41 NEWBORN-SCREENING FOR BIOTINIDASE-DEFICIENCY:EVALUATION OF A 4YEARS NATIONAL SCREENING PROGRAM AND A REPORT ON 10 PATIENTS. K.Widhalm,S.Bischof,S.Scheibenreiter; Dept.of Pediatrics,Univ. of Vienna,Austria

Biotinidase deficiency is an autosomal recessiv disease in which there is an inability to cleave biotin from biocytin,because of a complete or partial deficiency of biotinidase.Clinically seizures,skin rash,alopezia,developmental regression may occur.In Austria a nationwide screening for biotinidase-deficiency was started in Jan.1986:325672newborns have been screened on their filter-paper blood samples,out of these in 10 patients the dignosis biot.def.has been made by a enzymatic-spectrophotometric method of Knappe.Thus,the incidence in Austria is 1:32567;data from a worldwide screening report on an incidence of 1:61067.The mean biotinidase activity has been calculated to be 0,40+0,12nmol/min/mlpl.(normal range:4,01-7,98)this is 6,1+2,4%of the mean normal activity.6patients were classified as "profound" and 6patients as partial-deficient.In regard to therapeutic regimes we treated only these patients with a biot.def. less than 10%of mean normal activity.(n=6/10mgbiotin/d).The group of children with partial def. is under control up to now.Recently it has been published that also children with a residual activity betw. 10+30%should be treated.Due to recent knowledge clinical symptoms can be avoided and reversed by means of early treatment(5-10mg biotin/d).Therefore a neonatal screening seems to be highly justified and early treatment of all patients is clearly indicated.

44 ADENOSINE ACCUMULATION IN HEMORRHAGIC CEREBROSPINAL FLUID. G. Van den Berghe, S. Stevens, J. Vanhove & J. Jaeken, Department of Pediatrics, University Hospital Gasthuisberg, Leuven, Belgium.

Although adenosine (Ado) may play a critical regulatory role in brain, little information is available with respect to its metabolism in cerebrospinal fluid (CSF). In normal, cell-free CSF from children of various ages, degradation of 1 µM Ado reached only 0.028 ± 0.010 nmol/h/ml at 25 °C (mean ± SEM for n = 9). Both intact and hemolysed red blood cells (RBC, ~ 50,000/mm^3 of test volume) produced no or negligible Ado when incubated in the absence of CSF. Incubation of intact RBC with CSF similarly did not result in Ado accumulation. However, incubation of a hemolysate with CSF resulted in buildup of Ado at rates that were proportional to both amount of hemolysate and of CSF. Accumulation was enhanced in the presence of the adenosine deaminase inhibitor deoxycoformycin (1µM). Further studies showed that CSF contains a 5'-nucleotidase (activity : 7.4 ± 1.8 nmol/h/ml at 25 °C, n = 11) with the kinetic characteristics of an ecto-5'-nucleotidase (high affinity for AMP, inhibition by adenosine 5'-methylene diphosphonate, no stimulation by 2,3-bisphosphoglycerate). It is concluded that Ado may accumulate in hemorrhagic CSF as a result of the combination of red cell hemolysis providing AMP, the presence of a membrane-derived 5'-nucleotidase, and the low activity of adenosine deaminase.

42 DEVELOPMENTAL CHANGES IN ERYTHROPOIETIN (Ep) PHARMACOKINETICS IN FETAL AND NEONATAL SHEEP.

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Ep is the primary hormone responsible for erythrocyte production throughout development. It has been proposed that recombinant human Ep (rhEp) be used for the treatment of anemia in premature human neonates. Before doing so, it is important to examine pharmacokinetic parameters during development in animals. To do so we developed a sensitive and specific rhEp immunoprecipitation assay using polyclonal antisera. A non-compartmental approach was employed to determine pharmacokinetic parameters in 6 fetal (FET) (125-133 d; 2.8-3.4 kg), 6 newborn (NB) (10-19 d; 5.0-10.6 kg), and 5 adult (ADULT) pregnant sheep (120-130 d gest) following bolus injection of tracer amounts of 125I-rhEp. Results (*M ± SD*) demonstrated more rapid plasma clearance (Cl), shorter terminal half-life (t1/2 beta), greater plasma distribution volume (Vd), and greater steady state distribution volume (Vss) in the FET and NB groups (Table). We speculate that low plasma Ep levels observed in premature newborn infants are not due to decreased Ep production, but instead are the result of rapid Ep elimination and large distribution volume. For rhEp to be effective in the treatment of anemia in premature neonates, it is likely that larger rhEp doses per kg than those used in treating anemic adult patients will be needed.

	FET (n = 6)	NB (n = 6)	ADULT (n = 5)
Cl (ml/kg-h)	157 ± 79n,a	80.5 ± 13.4f	19.2 ± 6.5
t 1/2 beta (h)	1.72 ± 0.83a	1.92 ± 0.47a	3.59 ± 1.29 f,n
Vd (ml/kg)	117 ± 42.8n,a	73.0 ± 7.5f	51.8 ± 3.6 f
Vss (ml/kg)	304 ± 110n,a	168 ± 27.3f,a	78.7 ± 11.3 f,n

p<0.05 compared to FET(f), NB(n) & ADULT(a) (ANOVA)

45 PLASMA IMMUNOREACTIVE CATIONIC TRYPSIN (ICT) PATTERN IN RAT MODEL OF CYSTIC FIBROSIS (CF)-RESEMBLANCE TO HUMANS.Weizman Zvi.Pediatric Gastroenterology,Soroka Hospital,Ben-Gurion University,Beer-Sheva,Israel.

Plasma ICT is elevated in CF infants,before exocrine pancreatic insufficiency(EPI)develop, due to unknown mechanism.Reserpinized(RT)rats show CF--like secretory defects,including EPI,but plasma ICT has not been studied.This study explored plasma ICT pattern and mechanism in this model.ICT(RIA)in pancre--atic juice(PJ)and plasma,PJ volume&protein and pancre--as weight were determined in rats,RT for 4 or 7 days, post caerulein stimulation,vs.pair-fed controls (C).

Results:

	4 days		7 days	
	RT(n=8)	C(n=8)	RT(n=7)	C(n=8)
plasma ICT(ng/ml)	167.3∓12.8*	88.9∓6.1	39.2∓8.4*	66.8∓4.9
PJ ICT(µg/mg protein)	8.2∓2.4	7.6∓1.8	2.8∓1.3*	5.4∓2.1
PJ volume(mg/min/gm)	5.6∓1.3	4.2∓1.6	1.6∓0.7*	3.1∓0.6

(*P<0.01vs.C) Compared to controls:(A) 4 days RT rats show higher plasma ICT,and similar PJ volume & ICT. (B) In 7 days RT rats,plasma ICT,and PJ volume & ICT, all decline. Conclusions:1.This model resembles human CF,as to elevated plasma ICT before EPI.2.Elevated plasma ICT,is probably not due to ductular obstruction. 3.Other mechanisms are to be studied in this model.

43 SERUM IMMUNOREACTIVE ERYTHROPOIETIN IN CHILDREN WITH ACUTE LEUKAEMIA AT VARIOUS STAGES OF DISEASE, AND THE EFFECTS OF TREATMENT. Marit Hellebostad(1), Jens Marstrander(1), Sophie H. Slørdahl(2), P. Mary Cotes(3), Harald E. Refsum(4). 1) Dept. of Paediatrics, Ullevål Hospital, Oslo, Norway, 2) Dept. of Paediatrics, Rikshospitalet, Oslo, Norway, 3) Clinical Research Centre, Harrow, Middx., U.K., 4) Laboratory of Clinical Physiology, Ullevål Hospital, Oslo, Norway.

Most children with leukaemia are anaemic at the time of diagnosis and at various times during treatment. Serum erythropoietin (EPO) was estimated by a radioimmunoassay method in 27 children with acute leukaemia (n=26) or lymphoma (n=1) at diagnosis (n=16), in relation to high dose methotrexate (MTX, n=11) or cytosine arabinoside (Ara-C, n=8), and during oral maintenance therapy with MTX and 6-mercaptopurine (n=10). At diagnosis serum EPO was increased in the children with anaemia, and inversely related to haemoglobin (Hb, r=-0.94, p<0.00005). After high dose MTX, in some children serum EPO increased where Hb was unchanged or increased. After high dose Ara-C Hb declined, and serum EPO increased markedly in all cases. During oral maintenance therapy when Hb was in the normal range, serum EPO was slightly increased in some children. In conclusion, children with leukaemia respond to anaemia with an increase in serum EPO concentration, but in relation to treatment with high dose MTX and Ara-C, additional mechanisms may influence the EPO concentration.

46 HUMAN CHORIONIC GONADOTROPIN RELEASE BY HUMAN TERM PLACENTA IS DYNAMICALLY REGULATED BY GLUCOSE

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During gestation human chorionic gonadotropin (hCG) is secreted in an initial rise to maintain corpus luteum function. In early pregnancy, also spontaneous pulsatile hCG secretion regulated by a GnRH-like compound of placental origin has been described. - Question: Are there metabolic influences which regulates hCG release? - **Methods:** Explants of human term placenta (500 mg) were perifused in 1 ml chambers (ACUSYST, Endotronics) with a flow rate of 100 ul medium 199/min. The glucose concentrations were changed from 5.55 to 0 mmol/l resp. 16.0 to 5.55 mmol/l in pulses of 16 min. The experiments lasted for 5 hours. HCG was measured every 4 min by IRMA. - **Results:** 1. In hypoglycemic conditions, the lowered glucose concentration was followed by significant peaks (PULSAR analysis) of hCG reaching more than 40.9∓25.2 % (mean + SD) of basal level (duration 6.1∓1.8 min) (n=13). 2. Repeated lowering of glucose (max. 3 times) showed corresponding hCG bursts (height: 16 - 168 mIU/ml). 3. Decreasing glucose concentrations in perifusate per se were answered by elevated hCG bursts (n=3).- **Conclusion:** In vitro, human placenta reacts to diminished glucose supply with increased hCG release. This does not seem to be due to a total lack of fuel.-Supp. by DFG (Hell07/2-3)