

than 120 days gestation; (3) reflex bradycardia was blocked by atropine but not influenced by propranolol; (4) in fetuses the regression coefficients of SP or PP vs. R-R increased with gestational age, but not when SP or PP was correlated with HR because of the lower initial HR in older fetuses; (5) lambs had significantly higher regression coefficients for all correlations than fetuses. We have not yet evaluated if baroreceptor responses depend on gestational age and initial HR in combination.

Cardiovascular responses to autonomic blockade in intact fetal and newborn lambs. EERO K. VAPAAVUORI, ELLIOT A. SHINEBOURNE, ROBERT L. WILLIAMS, MICHAEL A. HEYMANN, and ABRAHAM M. RUDOLPH. *Cardiovas. Res. Inst., Univ. of California, San Francisco, Calif.*

Sympathetic and parasympathetic activity have been studied in exteriorized fetal lambs but not in intact fetuses in utero. We placed vinyl catheters in a systemic artery and hindlimb vein in 20 fetuses from 92 days of gestation to term and also in 3 newborn lambs. The animals were allowed to recover from surgery for 2-3 days and then studied daily for several weeks. Maternal and fetal pH, PCO<sub>2</sub> and PO<sub>2</sub> were normal in all experiments. The blood pressure (BP) and heart rate (HR) responses to selective intravenous injection of propranolol (1 mg/kg), practolol (1-2 mg/kg), atropine (1.0 mg/kg), phentolamine (0.1 mg/kg), phenoxymethylamine (5 mg/kg) and tyramine (0.25 mg/kg) were recorded. The adequacy of autonomic blockade was confirmed by absence of response to acetylcholine (5-15 μg/kg), isoproterenol (0.1 μg/kg) or methoxamine (50 μg/kg). Changes in HR from resting levels without significant BP change were observed as follows: propranolol 5-25% decrease, practolol 8-22% decrease and atropine 0-64% increase. Response to beta-adrenergic blockade did not vary significantly with gestational age. Phentolamine and phenoxymethylamine decreased systolic BP 2-14 and diastolic BP 2-12 mm Hg in 19/21 animals and tyramine increased systolic BP 7-60 and diastolic BP 10-46 mm Hg in 7/7 animals. No significant difference in sympathetic responses were observed in fetal and newborn lambs, indicating HR and BP to be under similar autonomic control at all ages studied.

Catecholamine uptake and storage of the newborn rat heart during post-natal development. GERALD F. ATWOOD and NORMAN KIRSHNER (Intr. by Madison S. Spach). *Duke Univ. Med. Ctr., Durham, N. C.*

The ability of atria, removed from Sprague-Dawley rats at ages 1-21 days, to take up and store catecholamines was studied to correlate this activity with the previously observed physiologic immaturity of the cardiac sympathetic nervous system in the neonate. The cardiac tissue was incubated in Krebs-Henseleit bicarbonate buffer containing 10<sup>-5</sup> M iproniazid and 10<sup>-7</sup> M H<sup>3</sup>-norepinephrine (H<sup>3</sup>NE). Total uptake and subcellular distribution at 1, 4, 7, 14, and 21 days were determined at various time intervals between 5 and 30 minutes. Uptakes at 0°C. served as controls.

Uptake rates were expressed on a per gram wet weight basis. There was a small amount of uptake observed during the first post-natal day (0.515 nanograms/minute) which increased only slightly by 4 days of age (0.683 ng/min). The most significant change occurred between 4 and 7 days (115%). Uptakes at 7, 14, and 21 days were similar to adult values. Since reserpine effectively blocks uptake of catecholamines into the storage granule,

10<sup>-5</sup> M reserpine was added to the incubation media to determine the role of the granule in the previously observed uptake. Reserpine inhibited the 30 minute uptake 57% during the first day of life increasing to 70% inhibition by 7 days of age. The uptake observed in the microsomal (granular) fraction showed similar developmental patterns and effect of reserpine. These studies suggest a marked inability of the newborn rat heart to take up and store norepinephrine due to either decreased number of storage vesicles or an immature uptake mechanism in the granule.

Energy production in the developing heart. ROBERT WELLS, BURTON E. SOBEL, and WILLIAM F. FRIEDMAN. *Univ. of Calif., San Diego Sch. of Med., La Jolla, Calif.*

The influence of growth on myocardial energy metabolism is not clear. Mitochondria are the main source of production of ATP in cardiac muscle. Accordingly, mitochondria from the hearts of 9 fetal and 7 newborn lambs, and 9 adult sheep were isolated in KCl-albumin-EDTA media, studied polarographically, and compared biochemically. No age-related differences were found in P/O ratios, a measure of efficiency of ATP production, with either succinate or glutamate as substrate; or in ATPase activities, in the presence or absence of DNP. However, mitochondria from fetal and newborn animals had significantly increased maximum O<sub>2</sub> consumption/mg protein in the presence of ADP (state III respiration) (0.19 ± 0.01 S.D. and 0.17 ± 0.01 μatoms/min.) compared to the adult (0.10 ± 0.01, p < 0.001). Thus, increased respiratory control ratios, a measure of the dependence of respiratory rate on ADP, were increased in the fetus (12.9 ± 0.6) and newborn (15.6 ± 2.6) compared to the adult (9.5 ± 0.5 p < 0.001). O<sub>2</sub> consumption in mitochondria uncoupled by DNP, was highest in the fetus and newborn (0.30 ± 0.02 and 0.29 ± 0.02 μatoms/mg protein) compared to the adult (0.16 ± 0.01, p < 0.01). These augmented respiratory rates in mitochondria from the youngest hearts may reflect increased electron transport, a view consistent with the finding of 56% of 65% greater cytochrome oxidase activities in fetal and newborn heart mitochondria, respectively, when compared to the adult. Thus, age-dependent differences exist in cardiac energy metabolism that are of potential importance to our understanding of myocardial function in the perinatal period.

Alteration of fetal pulmonary vasculature by maternal hypoxia. STANLEY J. GOLDBERG, RICHARD A. LEVY, BIJAN E. SIASSI, and JOANNE BETTEN. *Univ. of Arizona, Tucson, Ariz., UCLA, and USC Schools of Med., Los Angeles, Calif.*

A syndrome of pulmonary vascular obstruction in the newborn human in which massive right to left shunting occurs through the ductus arteriosus has been recently described. In an effort to simulate the syndrome in an animal model, pregnant rats were maintained in atmospheres containing 13%, 40% and 20% oxygen. The remainder of the atmosphere was nitrogen. In all other respects, pregnant rats were treated the same. Pregnant rats were removed from their experimental atmospheres during delivery so that all newborns were delivered into room air. Newborn rats were sacrificed at birth, the fourth, fifth, tenth, twelfth, thirteenth and twenty-first days of life. The entire lung was sectioned and stained so that intima and media could be easily distinguished. The medial to diameter ratio of all arteries between 50-150 microns (total = 474) were measured according to the technique of Wagenvoort. The mean ratio of neonatal arteries of progeny of hypoxic mothers was significantly thicker for each size group than those born of control or hyperoxic mothers. Thickening

was most pronounced in the smallest arteries. Control and hyperoxic artery groups were similar. Medial thickness decreased in all vessels with age; this decrease was greatest in the control and hyperoxic groups. This study demonstrates that maternal hypoxia produces quantitative changes in the fetal and newborn pulmonary arteries.

The effects of maternal hypoxemia on fetal and infant development. RUTH WHITTEMORE, GERALD ANDERSON, MARCELLO ORZALESI, and SHIRLEY DRISCOLL. *Yale Univ. Sch. of Med., Yale-New Haven Hosp., New Haven, Conn., and Harvard Univ., Boston, Mass.* (Intr. by Charles D. Cook).

Pregnant women with cyanotic cardiac defects have a high percentage of abortuses and infants small for gestational age. The primary aim of this study was to determine the effect of maternal hypoxemia, as measured by arterial blood gas tensions, on fetal and placental development, neonatal adaptation, and subsequent growth and development. 19 women with right-to-left shunts were studied and 21 of the 30 pregnancies resulted in live births. 11 of these infants were small-for-dates, all born to women who had no surgery or only palliative surgery over 10 years ago. Mothers with total correction of these shunts delivered infants of normal size. Urinary estriol excretion during pregnancy was studied in 6 patients; low urinary estriol levels and low arterial blood oxygen tensions ( $P_{O_2} < 60$  mm Hg) were associated with low birth weight of the infants. Placental size was larger than expected on the basis of birth weight. Blood  $O_2$  affinity and red cell 2,3-diphosphoglycerate (DPG) were studied in 2 cyanotic women and in their infants at birth. Blood  $O_2$  affinity was significantly decreased and DPG markedly increased in both mothers; the same changes, although to a lesser degree, were observed in their infants, indicating intrauterine adaptation to hypoxia. The postnatal growth and development of all small infants have equalled or exceeded the normal standards.

Echocardiography in the diagnosis of neonatal congenital heart disease. RICHARD A. MEYER and SAMUEL KAPLAN. *Univ. of Cincinnati, Cincinnati, Ohio.*

Since its introduction in 1954, diagnostic ultrasound has been used to record the movement of atrio-ventricular valves, to measure atrial and ventricular dimensions, left ventricular free wall thickness, left ventricular outflow dimension and to detect the presence of pericardial effusions. In this study echocardiograms were obtained in 50 normal neonates (age 5-96 hours) as part of a control study. In every instance distinct mitral and tricuspid valve echoes were easily recorded. Left ventricular end-diastolic diameters were 1.5-2.0 cm. and the diameter of the left ventricular outflow tract was 0.8-1.2 cm. Echocardiograms were obtained from 16 infants with a variety of cardiac malformations (age 2-16 weeks) in whom diagnoses were confirmed either by cardiac catheterization or autopsy. In 2 babies the diagnosis of hypoplastic left heart syndrome was made because of absence or gross distortion of reflected ultrasound from the mitral valves, and left ventricular end-diastolic diameters which were far below the values observed in our normal neonates. At autopsy the mitral and aortic valves were atretic and the left ventricles hypoplastic in both patients. In 3 babies the clinical diagnosis of hypoplastic left heart syndrome was untenable because of normal mitral valve reflection and left ventricular dimensions. Subsequent cardiac catheterizations confirmed the ultrasonic findings. In another baby the echocardiographic diagnosis of tricuspid atresia was confirmed at autopsy. This technique provides a non-invasive method of evalu-

ating the hearts of neonates. Infants suspected of having the hypoplastic left heart syndrome may be diagnosed by ultrasound without the necessity of cardiac catheterization.

The site of congenital and surgical heart block in children. KENNETH M. ROSEN, ASHWIN MEHTA, SHAHBUDIN H. RAHUMTOOLA, and ROBERT A. MILLER. *Cook County Hosp. and the Univ. of Ill. Col. of Med., Chicago, Ill.*

Catheter recordings of His bundle (BH) electrograms were obtained in five children with asymptomatic congenital heart block (CHB) and two children with symptomatic surgical heart block (SHB). In the SHB patients, block followed repair of tetralogy of Fallot in one and of A-V canal in the other. One patient with CHB had an associated secundum atrial septal defect. A-V dissociation was present in all patients with atrial rates of 80-100 and ventricular rates of 36-52 per minute. In the patients with CHB, BH spikes were unrelated to P waves and preceded every QRS. Intraventricular conduction was normal in four patients with CHB, who had H-Q intervals of 35-40 msec. (normal 35-55) and QRS duration of less than 0.10 seconds. One patient with CHB had a wide QRS (0.12 seconds) with initial delay suggesting type B pre-excitation. In the latter patient, H-Q was only 25-30 msec and the right ventricular (RV) electrogram preceded that of the left, suggesting either anomalous insertion of BH into the RV or an accessory infranodal communication to the RV. In the patients with SHB, H spikes followed P waves with P-H of 125 and 115 msec respectively. In the latter two patients, there was complete block distal to BH.

In conclusion, CHB was characterized by block proximal to the BH recording site (RS), consistent with block in either the A-V node or proximal His bundle. This was in contrast to SHB, where block was distal to the BH RS consistent with a lesion in the distal His bundle.

The effect of respiratory frequency on gas exchange in asthma.

ANDRE LAMARRE, ARTHUR C. BRYAN, ANTHONY MANSELL, and HENRY LEVISON. *Univ. of Toronto and Hosp. for Sick Children, Toronto, Ont., Canada.*

The presence of unequal time constants in the lung should lead to a progressive inequality of ventilation distribution and gas exchange failure at high breathing frequencies. However, in a group of 8 adolescent asthmatics we have not been able to demonstrate such a relationship between breathing frequency and gas exchange. These subjects were trained to alter respiratory rate ( $f$ ) over a wide range while maintaining their arterial carbon dioxide tension ( $P_{aCO_2}$ ) within 3 mmHg of their resting values. At rest ( $f = 14.7 \pm 4.8$ ) the alveolar arterial oxygen gradient (AaDo<sub>2</sub>) was  $37.0 \pm 9.9$ . At an intermediate rate ( $f = 30.0 \pm 3.77$ ) the AaDo<sub>2</sub> rose significantly to  $39.4 \pm 8.5$ . At high rates ( $f = 104.5 \pm 18.9$ ) the AaDo<sub>2</sub> fell significantly to  $34.1 \pm 9.4$ . The validity of alveolar arterial gradients at high rates is doubtful, but a similar effect although not significantly different, was seen in the arterial oxygen tension: rest  $72.3 \pm 9.00$ , intermediate  $70.4 \pm 7.3$ , fast  $73.3 \pm 9.5$ . There was no significant difference in alveolar ventilation (rest  $4.95$  L/min  $\pm 1.38$ , intermediate  $5.31 \pm 1.51$ , fast  $5.76 \pm 1.55$ ). To explain this conservative behaviour, we have postulated that the regional resistances and compliances must be non-linear acting in a direction to equalize the ventilation distribution as frequency increases. In non-laminar flow, resistance is flow dependent and over-distention of regional units will reduce their compliance. Both these factors will tend to stabilize distribution.