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 ± 2.9 and 10.6 ± 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 μ-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 ± 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 μl Eq/ml, normal <40), but was raised during phosphate treatment (mean = 150 μl 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_2 (50–100,000 u/d) suppressed parathyroid hyperactivity. Net tubular reabsorption of phosphate studied intensively in one patient was constantly saturated at 39–50 μmoles/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 μl Eq/ml. A primary renal disorder of phosphate reabsorption, which is insensitive to PTH and can be offset by dietary phosphate suplements, 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 α-methylacetoacetate. This compound and its precursor, α-methyl-β-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-u-^{14}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. (Intr. 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_6 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 epidyimal 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 ^{35}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 ^{35}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_2O 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_2O following 0.1 units aqueous pitressin intravenously. These and one other patient with DI were then sub-

jected to a continuous water loading test initiated by giving 25 cc/kg of water while on chlorpropamide in a dose sufficient to cause antidiuresis without hypoglycemia. Water excretion was impaired in all patients. Serum Na fell at least 10 mEq/L in each patient. Serum osmolality fell 25 mosm/kg in 2 patients and fell 20 mosm/kg and 15 mosm/kg in the other 2 patients. All patients gained weight. Chloride spaces increased from 3% to 5% after the water load. CH_2O remained negative throughout the entire test in 2 patients. A third patient developed a CH_2O of +0.9 cc/min/1.73 m^2. This maximum CH_2O occurred 6½ hours after the water load. A fourth patient developed a CH_2O of +2.5 cc/min/1.73 m^2. This maximum CH_2O occurred 2 hours after the water load, subsequently fell to .6 cc/min/1.73 m^2 and never again exceeded +2.1 cc/min. Since published evidence indicates that chlorpropamide acts by potentiating ADH, our data suggests that the subthreshold circulating ADH presumed to be present in our patients is not further suppressed by water loading. Therefore, a potential danger exists for anyone taking chlorpropamide who either requires intravenous therapy, or who may drink a large amount of fluid.

"Transient acetylcholinosis": Cause of Chinese Restaurant syndrome. H. GHADIMI, F. ABAGI, M. RATHI and S. KUMAR. *Downstate Med. Ctr., S.U.N.Y., and Methodist Hosp. of Brooklyn, N. Y.*

Both clinical data and biochemical findings in our studies suggest that the signs and symptoms following monosodium glutamate (MSG) ingestion represent "transient acetylcholinosis." Dose-related reactions occurred in 14 volunteers after MSG ingestion on empty stomach, including numbness of neck, heaviness of eyelids and legs, lacrimation, headache, nausea, urgency of urination and defecation, drowsiness, substernal pressure, abdominal discomfort, palpitations and colicky pain. The protean nature of the symptoms, the mode of appearance and recovery, variations in severity, all were remarkably similar to the diffuse, evanescent action of acetylcholine (ACh). In 4 subjects primed with atropine, there was blockage of symptoms even though MSG dose was doubled. On the other hand, prostigmine (⅓ usual dose) given with MSG markedly exacerbated symptoms in 4 subjects tested. Others have shown that glutamate is a suitable substrate for ACh synthesis. In 10 subjects receiving 150 MSG/kg body wt., cholinesterase (ChE) was measured at 0, 20, 40, 60, 90, 150, and 180 minutes. At 60 min., there was a drop of 30% below baseline. A significantly sharper drop was observed when prostigmine was administered simultaneously with MSG. On the other hand, control tests with histidine showed no fluctuation beyond 5%. Following infusion of ACh into a dog, the pattern of ChE activity was strikingly similar to that observed in man following MSG ingestion. Clinical response to ACh also paralleled human symptoms, except for severity. In 2 infants with Down's Syndrome, ChE changes after MSG also followed the pattern seen in adult volunteers. Judging by this criterion infants do develop Chinese Restaurant Syndrome following MSG ingestion.

Incorporation of heparin-S^{35} by cultured leucocytes as a diagnostic tool in cystic fibrosis (CF). MARK W. STEELE and JOAN B. RODNAN (Intr. by Richard Michaels). *Univ. of Pittsburgh Sch. of Med., Children's Hosp., Pittsburgh, Pa.*

By culturing leucocytes for 5 days in media with Heparin-S^{35} and PHG and then assaying for cellular incorporation of S^{35}, we were able to distinguish homozygous CF from: heterozygous CF and Hurler's; and homozygous normal and Hurler's. We also noted that cells after incorporating higher levels of Heparin-S^{35} disrupted when fixed in Carnoy's mixture; so that after staining with Toluidine Blue O, the slide was covered with heavy amorphous metochromatic debris.

	S*	N†	Mean S.A.‡	Range (S.A.)	Cell Disruption§
Presumed Normals	6	11	27	9–45	2/11
Heterozygous CF	8	15	41	19–83	3/15
Homozygous CF	6	12	129	47–349	12/12
Heterozygous Hurler's	1	2	48	41–55	0/2
Homozygous Hurler's	1	2	39	36–41	0/2

* # of Subjects.
† # of Assays.
‡ DPM/mg. protein.
§ # positive instances/N.

The mean S.A. for homozygous CF was significantly ($p < 0.01$) greater than that for all other subjects. The mean S.A. for heterozygous CF, heterozygous and homozygous Hurler's were all the same and different ($p < 0.01$) from the S.A. for homozygous normal. There was a significant positive ($r = 0.65$, $p < 0.001$) correlation between cell disruption and S.A. We suggest that these two complimentary assay systems could be useful in confirming the diagnosis of CF in questionable cases. Furthermore, contrary to metochromasia, cellular Heparin-S^{35} uptake might differentiate homozygous from heterozygous CF. Hence, if applicable to cultured amniotic fluid cells, the technique could allow detection of homozygous CF in utero.

The response to parathyroid extract (PTE) in infants of diabetic mothers (IDM). REGINALD C. TSANG, LEONARD I. KLEINMAN, IRWIN J. LIGHT, and JAMES M. SUTHERLAND. *Univ. of Cincinnati, Cincinnati, Ohio.*

Neonatal hypocalcemia (NHC) in infants of diabetic mothers (IDM) has been thought to be related to transient hypoparathyroidism or lack of responsiveness to parathyroid hormone. Previous reports of NHC in IDM have not documented its existence when compared to gestation matched infants. A previous study of low birth weight infants demonstrated the importance of early gestation on the incidence of NHC. In the present study 28 IDM were matched with infants of similar age, sex, gestation and perinatal complications. Seven IDM developed NHC compared with one in controls ($p < 0.025$). In IDM mean calcium levels were lower at 12, 24, 48, 60 and 72 hours of age. One IDM (maternal class D) developed temporary hypomagnesemia with NHC. During the first 3 days of life, in all infants tubular reabsorption of P (TRP) fell (93% to 87%), urinary P excretion rose (5 to 40 mg/24 hour) and urinary Ca and Mg remained low (<1 and <0.5 mg/24 hr respectively). In 6 IDM who were given PTE (5 units/kg) at 24 hours and 48 hours of age, 5 responded with temporary elevations of Ca at 12 hours post-injection compared with untreated IDM ($p < 0.05$). There was no significant difference in serum Mg and P levels, TRP and urinary P, Ca and Mg between treated and untreated IDM