SCREENING OFFSPRING OF EARLY HEART ATTACK VICTIMS FOR HYPERLIPIDEMIA. H. Peter Chase, Ronald O'Quin and Donough O'Brien. University of Colorado Medical Center, Dept. of Ped., Denver.

The incidence of coronary heart disease (CHD), particularly prior to age 60 years, has increased greatly in the U.S. in the past 3 decades. Evidence suggests a relationship between 1) genetics and CHD, and 2) elevated serum cholesterol (chol) or triglyceride (trigl) levels and CHD. Clearly an effective screening program might make possible early prophylactic therapy.

Seventy families were screened for hyperlipidemia in which a parent proband had an MI prior to age 50 years. Thirty-six of 54 probands (67%) still living had elevated trigl (43%) or chol (11%) or both (13%). Forty-nine control children with no family history of early CHD had a mean chol ± 2 SD of 155 ± 54 and a mean trigl ± 2 SD of 85 ± 46. One hundred and eleven children from the 70 families were ≤ 20 years old and 12% had high chol (>2 SD of normal),10% high trigl, and 4% high chol and trigl (26% abnormal lipids). Eight other children had normal lipid values and elevated lipoprotein levels (>2 SD above normal), for a total of 33% of offspring ≤ age 20 showing abnormalities. Fifty-two offspring were >20 years old and 21% had high trigl, 4% high chol, and 2% high chol and trigl. This study shows a 26 to 33% return rate from screening offspring of early heart attack victims for hyperlipidemia and it is recommended that this now become a routine medical practice.

THE MECHANISM OF KERNICTERUS--WHO ARE THE REAL CULPRITS? M. L. Cowger and J. J. Lee, Albany Med. Col., Dept. of Ped., and State Univ. of New York, Dept. of Chemistry, Albany.

To examine some common concepts concerning the development of kernicterus a scanning ultracentrifugation technique (450 mμ region) was used to clearly identify that fraction of bilirubin (BR) migrating with the protein (bound BR) and the free fraction. Titration data showed that bovine serum albumin (BSA) and human serum albumin (HSA) at pH 7.4 had an initial binding of 1:1 BR to protein. When more BR was added, binding continued, showing breaks at 4 and 10 in the case of BSA and 3 and 5 with HSA. A significant proportion of BR was in "solution" as aggregates at pH 7.4. As the BR to albumin ratio increased, the BR in "solution" increased. When the pH was reduced to 6.9 the binding of BR to albumin hardly changed but there was a dramatic decrease in the amount of BR in "solution." It is postulated that the development of kernicterus at acidotic pH is associated with the decrease of solubility of the free BR with partition into lipoidal sites, rather than decreased binding ability of albumin at pH 6.9. Sulfisoxazole and salicylate did not alter BR binding. This is in accord with tissue culture data showing the necessity of drug concentrations 200-300 fold higher than the BR before BR partitioned into cells. Another mechanism is being sought for the enhancement of the development of kernicterus in the presence of these drugs rather than competition. However, hemin did offer competition once a 1:1 ratio was exceeded. (Supported by NIH.)

APPARENT FANCONI SYNDROME FOLLOWING BOWEL SURGERY AND HEPATITIS REVERSED BY 25 HYDROXYCHOLECALCIFEROL(25 OHCC).Russell W. Chesney and Harold R.Harrison,McGill Univ.-Montreal Children's Hosp.Research Inst.,Dept.of Nephrology,Montreal and Johns Hopkins Univ.,Baltimore City Hosps.,Dept.of Ped.,Balt.

A premature male infant underwent extensive ileal surgery for perforation.He then required multiple transfusions and i.v. hyperalimentation for 6 weeks.At 3 months icterus,hepatomegaly and abnormal levels of liver enzymes appeared.Over the next several weeks osteoporosis,metabolic acidosis,glycosuria and proteinuria developed,with renal tubular acidosis and generalized aminoaciduria.Serum analyses showed hypokalemia,hypophosphatemia and hypouricemia.Urine phosphate clearance was 83% of creatinine clearance at a serum phosphorus of 1.6 mg/100 ml.Serum amino acids were normal.Plasma immunoreactive parathyroid hormone was 550 pmoles/ml,an elevated value.10,000 u of 25 OHCC were given daily for 6 weeks.Aminoaciduria disappeared and bone healing was noted.Serum PO_4 rose to 6.5 mg/100 ml and PO_4 clearance fell to 2% of creatinine clearance.Upon cessation of 25 OHCC therapy aminoaciduria, phosphaturia and glycosuria again recurred.2000 u of 25 OHCC daily were then administered and these urinary changes stopped.This patient probably developed secondary hyperparathyroidism after bowel surgery,malabsorption and complicating hepatitis.A 'Fanconi syndrome' picture was the consequence of this secondary hyperparathyroidism.25 OHCC therapy was more effective than vitamin D in reversing this picture,since hepatic metabolism of vitamin D_3 could not occur.

IN VITRO STUDY OF BETA CELL FUNCTION IN IDIOPATHIC HYPOGLYCEMIA WITH NESIDIOBLASTOSIS. Krystyna J. DeLuca, Michael J.MacDonald, Kenneth H. Gabbay, John F. Crigler, Jr., Harvard Med. Sch., Children's Hosp.Med.Ctr., Dept. of Ped., Boston, Mass.

A 75% pancreatectomy was performed on a 13 month old infant with hypoglycemic seizures from 7 months of age. Prior studies showed fasting (4-8 hrs) and postprandial blood glucose (G) of 38 ± 3 (n=21) and 42 ± 4 (n=6) mg%±SEM respectively, with serum insulin (IRI) of 35 ± 9 and 43 ± 10 uU/ml ±SEM. Hypoglycemia with inappropriate IRI levels followed standard tests with oral glucose, l-leucine, triglyceride, and IV tolbutamide (T) and IM glucagon. G and IRI after IV-GTT were normal. The pancreas showed nesidioblastosis. Acid ethanol extractable IRI content was 10.8 + 1.7 U/gm pancreas +SEM (n=6). Ten mg pieces of pancreas were incubated at G90, G300, and G300 + cytochalasin B (CB-10 ugm/ml), washed and reincubated in G90 + T (40 mg%) with the following results (uU IRI/mg/hr +SEM, n=6):

	G90	G300	G300 + CB
FIRST INCUBATION	72 ± 5	75 ± 9	74 ± 11
SECOND INCUBATION	115 ± 5	121 ± 15	106 ± 11

The absence of IRI response to G300, lack of enhancement by CB and marked effect of T suggests that the readily available pool of secretory vesicles is not G or CB dependent. These observations are consistent with the behavior of fetal pancreas and suggest lack of development of glucose control over insulin release.

Studies of insulin secretion in infantile hypoglycemia. Robert O. Christiansen and John D. Johnson, Stanford Univ. School of Medicine, Dept. of Pediatrics, Stanford, Calif.

Studies were carried out to evaluate insulin secretion and its suppressability by epinephrine in 6 infants with severe fasting hypoglycemia prolonged into the first year of life. All infants required constant glucose infusions to maintain blood glucose above 40mg%. Decreased hepatic glucose output was responsible for the hypoglycemia in two of the infants (one with isolated ACTH deficiency and one with fructose-1,6-diphosphatase deficiency), whereas increased peripheral utilization of glucose was causative in the remaining four infants (two with islet cell hyperplasia and two with insulinoma). In all cases the rate of glucose infusion was adjusted to produce a peripheral blood glucose of 80 to 100 mg%. The infants with reduced hepatic glucose output had significantly slower rates of glucose infusion and significantly lower plasma insulin concentrations. The infants were next infused with the same amounts of glucose containing epinephrine and propanolol for one hour. Epinephrine completely suppressed plasma insulin (to levels of <12uU/ml) in the infants with decreased hepatic glucose output and beta cell hyperplasia, but had little or no effect on insulin concentrations in the two infants with insulinoma. In all cases the efficacy of propanolol blockade was attested to by the absence of any change in plasma free fatty acid concentrations. Islet cell hyperplasia may be distinguished from insulinoma preoperatively in this way.

MECHANISMS OF THIAMINE STIMULATED BRANCHED CHAIN AMINOACID METABOLISM. L. J. Elsas, D. J. Danner, B. L. Rogers, and J. H. Priest, Emory Univ. Sch. of Med., Dept. of Ped., Atlanta (Intr. by R. W. Blumberg).

Thiamine pyrophosphate (TPP) is a coenzyme of branched chain ketoacid dehydrogenase (BCKA'ase). Responses to its precursor Vitamin B_1 occurred in a 7 year-old male with maple syrup urine disease (MSUD). B_1 (100 mg/day for 3 weeks) decreased urinary BCKA excretion from 0.9 to 0.2 gm/gm creatinine and increased decarboxylation of branched chain aminoacids (BCAA) by his lymphocytes (WBC) from 2-5% to 17-26% of control. During the subsequent 2 years on B_1 therapy, he had no ketoacidemia, and progressed developmentally. When urinary BCKA were below 0.2 gm/gm creatinine, further stimulatory effects of B_1 were not seen. BCKA'ase activity in mitochondria isolated from his cultured skin fibroblasts was augmented by 0.2 mM TPP and Mg^{2+} only at αketo-β-methylvalerate (KMV) concentrations above 5.0 mM. TPP had no stimulatory effect on control mitochondria. However, B_1 reduced maximal plasma isoleucine (Ileu) (20±4 to 9±2 mg%) reached by 3 controls after 150 mg/Kg Ileu, and increased their WBC BCAA decarboxylation 45 to 260%. TPP and Mg^{2+} prevented the decline (7 to 0.2 nanomoles CO_2/mg/15 min.) of KMV BCKA'ase activity in inner membrane-matrix from control mitochondria after 100 minutes of preincubation. We propose that TPP enables an alternate low affinity pathway for KMV utilization when BCKA'ase is impaired, as in MSUD, and augments KMV BCKA'ase by decreasing the rate of normal enzyme degradation.