151 cGMP AND cAMP CONTENT OF HUMAN UMBILICAL ARTERY: POSSIBLE ROLE IN PERINATAL PATENCY AND CLOSURE. Ronald I. Clyman, Jeffrey A. Sandler, Vincent C. Manganiello, Martha Vaughan (Intr. by Howard Sloan). NIH, Bethesda.

It has been suggested that guanosine 3',5'-monophosphate (cGMP) plays a role in smooth muscle contraction and adenosine 3',5'-monophosphate (cAMP) in relaxation. This hypothesis has been evaluated in term (gestational) human umbilical artery segments incubated at 37°C and in room air. 1) The basal cGMP content (1 pmol/mg protein) of artery segments incubated in room air was almost twice that of cAMP. 2) Bradykinin, histamine, serotonin, acetylcholine and K^+-ion, which cause umbilical artery constriction, can increase the cGMP content of the artery segments within 30 sec of exposure without altering the cAMP content. 3) Prostaglandin E_1, but not isoproterenol, caused accumulation of cAMP which is consistent with reports that umbilical arteries lack functional β-receptors and that only prostaglandin E_1 can bring about relaxation of umbilical arteries. 4) 1 μM atropine blocked the effect of 100 μM acetylcholine on cGMP content without altering the responses to histamine, bradykinin, serotonin, or K^+-ion. 5) Pyrilamine (an H-1 antagonist), but not metiamide (an H-2 antagonist), blocked the effect of histamine on cGMP from which it is inferred that histamine causes accumulation of cGMP in umbilical artery via its interaction with H-1 receptors. The results are consistent with the view that metabolism of the two cyclic nucleotides is independently controlled in the human umbilical artery and that cGMP is involved in contraction of the artery at birth.

152 ENDOCRINE EFFECTS OF CHRONIC ADMINISTRATION OF LSD TO PREPUBERAL MALE RATS. R. Collu, J. Letarte, G. Leboeuf and J.R. Ducharme. Dept. of Ped., Ste-Justine Hosp., and Univ. of Montreal, Montreal, Quebec.

No reports have appeared to our knowledge on the endocrine effects of the chronic administration of LSD to young animals. In this study, groups of Sprague-Dawley male rats were injected intraperitoneally 3 times a week for a month with either 100 or 500 ug/kg of LSD or with the vehicle starting at 21 days of age. At the end of the experimental period, the animals were sacrificed by decapitation. Endocrine organ weights were recorded and plasma and pituitary levels of GH, LH and FSH were measured by radioimmunoassay and brain levels of serotonin (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), noradrenaline (NA) and dopamine (DA) were assayed fluorometrically. Animals injected with either dosage of LSD had smaller body weights than controls, while tail length was reduced in the high dosage group only. Plasma levels of GH were decreased in the high dosage group and pituitary levels in the low dosage group (Mean ± SE. Plasma GH: LSD 40 ± 16, controls 138 ± 33 ng/ml. $P < 0.02$. Pituitary GH content: LSD 108 ± 16, controls 227 ± 8 ug. $P < 0.001$). Plasma and pituitary levels of LH and FSH were not modified by the drug. The low dosage of LSD decreased the brain levels of NA and increased those of DA, while the high dosage decreased those of 5-HIAA. These results suggest that LSD, when administered chronically to developing animals, can inhibit body growth probably by altering the secretion of GH through modifications of its neuroendocrine control.

153 RAPID DIPHENYLHYDANTOIN METABOLISM IN INFANTS. Richard G. Curless and Philip D. Walson (Intr. by J.J. Corrigan, jr.), Depts of Pediatrics, Pharmacology and Neurology, Univ. of Arizona, Tucson, Arizona.

The purpose of this study is to evaluate diphenylhydantoin (DPH) metabolism in infants with poorly controlled seizure disorders and consistently low serum DPH levels. Three infants with severe seizure disorders refractory to a variety of medications including DPH were found to have serum DPH levels of less than 2 mcg. per ml. 12 hours after a DPH dose. Each patient had been receiving DPH in a dosage of 10 mg.per kg. given twice a day for a minimum of three months preceding the present study. To evaluate DPH kinetics, a half-life was determined on each child in the following manner. After obtaining a base line serum DPH (12 hours after the last DPH dose) 1 mg. per kg. of DPH was injected through an intravenous line. Subsequent blood samples were drawn at one hour, two hours and four hours after injection. The DPH levels were determined by gas chromotography and DPH half-lives were determined using this data. The results indicate half-lives of 4.5 hours, 3.7 hours and less than 2 hours on the three patients. It is our conclusion that these three children must be treated with special consideration in terms of DPH therapy. The first two patients will require a DPH dosage interval of approximately 4 hours and the short half-life on the third patient indicates that DPH therapy is unlikely to produce adequate blood levels with any acceptable dosage regimen. We suggest that this mechanism of drug failure with DPH should be considered in any infant who has below therapeutic blood levels with an adequate oral dosage.

154 ACETAMINOPHEN DISPOSITION IN ADOLESCENTS. Michele Danish, Rafael Gorodischer, Steven Liebowitz, Luis Mosovich, Joseph Krasner and Sumner J. Yaffe. Dept. of Ped., State Univ. of New York at Buffalo.

Acetaminophen is a frequently used antipyretic and analgesic in infants and children. Dosage recommendations are empirically derived and not based upon pharmacokinetic studies in these age groups. We first investigated two groups of adolescents, 7 normal children, 10-18 years old (average 13.4 years) and 5 cystic fibrosis patients, 13-21 years old (average 15.6 years). The patients were given single oral doses of APAP, 1 g/1.73M^2, as the elixir. Serum and saliva samples were collected at hourly intervals for 6 hours following drug administration. Acetaminophen concentrations were determined by GLC. The serum half-lives of the normal adolescents ranged from 72 to 108 min. (average 85 min.) and were significantly lower than literature reports of adult half-lives which range from 114 to 142 min. The cystic fibrosis patients more closely resembled adults with a range of 100 to 132 min., averaging 112 min. This increase in average half-life in the cystic fibrosis patients may possibly be related to the older ages of this group. Saliva samples were collected simultaneously with blood samples as a means of establishing a non-invasive technique for measuring APAP body levels. Saliva half-lives correlated well with the measured serum half-life. Saliva:serum concentration ratios averaged 1.04:1.0 for the normal adolescent and 1.14:1.0 for the cystic fibrosis patients. These data provide evidence of a shorter T1/2 in adolescents and justify alteration in dosage as well as study of younger age groups.

155 GENTAMICIN PHARMACOKINETICS IN PATIENTS WITH CYSTIC FIBROSIS. Michele Danish, Louise Gerbracht, Luis Mosovich, William J. Jusko and Sumner J. Yaffe. Depts. of Ped. and Pharmaceutics, State Univ. of N.Y. at Buffalo.

Gentamicin is frequently employed for the management of gram-negative pneumonia in children with cystic fibrosis. It is of major importance to determine the disposition characteristics of the antibiotic in diseased patients so that optimum dose for treatment may be established. Six cystic fibrosis patients, age range 12-24 years, who required intravenous gentamicin infusions for the treatment of pneumonia were studied. Doses ranged from 1.0 to 1.9 mg/kg with an approximate infusion time of 1 hour. Serum, sputum and urine samples were collected at hourly interfals for 8 hours after the initiation of the infusion. There was total urinary recovery of the drug within the 8 hour period in all patients. The average gentamicin half-life (2.0 hours) and volume of distribution (18.8% of body weight) correlated well with normal adult data. However, gentamicin renal clearance averaged only 60.2 ml/min/1.73M^2, which was only 45% of the simultaneously measured creatinine clearance. Also significant was the lack of distribution of gentamicin to the sputum. The apparent sputum antibiotic concentration remained constant at 1 mcg/ml during the study period while the serum concentrations varied from 0.5-9.2 mcg/ml. However, in sputum collected from cystic fibrosis patients not receiving any antibiotics, a natural inhibitory activity of 0.5 mcg/ml was observed. Thus, as measured in the sputum, no appreciable amounts of gentamicin can be found at the presumed site of infection.

156 PRENATAL AND POSTNATAL METHYLMERCURY POISONING IN MOUSE AND MAN. Richard A. Doherty and Allen H. Gates (Intr. by Robert H. Schwartz)
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Recently in Iraq, 6530 children (34%) and adults (66%) were hospitalized due to methylmercury poisoning from eating homemade bread prepared from seed wheat treated with a methylmercury fungicide (Science 181: 230, 1973). There were 459 hospital deaths. Long term follow-up studies of infants exposed in utero are in progress.

We are using a mouse model to aid in evaluating risk to the mammalian fetus and newborn. 24 hours after a pulse dose of methylmercury, maternal (M) and fetal (F) mouse blood, plasma and liver mercury concentrations are equivalent yet F brain concentration is 3-fold higher than M brain. Mouse milk mercury concentration is highly correlated with plasma concentration ($r=0.94$) throughout the wide range of blood methylmercury concentration (10 to 3000 ng/ml) seen in the exposed Iraqi population. Normal human blood methylmercury concentration = 5 ng/ml . Suckling mice excrete mercury 35-fold less rapidly than adult mice: adult half-time of excretion = 7 days; newborn (birth to 9 days) half-time of excretion = 240 days.

Mouse and human data suggest that the fetus and suckling newborn may be at increased risk for toxic effects of methylmercury on developing brain. Prenatal and postnatal mouse and Iraqi human data will be used to discuss possible risk of human methylmercury poisoning from ingestion of pelagic fish.