STUDIES ON THE MECHANISMS OF INSULIN RESISTANCE IN CHILDHOOD OBESITY. Robert H. Fiser, Jr., George A. Bray, Mark A. Sperling, & Delbert A. Fisher, UCLA Sch. Med., Harbor General Hosp., Depts. Ped. & Med., Torrance, California.

We have shown that childhood obesity is associated with hyperinsulinemia involving the acute and chronic pools of insulin similarly. To define the mechanism(s) responsible for this, we have measured the response of plasma insulin, glucagon, growth hormone (GH) and free fatty acids (FFA) to various stimuli in 10 obese children and matched lean controls. To allow direct assessment of the uptake of glucose by peripheral tissue (impedance) we have utilized the technique of Shen (continuous infusions of glucose, insulin, epinephrine and propranolol) to suppress endogenous insulin secretion and hepatic glucose output. All patients had normal glucose tolerance. Basal insulin levels (94 vs. 10 μU/ml) and tissue impedance (247 vs. 86) were increased ($p < 0.01$) in obese patients. Younger obese children (3-6 yr.) had intermediate plasma insulin and tissue impedance values (30 and 168). The plasma glucagon and GH responses to arginine were blunted in obese patients. Fasting FFA and triglyceride (TG) levels and the FFA and TG responses to oral lipomul and heparin were similar in both groups.

These studies demonstrate progressive impairment of glucose uptake by peripheral tissues in childhood obesity and suggest a basic tissue defect in carbohydrate metabolism.

CONCEPTUAL HIATUS IN ACID-BASE PHYSIOLOGY James L. Gamble Jr. Dept. Physiology, Johns Hopkins School of Medicine, Baltimore

Discerning students have for years sensed there was something missing in understanding of linkage between buffering in extra- and intracellular fluids. At this time one can pinpoint the area of confusion to the process of buffering of metabolic change by tissues other than blood. Unlike the red cell, utilization of buffer in the tissues can be clearly dissociated from the change in the absolute value of pH. This dissociation is shown by the following data obtained in experiments with dogs. Intracellular pH of muscle was estimated by the bicarbonate method. When the intracellular pH was lowered by 0.24 units with respiratory acidosis, the full equivalence of the tissue buffer utilization amounted only to 7.5 mEq. On the other hand, with metabolic acidosis, 30 mEq were neutralized in the tissues while the muscle pH decreased a mere 0.04 units. In place of absolute values, metabolic buffering in the tissues relates to change in the gradient of hydrogen ion concentrations across the cell membrane and hence to a unique and undescribed reaction sequence.

Despite the lack of understanding of mechanism, simple rationales meet requirements for clinical diagnosis. Change in the extracellular bicarbonate is proportional to the metabolic disorder in the complete system. Small adjustments provide suitable correction for abnormal tensions of CO_2: 1.0-1.3 mEq/liter in the bicarbonate concentration for each deviation of 10 mm Hg in the P_{CO_2}. (NSF Grant GB 35524).

CONTROL OF PANCREATIC ALPHA CELL FUNCTION IN THE NEONATAL AND INFANT SHEEP. Robert H. Fiser, Jr., Paul R. Williams, Mark A. Sperling, William Oh, & Delbert A. Fisher, UCLA Sch. Med., Harbor Gen. Hosp., Dept. Ped., Torrance, California.

We previously reported an obtunded plasma glucagon response to stimuli in fetal sheep and suggested that relative hypoglucagonemia in the neonatal period might explain the tendency to hypoglycemia. The present studies were conducted to further test this hypothesis. Glucagon responses to alanine were measured after 4 or 24 hr. fast in 10 newborn and 5 infant lambs (3 months). With 24 hr. fasting glucose and alanine decreased 32 and 35% respectively ($p < 0.05$) in the newborns but glucagon levels did not increase (121 ± 31 vs. 101 ± 15 pg/ml). In response to alanine infusions glucagon increased 32% ($p < .01$) in the 4 hr. and 38% ($p < .01$) in the 24 hr. fasted newborns. Infant lambs fasted 24 hr. displayed similar glucose and glucagon levels to the newborn animals, but alanine levels were lower ($p < .001$). In response to alanine, glucagon increased 214% above base line ($p < .001$), a response significantly greater than that in the newborn animals. Theophylline pretreatment of newborn lambs augmented the glucagon response to alanine to levels observed in infant sheep ($\Delta = 245\%$, $p < .01$). These data show 1) residual immaturity of pancreatic glucagon secretion in neonatal sheep 2) maturation of this response with age and 3) that the diminished responsiveness in the newborn period may be related to a functional immaturity of the cyclic AMP generating system.

METHIONINE-ACTIVATING ENZYME (MAE) DEFICIENCY: A NEW CAUSE FOR HYPERMETHIONINEMIA IN INFANCY. G. Gaull*, H. Tallan*, F. Schaffner*, and D. Lonsdale*. Dept. Ped., N.Y. State Inst. Res. Ment. Retard., Staten Island, N.Y.; Dept. Ped. and Med., Mt. Sinai Med. School, N.Y., N.Y.; and Cleveland Clin., Cleveland, Ohio. (Intr. by K. Hirschhorn)

Hypermethioninemia in a neonate, originally found on mass screening, was not accompanied by homocystinemia, cystathioninemia, or hypocystinemia. At 6 months, when plasma methionine was 10-20 times normal, hepatic MAE was 5nmoles S-adenosylmethionine (SAM)/mg prot/h (normal mature MAE = 86 ± 16; normal 2nd trimester fetal MAE = 26 ± 3). Activities of cystathionine synthase, cystathionase and N^5-methyltetrahydrohydrofolate (Me-THF) homocysteine methyltransferase were normal. "Liver function" tests and a battery of serological tests for hepatogenic infectious agents were normal; the infant appeared healthy. Liver was normal by light microscopy, but electron microscopy showed breaks in the outer membranes of the mitochondria and some hyperplasia of smooth endoplasmic reticulum. Serum folate remained high (>16 ng/ml) 4 months after 15 mg/day for 3 weeks (should clear in 3-4 weeks), suggesting an inability to metabolize Me-THF to THF due to deficiency of SAM, the product of MAE and a cofactor for Me-THF homocysteine methyl transferase. Unequivocal hypersegmentation of polymorphs but no megalo-ovalocytosis of RBC was found. Skin fibroblasts and lymphoid cell lines are growing and will be assayed for MAE. The strikingly low hepatic MAE activity (below fetal) and its persistance to 8 months of age suggests this is a new metabolic disease.

HEPATIC PHOSPHOENOL PYRUVATE CARBOXYKINASE (PEPCK) DEFICIENCY - A NEW CAUSE OF HYPOGLYCEMIA IN CHILDHOOD. Robert H. Fiser, Jr., Harris L. Melsher & Delbert A. Fisher, UCLA Sch. Med., Harbor Gen. Hosp., Dept. Ped., Torrance, California.

A 9-month Mexican-American female has been followed for episodic hypoglycemia first documented in the immediate postnatal period. Three convulsions occurred with glucose levels (BS) 20 mg%. Physical exam has been normal to date. A 4 hr. fast resulted in hypoglycemia (30 mg%) and mild lacticacidemia. Basal and stimulated plasma growth hormone, glucagon and cortisol were normal. IV GTT normal; (K = 1.6). Glucagon increased BS two-fold. Plasma insulin was < 5 μU/ml during hypoglycemia. IV substrate infusion results were:

Substrate	Basal Glucose	Peak Glucose	Lactate
fructose	60 mg%	98 mg%	NC
galactose	49 mg%	64 mg%	NC
glycerol	32 mg%	44 mg%	NC
alanine x 5	43 mg%	41 mg%	40% ↑

Fasting alanine levels also were increased. A liver biopsy, at 5 1/2 months, showed reduced levels of pyruvate carboxylase and markedly low or undetectable levels of PEPCK. All other gluconeogenic and glycogenolytic enzymes were normal. The data are compatible with an inborn error in gluconeogenesis at the level of PEPCK. The pyruvate carboxylase reduction is likely a secondary effect. This child represents the first documented case of PEPCK deficiency.

REYE'S SYNDROME: A MODEL AND A HYPOTHESIS. Allen M. Glasgow and H. Peter Chase. University of Colorado Medical Center, Department of Pediatrics, Denver, Colorado.

4-Pentenoic acid (P.A.) an analog of hypoglycin, the compound that causes Jamaican vomiting sickness, was given to rats in an attempt to reproduce Reye's syndrome. Twelve rats given a single dose of 200 mg/kg of P.A. intraperitoneally developed hyperventilation, prostration and finally seizures and death. These animals had elevated ammonia (P.A.=162.4 ± 32.9 [S.E.M.] vs control [C]=44.6 ± 3.7 μg/100 ml; $p < .01$) and, in fasted rats, hypoglycemia (serum glucose P.A.=95.3 ± 14.6 vs C=146.9 ± 6.1 mg/100 ml; $p < .01$). In long-term experiments 15 rats were given 50 mg/kg of P.A. every 4 hours for 10 doses followed by a single dose of 200 mg/kg. Treated rats had enlarged livers (P.A.=7.49 ± .35 vs C=5.87 ± .16 gm; $p < .001$) that showed extensive small vacuole fatty degeneration, an elevated SGOT (P.A.=136.1 ± 22.6 vs C=66.4 ± 7.1 IU; $p < .02$), an elevated BUN (P.A.=29.7 ± 1.0 vs C=16.8 ± .8; $p < .001$) and normal bilirubin levels. P.A. (1mM) inhibited palmitate oxidation in rat liver slices 47 ± 10%. Evidence indicates the impairment of fatty acid oxidation results in the other metabolic abnormalities caused by P.A. The similarity in clinical and laboratory findings in this animal model, in Jamaican vomiting sickness, and in Reye's syndrome suggests that the pathophysiology, most likely secondary to impaired fatty acid oxidation, may be similar in all three. This model may prove useful for further studies of the pathophysiology and treatment of Reye's syndrome.