and between IDM and controls. This report demonstrates that IDM are prone to NHC, are capable of conserving Ca and Mg, and have a positive calcemic response to PTE.

Succinyl-CoA: 3-Ketoacid-CoA transferase (CoA transferase) deficiency, a new cause of keto-acidosis in infancy. J. Tyson Tildon and Marvin Cornblath. *Univ. of Maryland Sch. of Med., Baltimore, Md.*

In an infant with a unique form of persistent ketonemia and severe intermittent keto-acidosis, studies of post mortem brain, muscle and kidney tissue demonstrated the absence of CoA transferase, a critical enzyme in ketone metabolism. Other enzymes of glucose and ketone metabolism were present in both post mortem tissues and skin fibroblasts from this patient. The tissue culture fibroblasts in addition to having no CoA transferase activity, demonstrated an altered carbohydrate metabolism compared to that of normal cells. When initially harvested, these cells utilized glucose at a rate significantly less than that of controls (125 vs 680 mμM/mg/hr). However, after incubation of 2.5 mM glucose for 18 hours, glucose uptake by patient's cells increased 20 fold (2560 mμM/mg/hr) whereas, that by control cells remained constant (680 $\pm$ 90). Concomitant with this increase, glucose-6-^{14}C oxidation to $^{14}CO_2$ in patient's fibroblasts rose from 8 to 2261 $\mu\mu$M/mg/hr, while that in control cells remained constant (485 $\pm$ 175). This increase in glucose utilization was not due to new enzyme formation since incubation with puromycin had no effect. Mixing experiments demonstrated no transfer of permeable inhibitors or activating substances. These data indicate that the absence of CoA transferase was the probable cause of the keto-acidosis in this infant and of the abnormal glucose metabolism in the fibroblasts suggesting a regulatory role for this enzyme in peripheral tissue glycolysis.

Complete ornithine transcarbamylase deficiency: A cause of lethal neonatal hyperammonemia. Alexander G. M. Campbell, Leon E. Rosenberg, Philip J. Snodgrass, and Claude T. Nuzum (Intr. by C. D. Cook). *Yale Univ. Sch. of Med., New Haven, Conn., and Peter Bent Brigham Hosp., Boston, Mass.*

Hyperammonemia secondary to deficiency of one of the enzymes of the urea cycle causes infantile somatic and mental retardation, but has not, hitherto, been noted to cause death in the newborn period. A term infant, born to healthy parents after an uneventful pregnancy and delivery, thrived for three days, then lapsed rapidly into deep coma. Because a previous sibling had died under identical circumstances, an inherited metabolic derangement was sought. The blood ammonia concentration was 1208 μg% (normal <150 μg%). The blood urea nitrogen was 7 mg% and numerous other studies of plasma and urinary amino or organic acids were unrevealing. Despite a protein free diet, enemas, antibiotic therapy and an exchange transfusion, the blood ammonia remained about 1200 μg% and the child expired on the fifth day of life. Hepatic assays of the five enzymes of the urea cycle revealed absence of ornithine transcarbamylase (OCT) activity. No OCT activity was restored by changes in substrate concentration, enzyme concentration or pH, and mixing experiments excluded the presence of an inhibitor of OCT in the patient's cells. Activity of the other four urea cycle enzymes was in the range noted in other age-matched, autopsy-control livers. These findings document complete OCT deficiency for the first time and emphasize the lethality of this enzymatic defect. Hyperammonemia must be considered in a newborn with coma, particularly if there is a family history of neonatal death. In such situations, unrestricted dietary protein ingestion will have disastrous consequences.

(^{14}C) Galactose incorporation into skin fibroblasts in glycolipid storage disorders (sulfatidosis, Fabry's, Gaucher's, and Hurler's disease). Michel Philippart. *Univ. of Calif. Sch. Med., Los Angeles, Calif.*

The turnover of (1-^{14}C) galactose was studied in fibroblast cultures, which were grown for 48 h. in a medium containing 5 μc of label but without serum. Subsequently cultures were maintained for up to 5 weeks in a medium containing serum. Lipids were extracted from replicate cultures at various intervals between 2 and 35 d. Maximum incorporation of the label was usually observed at 2 d. It had decreased by about 65% 1 week later but in chronic Gaucher's disease 90% of the maximum activity was retained at 9 d. and 33% at 35 d. Labeled lipids were mixed with known carriers (lipids from spinal cord, neutral glycolipids from erythrocytes and hematoside from Gaucher spleen). Thin-layer chromatograms were run in a 2-dimensional system. Lipid spots were detected by exposure to iodine, scraped, eluted and read in a scintillation counter. About 35–62% of the lipid label was incorporated into trihexosyl ceramide but no degradation of this lipid was found in Fabry's cells. The label was not incorporated into sulfatides, even in sulfatidosis. This probably reflects the inability of fibroblasts to synthesize sulfatides. Increased incorporation of labeled galactose was found in cerebrosides from sulfatidosis but not from Gaucher cells. This may imply that galactose is not a good precursor of glucosyl ceramides.

These experiments suggest that significant portions of galactose may be incorporated as such into galactolipids, while other experiments with (1-^{14}C) acetate indicated that only a small fraction of this label is incorporated into glycolipids. The availability of galactose may represent a key factor in the rate of galactolipid synthesis. This hypothesis is presently being tested in patients with Fabry's disease, sulfatidosis and GM_1-gangliosidosis.

Detection of hyperlipoproteinemia: Family lipid studies in normal school children and children with diabetes mellitus. Allan L. Drash and Fay Hengstenberg. *Univ. of Pittsburgh Sch. of Med., Children's Hosp. of Pittsburgh, Pittsburgh, Pa.*

The possible relationship between hypercholesterolemia and the development of cardiovascular disease makes the early detection of lipid abnormalities of major importance. A screening technique [precipitable lipoprotein analysis (PLP)] for the detection of abnormalities of blood lipid and lipoprotein concentrations was carried out on 487 normal children in a public junior high school (80% of the school enrollment). Serum cholesterol (C) and lipoprotein electrophoresis (LPE) were obtained on all students with PLP values >40 units and on a comparable number with PLP values <40 units (total of 203 students studied). The corrected incidence of hypercholesterolemia (C > 200 mg%) was 8.6%. Abnormalities of LPE occurred in 25%. The parents and sibs of 26 children with hypercholesterolemia and, for comparison, the parents and sibs of 28 children with diabetes mellitus were studied for total lipid (TL), C, PLP, and LPE. The mean ages of the mothers, fathers, and sibs in the 2 groups are comparable. Unexpectedly TL and C concentrations were statistically higher in the families of hypercholesterolemic children than in the diabetic families. Abnormalities of LPE were also more com-

mon in the former group. Hypercholesterolemia is common in "normal" school children. Family studies in this population will lead to the detection of many adults with hyperlipoproteinemia and an increased probability of developing vascular disease.

The stale-fish syndrome: A new metabolic disorder associated with trimethylaminuria. JAMES R. HUMBERT, KEITH B. HAMMOND, WM. E. HATHAWAY, JEAN MARCOUX, and DONOUGH O'BRIEN. *Univ. of Colorado Med. Ctr., Denver, Colo.*

In a six-year-old girl with a history of recurrent pulmonary infections and a mild bleeding tendency, a strikingly fishy smell was detected in the sweat and urine. She resembled a Turner syndrome phenotypically and had splenomegaly. Chromosomes were normal. Hematocrit was 30–34%, WBC 3,150–9,000/cu mm, platelet count 150,000–250,000/cu mm. Red blood cell (RBC) survival studies showed a slightly decreased half-time due to splenic sequestration; RBC volume was normal, but plasma volume was increased (60 ml/k). RBC's showed increased resistance to filtration through a 3 μ pore filter; this finding suggested increased cell membrane rigidity. Bleeding time was prolonged, platelet aggregation to collagen and adhesiveness to glass beads was decreased. Leukocyte adhesiveness to glass was decreased in 16 of 23 tests performed; other tests of leukocyte function were normal. The patient's mother, sister, maternal grandmother and maternal uncle also showed decreased leukocyte adhesiveness, but no other defects. Examination of the patient's urine by gas chromatography demonstrated the presence of excessive trimethylamine (TMA). This substance, a metabolite of choline, has a characteristic odor of decaying fish. When an oral choline load was given to the patient, she excreted large amounts of TMA in her urine as compared to a normal control. In addition, oral loading doses of TMA produced the fishy smell in the patient but not in the controls. This patient represents a new clinical and metabolic syndrome in which a disorder of choline metabolism, possibly due to TMA oxidase deficiency, may explain the defective membrane function of platelets, neutrophils and RBC's, and the accumulation of trimethylamine.

Net acid balance (NAB) in metabolic acidosis. ROBERT W. WINTERS, JAMES C. CHAN, EUGENE L. KLENK, GAIL S. WILLIAMS, and RALPH B. DELL. *Columbia Univ. Coll. of Phys. and Surg., New York, N. Y.*

In previous studies from this laboratory the principles for the determination of the balance (intake minus output) of noncarbonic, non-metabolizable, non-metabolized acid (net acid) have been validated and applied to healthy, growing infants. To determine NAB requires the independent measurement of all components of net acid intake (sulfuric and organic acid production plus net acid generated by skeletal mineralization minus net base intake) and net acid output (renal net acid excretion).

In the present study NAB was determined over 3–8 day balance periods in 11 infants developing ($n = 3$) or recovering from ($n = 8$) diarrhea, ileostomy, renal or late metabolic acidosis. Four studies on infants having no significant change in acid-base status over the period of study served as controls. NAB was significantly positive during the development of acidosis and negative during recovery. A close ($r > 0.9$) linear relationship was found between NAB (mEq/kg) and the measured change in blood base excess (Δ BE, mEq/l) over the period of study such that the virtual volume of retained net base or acid approximated 50% of the body weight suggesting considerable involvement of non-ECF buffers. To our knowledge this study represents the first complete quantitative measurement of the total magnitude and the separate components of net base retained (during recovery) or net acid retained (during development) in metabolic acidosis.

Opposing metabolic effects of theophylline and dibutyryl cyclic AMP. DAVID BAUM, CAROL STOWERS, and JAMES FRENCH. *Univ. of Wash. Sch. of Med., Seattle, Wash.*

Both dibutyryl cyclic AMP (DCAMP) and theophylline have been used to increase cyclic AMP (CAMP) levels in studies suggesting CAMP to be a link between catecholamines and their metabolic effects. However, DCAMP and CAMP have different effects on *in vitro* lipolysis. Since theophylline increases CAMP levels by inhibiting its phosphodiesterase, theophylline and DCAMP could effect lipolysis differently. To provide an *in vivo* evaluation of the effects of DCAMP and theophylline upon lipolysis, comparison of glycerol and free fatty acid (FFA) levels was made in puppies receiving these agents under basal conditions and during epinephrine (E) stimulation.

Theophylline infusions given to six puppies resulted in plasma glycerol (160 ± 36% mean control; mean ± S.E.) and FFA (175 ± 32%) increases, while DCAMP given to five others produced falls in glycerol (−23 ± 6%) and FFA (−24 ± 9%) levels. Prolonged glycerol (245 ± 33%) and FFA (160 ± 36%) elevations were sustained in six puppies during 75-minute E infusions. Five puppies receiving similar E infusions with similar glycerol and FFA elevations had added increases in glycerol (147 ± 41%) and FFA (85 ± 19%) when theophylline was administered after 30 minutes of E. However, when DCAMP was added instead of theophylline in five other animals receiving E, glycerol (−108 ± 16%) and FFA (−82 ± 17%) levels fell.

These observations demonstrate that DCAMP and theophylline produce opposite effects on basal and catecholamine-stimulated lipolysis in the puppy, and suggest the need for added caution in the use of these agents as tools for the study of CAMP.

Propionyl-CoA carboxylase deficiency (propionicacidemia): A cause of non-ketotic hyperglycinemia. MAURICE J. MAHONEY, Y. EDWARD HSIA, and LEON E. ROSENBERG. *Yale Univ. Sch. of Med., New Haven, Conn.*

Propionyl-CoA carboxylase deficiency is now thought to be the primary enzyme defect in the disease previously called "ketotic hyperglycinemia". In a 10 month old girl with mental retardation and seizures, who never showed clinical attacks of ketoacidosis while eating a usual infant diet, we found hyperglycinuria, modest hyperglycinemia (2.4–2.9 mg%; normal 1.6 ± 0.3 mg%), and an impaired plasma clearance of glycine after an oral load. Studies of glycine catabolism by leukocytes in vitro were normal but a severe defect in propionate oxidation was present. In addition, propionyl-CoA carboxylase activity in extracts of cultured fibroblasts was less than 1% of normal. To investigate propionate metabolism in vivo, oral amino acid loads were given. Isoleucine, a propionyl-CoA precursor, led to vomiting, lethargy, ketonuria, hyperlactatemia, and hyperammonemia within 1 day. Valine, which is metabolized to methylmalonyl-CoA, the product of the deficient enzyme, caused hyperammonemia but no symptoms, no ketonuria, and no increase in lactate over a five day period. Plasma glycine remained between 3.1 and 5.1 mg% during the oral isoleucine and valine loads. Thus, propionyl-CoA carboxylase deficiency need not cause clinical attacks of ketoacidosis and must be considered in any infant with even slightly elevated plasma and urine glycine concentrations.