methionine and cystine into the proteins of various organs were also unchanged. In the rats on high-pyridoxine diets there was greater incorporation of <sup>35</sup>S from cystine into reduced glutathione and less into oxidized glutathione. Since the amounts of pyridoxine consumed by the experimental group was of the order of magnitude as that currently used in the treatment of homocystinuria, further studies are needed before it can be assumed that massive doses of water soluble vitamins can be used with impunity.

A potential danger of chlorpropamide therapy: Impaired excretion of a water load. MICHAEL A. LINSHAW, MARK SEY, ANGELO M. DIGEORGE, and ALAN B. GRUSKIN. *Temple Univ. Sch. of Med., St. Christopher's Hosp. for Child., Philadelphia, Pa.*

A modified Carter Robbins Test was used to diagnose central diabetes insipidus (DI) in 3 patients. After 2-3 months of oral chlorpropamide 250-500 mg/day, the test was repeated. In 2 patients CH<sub>2</sub>O remained negative even during a water load of 20 cc/kg and a 2½% saline load of 10 cc/kg/45 min. There was no further drop in CH<sub>2</sub>O following 0.1 units aqueous pitressin intravenously. These and one other patient with DI were then sub-