1224 DYSMORPHISM IN CONGENITAL LACTIC ACIDOSIS SYNDROME (CLAS). Geoffrey Sherwood and Brian H. Robinson Spon. by Sang W. Kooh. Dept. of Pediatrics, Hospital for Sick Children, Toronto, Ontario.

Three unrelated infants presented with severe tachypnoea associated with acute lactic acidosis (blood lactates 21, 14, 11 mM N≤2mM) at the ages of 24 hrs, 7 days and 2 weeks respectively. After initial treatment, the lactate values stabilized in the range 4-8 mM. Fibroblast analysis revealed reduced total pyruvate dehydrogenase (PDH) activity (22, 38 and 52% of control values) and normal pyruvate carboxylase activity. Only the pyruvate decarboxylase (E1) component of PDH was found to be defective. All infants were neurologically impaired on follow up. Auditory brain stem evoked potentials were abnormal and brain CAT scans revealed generalized atrophy especially of brain stem and cerebellum. All infants had similar facial dysmorphism with frontal bossing, hypoteleorism, snub nose, large philtrum and wide mouth. One infant had had two siblings who died with diaphragmatic herniae and acidosis at the ages of 11 and 1 hours. At least one of these had similar facial dysmorphism.

Summary: CLAS due to partial E1 deficiency may be associated with characteristic facial dysmorphism, a rare finding for inherited disorders of intermediary metabolism. The acidosis induced respiratory effort may result in diaphragmatic herniation and underlie familial forms of that disorder.

1225 GLUCAGON AND DIAZOXIDE (D) RESPONSIVITY IN NEONATAL HYPERINSULINISM (NHI). Geoffrey Sherwood, Julio M. Martin, Spon. by Sang W. Kooh, Dept. of Pediatrics, Hospital for Sick Children, Toronto, Ontario.

Normoglycemia was maintained with ease in 14 persistently "hyperinsulinemic" newborn with constant intravenous (IV) glucagon infusions (approx 0.25 mg/Kg/24 hrs) and full oral milk feeds. Glucose supplementation was not required. Response to D (15 mg/Kg/24 hrs) an inhibitor of insulin secretion was repeatedly tested by determination of glycemic status during glucagon withdrawal. All infants were D responsive up to 5 wks of treatment and 9/14 underwent subtotal (95%) pancreatectomy as is accepted therapy; 4 at 2 wks, 3 at 3 wks and 4 at 5 wks. Pancreatic histology revealed islet cell dysplasia ± adenomatosis in all cases except one. However when medical management was continued in the remaining 3/14 these became D responsive at 6-7 wks. D was later discontinued at 2-3 years and hypoglycemia did not recur. Neurological follow up in all infants, except those referred late, was normal.

Additional facets of these 14 cases include (1) 3 who were siblings only 1 of whom underwent surgery (2) 1 who was growth retarded at term (birth weight 2.1 Kg).

Glucagon delivered as a constant IV infusion, even in the absence of IV glucose, provides a useful temporizing therapeutic approach to NHI. We now believe that such management should be continued for at least 6-7 wks before diazoxide therapy is deemed to have failed. Thereby surgery can be avoided in some cases. Furthermore glucagon deficiency may represent a major although temporary causative factor of the hypoglycemia associated with NHI during the early clinical course.

1226 NEONATAL CARBOHYDRATE HOMEOSTASIS DURING SURGERY. G. Srinivasan, R. Jain, D. Kiam, C. Kannan and R.S. Pildes. Depts. of Pediatrics, Anesthesia and Medicine. Cook County Hosp. Chicago, Ill.

Hyperglycemia (H), plasma glucose >150mg%, is often noted among newborns (NB) undergoing surgery with general anesthesia. To find the cause of H, baseline, preinduction, postinduction and postsurgical plasma samples were drawn for glucose (G), insulin (I), and cortisol (C). Glucose infusion was maintained constant with infusion pumps for 4-6 hrs prior to and during surgery. Additional fluid loss during surgery was replaced by I.V. fluids without dextrose. Sixteen NB undergoing elective surgery were included in the study. Mean weight ±S.D. at time of surgery was 3040±1546g; postnatal age ranged from 1 day to 40 weeks and duration of general anesthesia, 83±35 minutes. Glucose was infused at a rate of 4.0±1.2mg/kg/min.

	Baseline	Preinduction	Postinduction	Postsurgery
G(mg/dl)	88.3±11.0	97.3[a]±21.5	129.5[b]±36.2*	210.4[c]±109.3*
I(μU/ml)	14.1± 3.5	14.4 ± 3.5	14.8 ± 3.4	20.2 ± 12.5
C(μg/dl)	11.9± 8.3	12.4 ± 8.7	13.4 ± 8.2	22.2 ± 10.6*

*p<0.001 vs. baseline; b vs a, p<0.001; c vs b, p<0.004.

H was found in 10/16 N.B.; infants with H had sig. (p<.01) lower weight (2241±712g vs 4367±1248g) than infants without H but there were no sig. differences in postnatal age or duration of surgery between these two groups. In conclusion: (1) G rises significantly soon after induction and remains elevated during surgery. (2) I changes are minimal and variable. (3) C does not change significantly until end of surgery. Factors other than C and I appear to cause H during surgery.

1227 URINE CARNITINE EXCRETION IN SECONDARY CARNITINE DEFICIENCY. Charles A. Stanley, Gerard T. Berry, Marc Yudkoff, Richard I. Kelley, Stanton Segal, University of Penna. School of Medicine, Children's Hospital of Philadelphia, Philadelphia, PA.

Low levels of plasma and tissue carnitine (carn.) occur in defects in acyl-CoA metabolism, e.g., isovaleric acidemia (IVA), medium-chain acyl-CoA dehydrogenase deficiency (MC-ACD), propionic acidemia (PA), and methylmalonic acidemia (MMA). To see whether this secondary carn. deficiency is due to urinary wastage, we measured free (F), esterified (E), and total (T) carn. in plasma and urine in 4 patients with IVA, MC-ACD, PA, and MMA and in 6 control children on their usual diet. Plasma carn. (uM/l), urinary excretion rates (uM/gm creatinine), and (T) carn. fractional excretion (FE-T; % creat.clearance) were (m ± SEM):

	plasma carnitine			urine carnitine			FE-T
	F	E	T	F	E	T	
IVA	17	13	30	114	140	304	5.6
PA	15	17	32	0	143	143	2.5
MMA	19	10	29	64	293	357	6.4
MC-ACD	9	4	13	23	69	92	5.7
Controls	38±4.5	9±3	47±5	145±34	170±26	317±39	4.1±.7

In the patients with IVA and MC-ACD, fasts of 12-24 hr did not increase urine (T) carn.

These data suggest that carn. deficiency in these acyl-CoA metabolic defects is not due to excessive excretion, but may reflect reduced synthesis.

●**1228** DIABETES MELLITUS AND VASCULAR DISEASE: POSSIBLE ROLE OF HYDROXYACIDS IN ITS GENESIS. M.Stuart, J.Graeber*, Y.Setty*, R.Walenga*, T.Conner*, B.Glaser*. Upstate Med. Ctr., Syracuse, and Johns Hopkins Hospital, Baltimore.

Studies to date have not elucidated the cause(s) for diabetic neovascular proliferation. We report that a metabolite of arachidonic acid (AA), 15 hydroxyeicosatetraenoic acid (15HETE) is present in vessels, plays a role in neovascularization, and is ↑in infants of diabetic mothers (IDM). When human umbilical arterial microsomes were incubated with ^{14}C AA, besides the cyclooxygenase products, three hydroxyacids were observed. Two of the HPLC purified metabolites were confirmed by G.C-MS to be 11HETE and 15HETE. We next evaluated the production of these hydroxyacids in umbilical arteries from 12 control neonates and 16 IDM. Incubation of 1 mg total membrane protein with ^{14}C AA for 10' generated 322±152 (1SD) pmol total HETES and 81±24 pmol 15HETE in controls. Total HETE production in the IDM was ↑ to 478±190 ($p < 0.05$), while the ↑ in production of 15HETE was of even greater magnitude (122±40; $p < 0.005$). Finally, we evaluated the effect of 15HETE on a crucial aspect of angiogenesis i.e. endothelial cell migration using a modified Boyden chamber (Nature 288:483). Upper wells contained fetal bovine aortic endothelium in MEM-10, while lower wells contained the potential migration modulators. Control MEM 10 or AA caused no migration. Bovine retinal extract, a known potent migration stimulator,↑ migration by 269±10%. 15HETE ↑migration by 115 ±28%. Previous studies in the IDM have shown that neonatal platelet AA metabolism at birth accurately reflects maternal platelet function. Our study, using vascular tissue obtained from the diabetic milieu, demonstrates a potential role for 15HETE in the pathogenesis of diabetic neovascular proliferative disease.

●**1229** [^{15}N]LYSINE METABOLISM IN HYPOGLYCIN-TREATED RATS: EVIDENCE FOR THE SACCHAROPINE PATHWAY AS THE MAJOR PATHWAY IN VIVO. D. Hyman, T. Ito, J. Aberhart, and K. Tanaka, Yale Univ. Sch. of Med., New Haven, CT and Worcester Fdn. Exp. Biol., Shrewsbury, MA (Spon. by L.E. Rosenberg).

The mechanism of the initial steps in lysine metabolism in vivo is unsettled, although enzymic evidence suggests that metabolism proceeds via conjugation of the ε-amino group with α-ketoglutarate forming saccharopine (SAC). An alternate pathway involves removing the α-amino group and cyclization to form pipecolic acid (PIP). Both hypotheses propose that α-aminoadipic acid (AA) is produced after these initial steps. Elucidation of this pathway is important to understand the metabolic basis of saccharopinuria and pipecolic aciduria. We administered [^{15}N]-lysine labelled at the α or ε position to hypoglycin-treated rats and determined ^{15}N enrichment of aminoacid intermediates using GC/MS. Hypoglycin inhibits glutaryl-CoA dehydrogenase, causing accumulation of glutaric acid, AA, and SAC in urine. When L-[α-^{15}N]lysine was administered, SAC and AA were enriched 18.2 and 17.6 atom %, respectively. PIP was not enriched. Peak enrichment of blood AA occurred slightly later than peak lysine enrichment, suggesting a precursor-product relationship. L-[ε-^{15}N]lysine administration caused enrichment of urinary SAC comparable to that with L-[α-^{15}N]lysine but urine and plasma AA were not enriched. Urinary PIP was 15.7 atom % enriched. With D-[ε-^{15}N]lysine there was 80.6 atom % enrichment in urine PIP, and no enrichment of SAC or AA. These data indicate that L-lysine is mainly metabolized via SAC and AA, with a small portion metabolized to PIP, a dead end product.