139 MORPHOLOGIC ANALYSIS OF THE PULMONARY VASCULAR BED (PVB) IN INFANTS WITH IN UTERO EXPOSURE TO PROSTAGLANDIN INHIBITORS. By Daniel Levin, David Fixler, Frances Morriss, Jon Tyson. Univ. of Texas Health Science Center, Dept. of Ped., Dallas.

Maternal ingestion of prostaglandin synthetase inhibitors may be associated with premature closure of the ductus arteriosus (DA) and/or direct stimulation of pulmonary vessels. The effects of this on the developing PVB are unknown. We studied the lungs of an infant whose mother took aspirin repetitively throughout the pregnancy. The infant's serum salicylate level at 24 hours of age was 1.2 mg/dl. He had pulmonary hypertension, tricuspid insufficiency and a closed DA documented at 10 hours of age. The other infant whose mother took indomethacin 10-12 days prior to delivery had a syndrome of persistent hypoxemia. All lungs were fixed by perfusion and 5th generation (resistance) vessels identified. Compared to control, the medial width/external diameter (m/d) ratios were increased, 0.25±0.01(S.E.)(n=55)($p<0.01$) and 0.34±0.01(n=50) ($p<0.001$) respectively; control 0.21±0.01(n=138). The number of resistance vessels/cm^2 lung calculated in 10 to 30 randomly selected sections was 89±10(S.E.)($p<0.001$) and 348±41(N.S.) respectively; control 341±18. The infant with chronic aspirin exposure had premature closure of the DA, an increased m/d ratio due to decreased external diameters, and a decreased number of vessels/cm^2 lung. The infant with short term indomethacin exposure had hypoxemia, increased m/d ratio due to increased muscle, and a normal number of vessels/cm^2. These changes may be due to differences in exposure to these drugs and their effects on the DA or the pulmonary vessels in utero.

140 ONTOGENESIS OF AUTONOMIC INNERVATION IN MAMMILIAN MYOCARDIUM. William J. Marvin, Jr., Robert Roskoski, Jr., and R. Kent Hermsmeyer. (Spon. by R. M. Lauer) Univ. of Iowa, Col. of Med., Depts. of Peds., Biochem., and Pharm., Iowa City, Iowa 52242

This study was designed to assess: the ontogenesis of autonomic innervation in the intact embryonic and neonatal rat heart and the development of innervation of rat heart cells in primary tissue culture. Choline acetyltransferase activity (CAT), a marker for acetyl choline synthesis, was determined by radioimmunological assay in intact hearts. CAT was first detectable on the 18th gestational day (atria/ventricles = 8/2 pM/mg of protein) and reached plateau levels on the 14th postnatal day (atria/ventricles = 36/12 pM/mg of protein). Functional innervation, evidenced by cardioinhibitory vagal response, appeared at birth. Fluorescent staining demonstrated the absence of adrenergic innervation at birth. In culture preparations of newborn rats, CAT activity was not present, indicating the loss of cholinergic neurons during tissue culture preparation. Sympathetic neurons were added to rat heart cell cultures, which were free of demonstrable cholinergic and adrenergic neurons. Scanning electron microscopic, time lapse photographic, and glyoxic acid fluorescent staining indicated the development of innervation in these cultures. Conclusions: In the newborn rat heart cholinergic, but no adrenergic neuroeffector transmission is present. The trophic influence of innervation upon myocardial growth and sensitivity can be assessed with the addition of sympathetic neurons in vitro.

141 DEPENDENCE OF HEART RATE VARIABILITY ON INSTANTANEOUS HEART RATE IN SLEEP. Norman M. Mazza, Mary A. Epstein, Gabriel G. Haddad, Hung-Fai S. Law, Judith S. Katz, Robert B. Mellins, and Ralph A. Epstein, College of Physicians and Surgeons and School of Engineering, Columbia University, New York

Beat to beat variability of the heart rate is believed to be under autonomic control and is widely used as an index of well being in the fetus and young infant. Autonomic activity, heart rate and heart rate variability all vary with sleep stage. It thus becomes important to determine whether heart rate variability is directly dependent on heart rate in all stages of sleep. Nine normal sleeping infants were studied at monthly intervals during the first four months of life. Sleep was staged using behavioral, EEG, EOG, and EMG criteria. The time between heart beats (RR interval) was recorded with an accuracy of ± 0.1 msec using a minicomputer and specially designed preprocessor. The ΔRR was calculated as the absolute value of the difference between one RR and the next. A significant positive correlation was found between ΔRR and RR ($p< 0.001$), in Quiet, Indeterminate and REM sleep. The mean slope of the linear regression in each stage was significantly positive ($p<0.001$). An increase in ΔRR of at least 10 msec results from a 100 msec increase in RR in all stages of sleep.

Because there is an inverse relationship between heart rate variability and heart rate in all stages of sleep in infants, beat to beat variability should be corrected for heart rate in order to assess autonomic control.

142 FAILURE OF INDOMETHACIN TO CLOSE THE DUCTUS ARTERIOSUS Jeane McCarthy, Andrew Juris, Lenore Zies, Frank Ferrero, Gerard Kaiser, Otto Garcia, Dolores Tamer, Pedro Ferrer, Henry Gelband, Depts. Pediatrics & Cardiovascular Surgery, Univ. of Miami School of Med., Fla.

Indomethacin (IND) has recently been shown effective in closing the patent ductus arteriosus (PDA) in small premature infants. However, this mode of therapy has not been evaluated in older infants or children. We have given IND to 6 patients (pts.) with isolated PDA's ranging in age from 51 days to 6 years. All pts. had typical auscultatory findings of a PDA, widened pulse pressure and 5 pts. had electrographic evidence of left ventricular hypertrophy. Four pts. demonstrated cardiomegaly and increased pulmonary blood flow on chest x-ray. Three pts. had the diagnosis of PDA confirmed by cardiac catheterization to exclude associated cardiac anomalies. Echocardiography in 5 pts. revealed LA/AO ratios ranging from 1.2 to 2.0. IND was given orally in a dose ranging from 0.2 mg/kg to 1 mg/kg (1 pt.). Four pts. received 0.3 mg/kg for 2 doses 24 hours apart. In all 6 pts., the clinical & laboratory findings of a PDA remained after the course of IND was completed. Documentation of the patency of the PDA was demonstrated at surgery in 3 pts.; 3 additional pts. are awaiting surgical ligation. Our data suggest that there is an age-related mechanism for prostaglandin inhibition which was probably absent after 50 days of age in our pts. At the present time there seems to be no role for IND in the medical therapy of PDA's in older infants and children.

143 INFANT FOLLOW-UP AFTER INDOMETHACIN (IND) CLOSURE OF THE PATENT DUCTUS ARTERIOSUS (PDA). T. Allen Merritt, Charlotte L. White, Michael J. Hirschklau, William F. Friedman and Louis Gluck. Univ. of Calif., Dept. of Ped. La Jolla.

Six infants receiving IND for pharmacologic closure of a PDA were followed for 10-13 months. Neurologic, visual, hearing, cardiac, and renal evaluations were performed and compared to 11 infants with PDA matched for gestational age (31±3 wk), birthweight (1481±558g), and RDS who underwent operative closure of the PDA between July 1975 and October 1976. All 6 IND treated survived; 2 of 11 control infants died. There was no retrolental fibroplasia in either group. Hearing was normal in all but one control infant. Neurologic evaluations were normal in 5 IND infants with global hypertonia in one, while 3 control infants had transient neurologic anomalies including neck extensor hypertonicity in 1 and asymmetric deep tendon reflexes in 2 infants. Bayley Scales of Infant Development are within ± 2 S.D. for postconceptual age in 5 of 6 IND infants. Control Bayley Scales are incomplete. Cardiac evaluation: no residual shunt in either group. Both the IND and control infants had normal BUN and creatinines at 6-13 months of age suggesting that renal impairment with IND (2.5-5.0 mg/kg) was transient as previously reported. These findings indicate that at 10-13 months of life IND neonates are indistinguishable from those requiring surgical ligation of PDA. Additional follow-up of both methods of ameliorating this physiologically disadvantagous shunt is warranted.

144 RENAL VASCULAR PROTECTION BY PROSTAGLANDINS DURING HYPOXEMIA IN UNANESTHETIZED FETAL LAMB. Ronald W. Millard Hank Baig, and Stephen Vatner (Spon. Alexander Nadas,) Harvard Medical School, Children's Hospital, Dept. of Cardiology, Boston, Mass. 02115

Fetal hypoxemia is thought to induce marked vasoconstriction, particularly in the renal (K) circulation. To study regional vascular responses to hypoxemia, 10 fetal lambs (110-135 days gestation) were instrumented with Doppler flow (F) probes on K, mesenteric (M), and iliac (I) arteries and with aortic and vena caval catheters for injection of radio-nuclide microspheres. After recovery from operation administration of 10% O_2 to conscious ewes reduced fetal P_aO_2 from 22 to 11 mmHg, heart rate from 175 to 129 beats/min, and increased mean arterial pressure from 44 to 53 mmHg. Hypoxemia reduced KF(23%), significantly less, $P< .05$, than MF (42%) and IF (80%). Pretreatment with meclofenamate, 10 mg/kg, an inhibitor of prostaglandin synthetase, did not alter normoxic control values nor any responses to hypoxemia except in the K bed, where F fell by 55%. The hypoxemia induced decreases in KF and increases in K resistance were significantly greater, $P<.01$, than observed without meclofenamate, and were no longer significantly different from M and I responses. Thus, hypoxemia induces a differential pattern of response in the unanesthetized fetus with constriction less in K, than M and I beds. Prostaglandin control of the K bed is important even in the fetal circulation and appears to protect the K bed during hypoxemia. Where maintenance of KF is important, as during stress, the administration of prostaglandin synthetase inhibitors could be deleterious.