19 TWO DIFFERENT CYSTEINE SUBSTITUTIONS IN THE SAME α1(I) CB6 PEPTIDE OF THE α1(I) COLLAGEN CHAIN PRODUCE A LETHAL AND A MILD FORM OF OSTEOGENESIS IMPERFECTA (OI).

B. Steinmann, A. Nicholls and F.M. Pope.
Children's Hospital, CH-8032 Zurich, Switzerland and MRC, Harrow, UK.

Various structural defects of collagen type I have been established in OI and molecular heterogeneity is reflected by clinical variability. We recently reported a cysteine substitution in the C-terminal cyanogen bromide peptide α1(I) CB6 of a newborn with lethal OI arisen by new mutation in one of the α1(I) collagen genes (Steinmann et al., J.Biol.Chem.259:11129, 1984). At that time we speculated, and later confirmed that a cysteine was substituted for a glycine, residue 988 of the helical portion, as a result of a single base change (Cohn et al., in prep.). We now report that in another patient and his mother with mild OI (Nicholls et al., Brit.Med.J. 288:112, 1984) half of their α1(I) chains also contain a cysteine in the α1(I) CB6 peptide as determined by CNBr mapping on 2-dimensional gel electrophoresis in SDS. In contrast to the 1st patient, production, secretion, intracellular degradation, posttranslational modification and helix stability of the collagen were normal. Since the stability of the collagen helix strictly depends on the presence of glycine in every third position, we conclude that in the patient with lethal OI the cysteine substitution in the glycine position impairs triple-helix formation and stability for sterical reasons, whereas in the two patients with mild OI cysteine is substituted for an amino acid in the X or Y position of one of the repeating Gly-X-Y triplets. How this latter structural anomaly produces the mild phenotype is unknown at present.

20 INCREASED β- AND ω-OXIDATION OF FATTY ACIDS IN THE SILVER RUSSELL SYNDROME

PJ Willems[1], I Stolte-Dijkstra[2], H Schierbeek[1], R Berger[1] and GPA Smit[1]
Depts of Pediatrics[1] and Human Genetics[2], University of Groningen, Groningen, The Netherlands

We found evidence for an increased oxidation of fatty acids in two Silver-Russell patients (dwarfism of prenatal onset, typical craniofacial appearance and dystrophy).Fasting studies showed elevated blood and urine levels of β-hydroxybutyrate (BHB) and aceto-acetate (AA) and a massive urinary excretion of C_6-C_{12} dicarboxylic acids. After 20 hrs of fasting BHB in blood was 3.50 and 3.50 mmol/l while AA was 1.02 and 1.12 mmol/l in the two Silver-Russell dwarfs, respectively. Seven controls of comparable age (1-2½ yr) had significanly lower blood levels of BHB (mean: 1.68 mmol/l) and AA (mean: 0.63 mmol/l). GC-MS analysis of urine organic acids of both Silver-Russell patients showed a very similar pattern with a massive excretion of BHB (<10 mmol/l) and C_6-C_{12} dicarboxylic acids (adipic acid, suberic acid, sebacic acid, C_{12}-dicarboxylic acid, cis/trans unsaturated suberic acid and sebacic acid, cis unsaturated 3-OH-derivates of sebacic acid and C_{12}dicarboxylic acid). In contrast controls had a low excretion of BHB (<1 mmol/l), while C_6-C_{12} dicarboxylic acids were present in very small amounts or not detectable. The combination of both an activated β-oxidation resulting in high blood and urine levels of BHB and AA, and an activated ω-oxidation resulting in a massive urinary excretion of dicarboxylic acids is very typical.
We suggest that this increased oxidation of fatty acids is a distinct feature in the Silver-Russell syndrome and might provide an explanation for the dystrophy which is so characteristic.

21 INCREASED FOOD-INDUCED THERMOGENESIS (FIT) IN DIABETIC CHILDREN (DC) RECEIVING CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) THERAPY.

D Molnár, G Soltész, T Decsi, A Hamar, J Mestyán Dept. Paed. University of Pécs, Pécs, Hungary

Since the effect of CSII therapy on thermogenesis is not known, therefore resting metabolic rate (RMR) and FIT was measured by indirect calorimetry in 7 DC receiving CSII therapy and prae-meal insulin bolus and in 7 age-matched controls (C). Pump treatment for at least one week before the study resulted in normal fasting BG (DC vs C, mean±SE 3.9±0.4 vs 4.5±0.2 mmol/l), free insulin (67.9±21 vs 73.5±13 pmol/l), GH (109±49 vs 80±38 pmol/l), FFA (510±108 vs 482±107 μmol/l), beta-hydroxybutyrate levels (110±35 vs 113±30 μmol/l). DC had fasting hypoglucagonaemia (32±13 vs 118±13 pg/ml, $p<0.05$). Postprandial changes after a standardised breakfast (C 60.3, DC 57.4 KJ/kg lean body wt.) of these metabolites and hormones were similar in C and DC, except for the lower postmeal nadir of FFA in DC (139±24 vs 352±62 μmol/l, $p<0.05$) and RMR was also normal (C 6.4 ±0.2, DC 5.9±0.4 KJ/kg lean body wt./60 min). FIT however, was significantly ($p<0.05$) higher in DC than in C (4.91±0.4 vs 3.07±0.66 KJ/kg lean body wt./180 min). In spite of optimal control, the "metabolic efficiency" was subnormal in DC as suggested by the higher FIT, which might have been due to the peripheral rather than portal delivery of insulin with this mode of therapy.

22 DEFECTIVE REDUCING ACTIVITY OF NEWBORN PLATELETS

D.Del Principe,R.De Santis,A.M.Pentassuglio,R.Pacitti,G.Mancuso,and A.Menichelli. Dept.of Pediatrics,University of Rome,Rome,Italy.

Activation of platelet(Plt)plasma membrane is associated to Cytochrome C(Cyt.C)reducing activity.We studied this activity in newborn Plts stimulated by low or high molar ADP, collagen,thrombin and opsonized-zymosan(opZ).Cord blood was collected from placental end of the cut umbelical cord.The platelet-rich plasmas(PRPs)were layered on Ficoll 23%(w/v) to eliminate leukocyte contamination.Zymosan was opsonized with adult citrated-plasma(AB Rh-).Cyt.C reduction was determined spectrophotometrically,and aggregation(in PRPs or Plt suspensions)by the change in light transmission.The Cyt C reduction was undetectable(n=20)in newborn Plts stimulated with all stimuli(adult controls:10-20 nmol/10^9 Plts/10 min)including collagen(4 μg/ml)and thrombin(1.67 U/ml)able to induce their aggregation.Newborn Plts did not aggregate after low molar concentrations of agonists(Hathaway,1970)or after immunologic stimulation(Del Principe,ESPHI 1985).opZ plus subthreshold ADP elicited a 90% aggregation,but not Cyt.C reduction.The defective membrane redox reactions reflect an alteration in the process leading to membrane activation,and possibly account for the impaired functional response of newborn platelets.

23 FUNCTIONAL AND MORPHOLOGICAL HETEROGENEITY OF NEWBORN RABBIT SUPERFICIAL (SF) AND JUXTAMEDULLARY (JM) PROXIMAL CONVOLUTED TUBULES (PCT).

Christer Holmberg, C. Craig Tisher and Juha P.Kokko. Children's Hospital, University of Helsinki, Helsinki, Finland and Department of Medicine, University of Texas, Dallas and University of Florida School of Medicine, Gainesville,USA.

Adult SF and JMPCT have different functional properties. Permeability characteristics predict that passive forces play a significant part in volume reabsorption only in the most SFPCT but active transport in JMPCT. As salt and volume reabsorption in newbornes differ from that in the adult animal morphological and electrophysiological studies were conducted on PCTs from rabbits 36 h from birth to investigate if one homogenous or two different populations of PCT are present at birth.

Segments of PCT were dissected and perfused in vitro and their Na to Cl permeability ratio was measured electrofysiologically by imposing an iso-osmotic 50 mM NaCl gradient across the epithelium. Transmission and scanning electron microscopy studies were performed on the same segments. The morphological studies clearly disclosed that SFPCT are less mature than JMPCT at birth. Also the SFPCT had a lower Na permeability than Cl (0.55±0.06, n=6) while the JMPCT had a higher Na permeability than Cl (1.37±0.11, n=6).

Thus intrinsic heterogeneity of PCT is present at birth. Since the SF Na to Cl permeability approximates that of free diffusion the results suggest that epithelial discrimination in PCT is part of a maturation process, and as the relative number of Cl permselective tubules in the newborne was greater than in the adult, passively driven volume reabsorption seems to be more significant in the neonatal kidney than in the adult.

24 THE DEATH OF A NEWBORN TWIN

Elizabeth M Bryan (Introduced by David Harvey) Institute of Obstetrics and Gynaecology, Queen Charlotte's Maternity Hosp. London, United Kingdom.

The perinatal death of one twin may be as great a loss to the mother as that of a single baby. This is rarely appreciated. The experiences and needs of a sample of 14 bereaved mothers of multiple births (12 twin, 2 triplet) obtained through the Twins and Multiple Births Association, were explored by semi-structured questionnaires. Results - All mothers perceived the survivor as a twin. 6 had feelings of rejection towards this child initially. Others overprotected and continued to have unjustified anxiety. The initial difficulties of simultaneously celebrating a birth and mourning a death were revived at anniversaries. All mothers had wanted to talk about the dead baby but many had been discouraged and made to feel guilty about their grief. Suppression of grief sometimes led to unresolved mourning. Some felt they had been given inadequate information and all wanted to know the twins' zygosity. The fear of a fantasy twin was expressed by some who had no tangible reminders. Suggestions for future professional practice - Acknowledgement of the importance of the dead baby. Encouragement of mother to talk about him. Provision of counselling facilities. Provision of ultrasound scan to reduce fear of fantasy twin; of photographs of babies including, with liveborns, of both together, of zygosity determination.