born, 21 were born alive. Treatment and support aiming at sobriety could be started at different stages of pregnancy and with varying response. Early sobriety resulted in average size at birth, sobriety from mid-pregnancy gave a mean suppression of size at birth of 1 SD from the mean Swedish growth charts, and abuse throughout pregnancy a mean suppression of 1.7 SD. Pathological evoked response electroencephalograms (ER) were found in all three groups at birth. Only 1 of 14 investigated infants had a normal ER.

The incidence of the complete alcohol syndrome was 1/600 deliveries. In children born 1975-77 in Göteborg every sixth case of cerebral palsy was associated with an alcoholic pregnancy.

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THEOPHYLLINE (T) METABOLISM IN THE PREMATURE NEONATE.

The recent use of methylxanthines in the treatment of apnea of prematurity and their possible efficacy in the prevention of hyaline membrane disease has underlined the need for detailed investigation of their disposition in the premature neonate. The metabolism of T was studied in 10 premature newborns(g.a. 27-35 wks) during the first month of life and in 3 adult volunteers for comparison. T was injected i.v. and blood and urine assayed for T, Caffeine (C) and their metabolites by HPLC. T was found to be methylated to C only in the preterm group. 1 Methyluric (1-MU) and 1-3 Dimethyluric (1,3-DMU) acids were the major metabolites of T in the newborn. Demethylation to 3 Methylxanthine (3-MX) was seen only in the adults. The molar ratios of the metabolites in urine are reported in the table:

	3-MX	1-MU	1,3-DMU	T	C
Premature neonates	-	.11	.40	.43	.04
Adults	.19	.28	.41	.12	-

This study confirms the possibility of a methylative pathway from T to C in the newborn, but not in the adult. Hydroxylation accounted for about 90% of T metabolism in the premature neonate, while N-demethylation was absent at birth. This finding is in contrast to what seen for other drugs (e.g. diazepam).

66 F.F.RUBALTELLI,E.ROSSI* and G.JORI*. Dept. Pediatrics and CNR Center for Physiology and Biochemistry of Hemocyanins. Univ. of Padova, Padova, Italy. Evidence for visible light-induced covalent binding between bilirubin and serum albumin "in vitro" and "in vivo".

Acetone-induced precipitation of the 1:1 serum albumin-bilirubin complex, followed by treatment with 7M guanidine, allows complete removal of bilirubin from albumin by gel filtration. After illumination in the 440-470nm wavelength region (300 µW/sq.cm/nm), bilirubin or its photoproduct(s) cannot be removed any more from albumin. This was also confirmed by gel filtration on Sephadex G-75 (30% acetic acid as eluant) of BrCN-treated albumin, after 30 min. irradiation. This suggests the formation of a covalent binding which was detected also "in vivo" in the sera of jaundiced newborns. After 7 hrs.phototherapy with 4 F20T12/BB Westinghouse lamps (irradiation intensity at the infant level = 22 µW/sq.cm/nm, in the range of 440-470 nm), the covalent adduct began to appear. The quantity of the adduct was dependent upon the amount of light energy received during treatment. The adduct disappeared at 15 to 20 days after treatment.

67 H.T.VERSMOLD, G.LISTER*, P.R.DALLMAN*, A.M.RUDOLPH*. Department of Pediatrics, Univ.of Munich, Germany, and the Cardiovascular Research Institute, Univ.of California, San Francisco, U.S.A. Limits of O_2 Delivery during Propanolol-Induced Reduction of Cardiac Output in Lambs after Birth: A Longitudinal Study.

To test the ability to increase O_2 extraction when cardiac output is decreased, we assessed total body O_2 delivery before and after ß adrenergic blockade during the early postnatal period. 8 lambs were studied chronically over the first 2 month of life. Cardiac output (CO), heart rate (HR), hemoglobin (Hb), Hb O_2 affinity and 2,3-DPG, oxygen consumption (VO_2), systemic O_2 transport (SOT), and arteriovenous O_2 content difference were measured while the lambs were resting and unsedated, and again after intravenous propanolol (PROP), 1mg/kg. After birth CO, HR and VO_2 at rest decreased steadily while fractional O_2 extraction (VO_2/SOT) remained constant. After PROP CO was consistently reduced by 1o - 2o %, and there were no significant differences with age. Most of the decrease in CO was explained by the reduction in HR.Upon this decline in CO there were significant decreases in VO_2 after PROP during the first postnatal week, and at 4 weeks. This was when O_2Hb affinity was greatest (≤1 wk) or Hb was lowest (3-4 wk). Moreover, only when resting mixed venous Po_2 was less than 29 torr was VO_2 consistently and predictably decreased after PROP.

Compared to the lamb in human infants P_{50} after birth is lower, and Hb is decreasing relatively more. We conclude that in the human infant like in the lamb there is very little reserve to increase O_2 extraction or arterialvenous O_2 content difference early in infancy when P_{50} or Hb is low.

68 M.S. TANNER *, B. PORTMANN *, and C.F. MILLS *, (Intro by Prof. J.K. Lloyd) Department of Child Health, St George's Hospital Medical School, London; Liver Unit, King's College Hospital, London; and the Rowett Institute, Aberdeen, U.K.

Raised hepatic copper in Indian Childhood Cirrhosis.

Percutaneous liver biopsies from 19 children with liver disease were studied. Indian Childhood Cirrhosis was diagnosed in 5, and in these orcein staining demonstrated widespread granular deposits within hepatocytes The hepatic copper content in these 5 cases was greatly increased at 1389 ± 525 µg/g dry weight (range 1045 - 2303 µg/g, normal range 15 - 55 µg/g) The other 14 children had various hepatic disorders. None had widespread granular orcein staining Hepatic copper concentrations were normal in 12, and slightly elevated in 2 (170 and 292 µg/g). The absence of prolonged jaundice, histological cholestasis, or serum lipoprotein X in the cases of ICC indicated that hepatic copper accumulation was not secondary to cholestasis Serum ceruloplasmin concentrations were greater than 20 mg/dl in all 19 cases. A survey failed to detect any cases of ICC in Asian children born in the UK, so implicating environmental factors. We suggest that copper is implicated in the aetiology of ICC, that early treatment with penicillamine may be effective,and that reduction of copper intake may be preventative.

69 B. STEINMANN*, L. TUDERMAN*, G.R. MARTIN* AND D.J. PROCKOP* (intr. by R. GITZELMANN). Dept. Pediatrics, University of Zurich, CH-8032 Switzerland.

FIRST DEMONSTRATION OF A STRUCTURAL MUTATION OF PROCOLLAGEN IN A PATIENT WITH EHLERS-DANLOS SYNDROME (EDS).

Three patients with severe hypermobility of the joints but only mild hyperelasticity of the skin were previously reported (Science *182*,298-300,1973) to have partial deficiency of procollagen N-protease, one of the two enzymes necessary for the conversion of procollagen to collagen. One 9 year old patient was reinvestigated. In a biopsy sample of her skin, collagen was more extractable in neutral 0.5 M NaCl containing protease inhibitors. In addition to the normally occurring α1- and α2-chains, α2-precursor chains (pNα2), but no pNα1 were detected by SDS-PAGE. Digestion of the collagen with animal collagenase generated the three N-terminal fragments $\alpha1^A$, $\alpha2^A$ and $pN\alpha2^A$ but only the two normally occurring C-terminal fragments $\alpha1^B$ and $\alpha2^B$. Digestion of the extracts with purified procollagen N-protease did not remove the N-propeptide from the pNα2 chains. This excluded the possibility of incomplete conversion of pN-collagen owing to partial procollagen N-protease deficiency. The findings were corroborated by the study of radioactive procollagen produced by cultured skin fibroblasts. The latter had normal N-protease. Results suggested that the proα2-chains had a structural defect near the N-protease cleavage site preventing the enzymatic removal of the N-propeptide. Since equal amounts of pNα2- and α2-chains were produced, gene dosage was evidenced in this sporadic case of EDS probably caused by a new mutation.

70 I. SIPILÄ*, O. SIMELL* and P. ARJOMAA* (Intr. by K. Raivio). Children's Hospital, University of Helsinki, Finland. Guanidinoacetate (GAA) excretion and plasma amino acids after an arginine load in patients with hyperornithinemia and gyrate atrophy of the choroid and retina (GA).

GA is an autosomal recessive disease characterized by progressive atrophy of the choroid and retina starting by age 5-9 years, and atrophy and formation of tubular aggregates in type I muscle fibers. Plasma ornithine concentration is 10-20 times increased. To quantitate in GA the efficiency of the first reaction in creatine production from arginine, we gave a 5 min i.v. load of arginine-HCl, 1.1 mmoles/kg, to 7 patients and 4 controls. Urinary excretion of GAA was measured in 15-60 min collections for 6 hours, and plasma amino acids at 15-60 min intervals. The plasma arginine values increased similarly in patients and controls. Plasma ornithine concentrations at 0 and 30 min (peak value) were 757±134 µM (mean ±SD) and 1600±279 µM in the patients and 43±9 µM and 209±64 µM in the controls, respectively. In the patients, only the 15 min arginine value exceeded that of ornithine; the controls always had higher arginine. The basal GAA excretion by the patients was only 10% of that of the controls. In the patients, the excretion was increased for the first 30 min after the load, but returned then to the low levels. In the controls, excretion was increased throughout the collections. Thus, the high ornithine concentration may inhibit GAA formation and subsequently creatine and phosphocreatine synthesis; the resulting lack of high energy phosphagens may be a mediator in the muscle and eye atrophies in GA.

71 H.P. SCHWARZ*, K. ZUPPINGER, T. SCHAEFER*, H.P. SIEGRIST*, U. WIESMANN and N. HERSCHKOWITZ. Department of Pediatrics, University of Bern, Switzerland. Galactose enhances sulfatide synthesis in glucose-deprived cultured mouse brain cells.

Glucose-deprived brain cell cultures have a markedly reduced sulfatide synthesis (SfS). As SfS is glucose dependent, galactose (gal) was studied to delineate its role as a substitute for glucose (glu). SfS is a mandatory step in the formation of myelin. Gal is necessary to form cerebroside which is converted to sulfatide by incorporation of sulfate. Neonatal mouse brains were dissociated and cultured for 10 days. Cell cultures

were then kept for another 3 days in media containing either glu or gal alone or combined. SfS of cultures continued at glu 26.1 mM served as control (100%). Gal alone at any concentration (1.3-26.3 mM) was unable to replace glu, SfS remained severely depressed (1.5 to 2.9%). At high glu levels above 12.6 mM addition of gal did not influence SfS, thus excluding a toxic effect. At glu 7.5 mM which left cultures glu-deprived below 0.2 mM for at least 1 day, SfS fell to 35.9±10.6% (SD). Under this condition, SfS could be raised to 52.9±13.5% when gal 0.6 mM was added or even to 67.9±15.6% with gal 12.2 mM (p less than 0.05, resp. 0.001). Therefore, gal may not be necessary for SfS in glu-replenished states. Under glu-deprivation, however, gal could become essential for maintaining structural brain metabolism measured as SfS.

72 A. LUCAS*, T.E. ADRIAN*, S.R. BLOOM* and A. AYNSLEY-GREEN. University Dept. of Paediatrics, John Radcliffe Hosp., Oxford, and Hammersmith Hosp., London. GUT HORMONES IN THE NEONATE.

Gut hormones exert important effects on gut growth, secretion and motility and on intermediary metabolism, and may play a key role in the postnatal adaptations to enteral feeding. Using sensitive radioimmunoassays we have measured 10 entero-insular hormones in the plasmas of (a) 203 healthy term or preterm infants at birth, or during the first 24 days of life either before or at 30, 60 or 120min. after feeding and (b) 10 six-day old preterm neonates who had never been fed orally since birth on account of hyaline membrane disease. Each infant contributed, with ethical approval, only one plasma sample, removed at the time of a routine clinical blood test. Basal levels of gastric inhibitory polypeptide (GIP), pancreatic polypeptide (PP), enteroglucagon (EG), neurotensin (NT), motilin, and gastrin all rose steeply during the neonatal period, the latter four hormones reaching levels which exceeded significantly those seen in healthy fasting adults. In contrast plasma concentrations of GIP, EG, NT, motilin and gastrin did not show postnatal elevation in the unfed group of infants. In addition for 8 hormones; secretin, GIP, PP, NT, EG, motilin, gastrin and insulin, we observed a progressive postnatal increase in the endocrine response to a feed. Profound changes occur therefore in gut hormone physiology after birth and these changes may in part be due to enteral feeding itself. This data is of relevance to the design of optimal feeding regimes for high risk neonates.

73 N.C.R. RÄIHÄ, A.L. JÄRVENPÄÄ*, D. RASSIN*, and G. GAULL*, Depts. Pediatrics, and Obstetrics and Gynecology, University of Helsinki, Finland and Dept. Pediatric Research, N. Y. State Inst. Res. Ment. Retdn., Staten Island N. Y., U.S.A. Milk protein quality: Biochemical and growth effects in full-term infants.

Our previous studies have shown that both quantity and quality of ingested milk protein affects the metabolic homeostasis of low birth-weight infants. In this study, 37 well full-term infants were fed ad libitum for 12 weeks with either breast milk (BM) or with one of two formulas (F_1=1.5% prot., whey prots.: caseins, 60:40 or F_2=1.5% prot.; whey prots.: caseins, 18:82). No differences between feeding groups were found in weight gain, linear growth or head circumference during the study period. Significantly, greater negative base excess and higher BUN were found in the formula fed infants as compared to those on BM. Blood cholesterol at 12 weeks was much higher in the infants on BM when compared to those on F_1 and F_2 ($p<0.0001$). Plasma and urine taurine concentrations were higher in the infants on BM throughout the study and at 4, 8 and 12 weeks of age the urine taurine was 25 to 50 times higher in BM infants than in F_1 and F_2 infants. Plasma valine and isoleucine concentrations were significantly increased in the formula fed infants as was the valine/glycine ratio, suggesting the possibility of protein overloading in the formula fed infants.

74 A.L. JÄRVENPÄÄ*, N.C.R. RÄIHÄ, P. KUITUNEUN*, D. RASSIN* and G. GAULL*, Depts. Pediatrics and Obstetrics and Gynecology, University of Helsinki, Finland and Dept. Pediatric Res., N. Y. State Inst. Res. Ment. Retdn., Staten Island, N.Y. U.S.A. Effect of taurine supplementation to the diet on bile acid conjugation in low birth-weight infants (LBWI).

Previous results have shown that plasma and urine taurine concentrations decrease when LBWI are fed with taurine deficient formulas. In this study, 63 well LBWI with gestational ages of 31 to 36 weeks were randomly assigned to either breast milk (BM) or formula (1.5%, prot. 60:40 whey: caseins) without (F1) or with addition of taurine (30 µmol%, F_2). Duodenal fluid bile acids and glycine-taurine ratio (G:T) were determined with high-performance liquid chromatography. The plasma taurine levels and urine taurine excretion fell significantly in the infants fed with the taurine deficient F_1 formula. At the age of 7 days the G:T ratios were 0.64 (BM), 0.44 (F_1) and 0.47 (F_2). In the infants on BM and F_2 the G:T ratio remained on the same level throughout the study and at the age of 36 to 40 days it was 0.58 and 0.69 respectively on the two diets. In the infants fed with formula F_1, the G:T ratio increased significantly after the age of 21 days being 1.32 at a mean age of 39 days ($p<0.001$). Our results indicate that dietary taurine intake affects duodenal bile acid conjugation.

75 T. TIKANOJA* and O. SIMELL* (Intr. by J. Perheentupa). Children's Hospital, University of Helsinki, Helsinki, Finland. Plasma amino acids in healthy newborns after a feed of breast milk or formula.

Postprandial concentrations of plasma amino acids were followed in 20 full-term healthy infants, aged 4.5-8 days, to quantitate differences in response to a physiologic feed of breast milk or formula. The study had been approved by the ethical council of the hospital; the parents of each infant had given their informed consent. After a 4 hr fast, 10 infants received from bottle a normal feed (1/36 of body wt) of pooled breast milk; 10 infants received milk formula. The true protein contents of the milks were 0.8% and 1.5%, respectively. Venous blood samples were drawn just prior and 30, 60, 120 and 210 min after the beginning of the feed. Peak plasma concentrations were reached with both milks in 30-60 min and starting values in 210 min. Valine, leucine, tyrosine, lysine and arginine showed highest molar increased amounting 50-100% above their fasting concentrations. The rises in plasma amino acids were approximately equal after both meals despite differences in the proteins of the milks. Thus, (1), the absorption of amino acids is significantly more efficient from breast milk than from formula, or (2), the postprandial amino acid curves are strictly regulated by the metabolic clearances and poorly reflect absorption in the newborns.

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Orotic aciduria, an indicator of adequacy of treatment in lysinuric protein intolerance (LPI).

The basic defect in LPI is in the transport of the diamino acids in kidney tubuli, jejunum and liver cells. This leads to a deficiency in the liver of the urea cycle intermediates arginine and ornithine, a malfunction of the cycle and an accumulation of ammonia. Like in the other conditions in which hyperammonemia is associated with accumulation of carbamyl phosphate, urinary excretion of orotic acid is excessive. Orotic acid is an intermediate of the synthesis of the pyrimidines from carbamyl phosphate. We measured orotic acid excretion in controls and patients with LPI. The controls in all situations excreted less than 20 µg/kg/hr. The patients excreted normal amounts during fasting (4.6, 2-8, 5 for mean, range, number of subjects). Their excretion was increased in 24-hr urines during a self-chosen low-protein diet (125, 3-366, 7), in 4 to 6 hr urines after a milk load with 0.5 g of protein/kg (488, 251-1747, 3), in 2-hr urines after oral ammonium lactate, 2.5 mmoles/kg (212, 15-1126, 10), and in 6-hr urines after iv alanine, 6.6 mmoles/kg in 90 min (790, 47-1831, 11). If the loads were given with an iv infusion of arginine, ornithine or citrulline, the orotic aciduria did not appear. Given orally, citrulline was the most efficient of the three in preventing orotic aciduria. Orotic aciduria thus is a reliable indicator of the function of the urea cycle in LPI and enables us to monitor the home treatment.

77 M. DURAN, F.A. BEEMER, S.K. WADMAN, J.L. JOHNSON, W.R. WAUD, K.V. RAJAGOPALAN, University Children's Hospital Het Wilhelmina Kinderziekenhuis, Utrecht, The Netherlands and Duke University Medical Center, Dept. Biochemistry, Durham NC, USA.
Combined deficiency of sulfite oxidase and xanthine oxidase as a result of defective synthesis of molybdenum-cofactor.

A girl is presented with congenital abnormalities including asymmetry of the skull and slight mediofacial dysplasia. The eye lenses were dislocated. Severe neurological abnormalities and deep mental retardation were observed. On routine screening a low serum urate (0.01-0.07 mmol/l) was observed. Chromatography of urinary purines revealed xanthinuria. In addition the sulfite test in the urine was repeatedly positive. Sulfite oxidase deficiency was suggested by high excretions of S-sulfocysteine, taurine and thiosulfate and low levels of urinary sulfate. Deficiencies of both xanthine oxidase and sulfite oxidase were demonstrated in a liver biopsy specimen. Because sulfite oxidase and xanthine oxidase are known to require an activated form of molybdenum (Mo-cofactor), investigations of Mo metabolism were carried out. A complete absence of hepatic Mo-cofactor activity was demonstrated and analysis by atomic absorption revealed a severe depletion of hepatic Mo as well. A near normal amount of inactive xanthine oxidase protein was present, but several immunological techniques failed to detect any sulfite oxidase apo-enzyme. It is suggested that a defective synthesis of Mo-cofactor causes the biochemical abnormalities. Treatment with oral supplements of molybdenum did not result in biochemical or clinical improvement.

78 K.O. RAIVIO, H. KRUMHOLZ, C. LAZAR and M.A. BECKER Children's Hospital, University of Helsinki, Finland, and V.A. Hospital, San Diego, CA.
5-phosphoribosyl-1-pyrophosphate (PRPP) synthesis in glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The supply of ribose for nucleotide synthesis is considered a major function of the oxidative pentose shunt (PS). We have evaluated this function on the basis of ribose-5-phosphate (R5P) and PRPP concentration and generation in normal and G6PD-deficient fibroblasts. PS in normal cells accounts for 0.8% of glucose utilization. It can be stimulated over 10-fold by methylene blue (MB) and inhibited 85% by 6-aminonicotinamide (AN) without affecting PRPP levels or generation. PS in mutant cells is 30% lower than normal and barely affected by MB or AN. Basal R5P,