LEAD: TOXICITY AND TISSUE LEVELS IN THE EMBRYO. Joseph Kochen* & Yigal Greener*, Albert Einstein Col. of Med., Montefiore Hosp. & Med. Ctr., Dept. Ped., Bronx, New York (Intr. by Laurence Finberg)

Lead (Pb) injected into yolk sacs of day 4 chick embryos results in progressive central nervous system (CNS) bleeding which subsides by day 10-12 and is followed by the development of hydrocephalus. The use of Pb 210 permitted a correlation between the dose of Pb, tissue Pb levels, morbidity, and mortality. Increasing the Pb dose resulted in increasing CNS damage, mortality, and increasing concentrations of total body, blood and brain Pb. Injection of Pb after day 11 was accompanied by a marked decrease in morbidity and mortality. This was associated with reduced brain Pb concentrations, but no decrease in blood Pb levels. This indicates the development of a blood-brain barrier to Pb at this period in development and corresponds to the formation of specialized endothelial junctions in the CNS. Administration of Ca Edta at intervals after Pb injection on day 4 enabled delineation of the minimum period required for the occurrence of Pb toxicity. Edta given 2 minutes after Pb resulted in complete protection against Pb induced CNS damage and mortality. At intervals up to 8 hours there was a substantial diminution in morbidity and mortality. At longer intervals little protection was afforded by Edta. Blood and body Pb levels remained unchanged, irrespective of Edta administration; however, brain Pb levels increased with increasing Pb-Edta intervals. These results demonstrate a relationship between CNS damage and brain Pb levels and indicate that a brief exposure to Pb early in development suffices to produce CNS damage and embryo death.

EMR, DNA AND CELL SIZE IN PRE- AND POSTNATALLY DEPRIVED RATS. Ingeborg Krieger and Qamar Taqi, Wayne State Univ. School of Medicine, Children's Hospital of Michigan, Detroit.

In infants EMRs are lower in prenatal than in postnatal onset growth failure. The significance of this was investigated in rats with similar types of growth failure by relating their EMR to body weight (Bwt), combined organ (O: liver, kidney, heart, and brain) weight (Owt), DNA (ODNA), and protein (OPr). Mature rats were fed a 6% protein diet 1 month prior to and during mating, gestation, and lactation. Offsprings were fed 27% protein at weaning (A). Offsprings of normal rats were fed low protein from weaning to 10 weeks and high protein up to weight recovery (B). The insult caused permanent stunting in group A rats; 3/4 of group B rats had normal weights by 24 weeks. Sleeping EMRs were measured in 4 rats of each group before sacrificing, at weaning, 10, 16, and >16 weeks, and in litter-mates weekly up to maturity. The relation of the EMR with Bwt, Owt, and OPr was curvi-linear; that with ODNA was linear. These relations were similar for normal controls. The EMR per Bwt, Owt, and OPr decreased with age as cell size increased. The insults affected ODNA and OPr of liver, kidney, and heart in both groups but not of brain. Recovery paralleled weight recovery. Recovery of cell size occurred first. The data show that the EMR reflects cell number rather than cell mass. Comparison of the EMRs suggests that the insult of group A rats was not comparable to that which caused dwarfing in infants with growth failure of prenatal onset.

INFORMATION TRANSFER BY CELLULAR MESSENGER RNA

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Total cell RNA purified from cultured mouse cells induced to synthesize interferon causes mouse interferon synthesis in heterospecific cell cultures. Metabolic and physicochemical criteria support the conclusion that genetic information is transferred as the messenger RNA (mRNA) for mouse interferon. The species specificity and physicochemical properties of the product suggest that it is mouse interferon. These results confirm the report by De Maeyer, De Maeyer-Guignard and Montagnier (Proc. Natl. Acad. Sci., 69, 1203 (1972)). By means of RNA transfer, we have devised a relative quantitative assay for interferon mRNA activity. Because the biological activity of the mRNA can be assayed, new opportunities exist for the study of the control of a specified gene and the metabolism of a specific messenger RNA.

AGE-DEPENDENT ACTIVITY OF L-GLUTAMIC ACID DECARBOXY-LASE (GAD) IN HUMAN KIDNEY. G.A. Lancaster, F. Mohyuddin & C.R. Scriver. MRC Genetics Group, Montreal Children's Hosp. & McGill Univ., Montreal.

The conversion of L-glutamate (L-glu) to γ -aminobutyrate (GABA) in mammalian brain & kidney is catalyzed by pyridoxal-phosphate (PLP)-dependent GAD. GABA is an important neuro-inhibitor in CNS, but another role must exist for GABA metabolism in kidney cortex. We assayed GAD by an isotopic method (Lancaster et al, BBA 297:229, 1973) at normal tissue L-glu conc. (4-8mM) $\pm$ PLP (0.24mM) in frozen post-mortem human kidney obtained between 15wk gestation and 10yr. GAD is stable in tissues or homogenates stored at -20°C; PLP-saturated renal GAD activity is low (<0.5nmoles CO₂ formed/mg wet wt·h) before 40wks gestation, then rises at term and plateaus in the infant & child at 5-10x fetal level. Kidney GABA conc. parallels GAD activity. Endogenous GAD activity is often inappropriately low for age, but can be stimulated by PLP in vitro, indicating, under-saturation by co-enzyme in vivo; once bound in vivo, PLP is not easily removed from GAD in vitro. Augmentation of renal GAD activity at term parallels the need for human kidney to extract glutamine from plasma to support renal ammoniogenesis. The GABA pathway permits disposal of the residual glutamate carbon chain as a non-titratable acid.

PHARMACOKINETICS OF DICLOXACILLIN IN PATIENTS WITH CYSTIC FIBROSIS. Mary E. Mattar, William J. Jusko, Louise Gerbracht, Luis Mosovich and Sumner J. Yaffe. Department of Pediatrics and Pharmaceutics, State University of New York at Buffalo.

The frequent episodes of peribronchial pneumonia seen in patients with cystic fibrosis require antibiotic administration often with anti-staphylococcal agents. Until now the data upon which to base dosage regimens have not been available. Serum dicloxacillin concentrations and urinary excretion rates were measured in 10 patients ranging in age from 9 to 22 years and in 5 normal adult subjects at various times after oral administration of a single dose (6.25 mg/kg) of antibiotic suspension in order to investigate absorption and disposition kinetics. The disease did not appear to cause impaired absorption of the antibiotic since the total urinary recovery of the drug in the patients usually exceeded that of normal subjects. However, the peak plasma levels and areas under the concentration versus time curves of dicloxacillin were much lower and more variable in the patients than in the normal subjects. Less antibiotic is therefore available for therapeutic effect. This was the result of unusually high renal clearances of dicloxacillin (3x normal). It was significant that the dicloxacillin:creatinine clearance ratios (1.55 versus 0.87, respectively) were larger in the patients than in normal subjects. Because of this rapid renal excretion, treatment of cystic fibrosis patients with dicloxacillin warrants use of increased doses. Measurements of the serum concentration of the antibiotic may be needed to assure adequacy of therapy.

ONTOGENY OF TRACHEAL FLUID, PULMONARY SURFACTANT AND PLASMA CORTISOL IN THE FETAL LAMB. E. Joseph Moscher, Arnold C.G. Platzker, Philip L. Ballard, Joseph A. Kitterman, John A. Clements and William H. Tooley. Spec. Ctr. of Res., Pulm. Dis. and Dept. of Ped., Univ. of Calif., San Francisco, Calif.

We examined fetal plasma cortisol and the flow rate, electrolyte composition and surfactant content of tracheal fluid in chronic experiments with 9 fetal sheep. We catheterized a fetal artery and inserted a tracheal catheter to divert fluid into an intrauterine bag which was emptied every 12 hr. Surfactant was assayed on a surface balance and cortisol was determined by the protein binding radioassay. From 120-150 days of gestation there was no change in mean fluid Na⁺ (149 meq/L), Cl⁻ (153.9/meq/L), Ca⁺⁺ (2.2 mg/100 ml) and pH (6.21). The rate of fluid production was 4.5 ml/Kg/hr. K⁺ increased from 4 meq/L at 120-130 days to about 9 meq/L (145-150 days) while plasma Na⁺, Cl⁻, Ca⁺⁺, pH and K⁺ were constant at 146 meq/L, 109.1 meq/L, 12 mg/100 ml, 7.4 and 4.3 meq/L, respectively. Cortisol was less than 1.5 μ g/100 ml total (0.3 μ g/100 ml free) until 120 days when it increased rapidly to 10.5 total (3.2 free) at 148 w.s. Surfactant first was detected in tracheal fluid between 125-130 days and increased exponentially after 135 days to a value of 200 μ g/Kg/hr at 147 days. Thus, fluid:plasma gradients exist for Cl⁻, Ca⁺⁺, H⁺ and, in late gestation, K⁺. It appears that an increase in fetal cortisol is not the stimulus for appearance of surfactant in the lamb, although this hormone may induce the rapid accumulation of surfactant prior to delivery.