- **277** THE DEVELOPING FETAL CANINE HEART: EFFECTS OF ELECTRICAL STIMULATION AND ACETYLCHOLINE. Jeffrey P. Moak, Allan J. Hordof, Peter Danilo Jr., Columbia University, Department of Pediatrics, N.Y., N.Y. 10032

We studied the electrophysiologic characteristics of intact fetal canine hearts perfused with physiologic salt solution via an aortic cannula. Epicardial stimulating and recording electrodes were placed on the right atrium and ventricle. Electrophysiologic variables were measured during both spontaneous sinus rhythm and atrial stimulation. Hearts from 2 groups of fetuses were studied: Group I, gestational age=38 days; Group II, gestational age=50 days. (Total gestation =63 days). The spontaneous sinus cycle length (CL) was: Group I 289 ± 7.8 and Group II 284 ± 14.3 msec (X $\pm$ SE) (P>.1) corrected sinus node recovery time (CSNRT) was: Group I 75 ± 4.1 msec and Group II 110 ± 8.6 msec (P<.005). Acetylcholine (ACh) 1×10^{-8} M, increased Group I CSNRT to 112 ± 9.2 msec (P<.001) but had no effect on CSNRT of Group II. There was no significant difference in the shortest paced CL with 1:1 A-V conduction: 162 ± 7.8 msec (Group I) and 150 ± 0.4 (Group II) (P>.1). The threshold concentrations of ACh to significantly increase the CL at which 1:1 A-V conduction occurred were 1×10^{-8} M for Group I and 1×10^{-7} M for Group II. Wenckebach periods occurred (for Group I) at CL= 278 ± 13.1 msec and at 216 ± 10.3 msec for Group II. Atrial effective and functional refractory period were: Group I 63 ± 7.2 msec and 73 ± 6.2 msec, and Group II 58 ± 6.5 and 68 ± 6.5 msec, (P>.1). ACh had no effect on atrial refractory periods. These data indicate that there are functional differences in electrophysiologic properties of the developing canine fetal heart and that there are changes related to development in the effects of ACh.

- **278** RENAL PROSTAGLANDIN E₂ SYNTHESIS (PG SYN) AND DEGRADATION (PG DEG) IN THE DEVELOPING RAT. Donald Moel, Richard Cohn, and John Penning, (Spon. by Carl Hunt). Northwestern Univ., Children's Mem. Hosp. Dept. Peds., Chicago.

Postnatal development of GFR and RBF is associated with a fall in renal vascular resistance that may be mediated by vasoactive substances. We examined differences in the regulation of one such substance, PGE₂. The present studies examined renal cortical (C) and medullary (M) PG syn and PG deg in neonatal rats (N) aged 17 days (30.7g), young rats (Y) 33 days (101g), and adult rats (A) 120 days (413g). PGE₂ syn from ¹⁴C-arachidonic acid was determined in C and M microsomes by thin layer chromatography (TLC). PGE₂ degradation was determined by following the disappearance of ³H-PGE₂ substrate in cytosolic fractions of C and M by TLC. Mean values ($\pm$ 1SE) for PG syn (% arachidonate conversion) and PG deg (% PGE₂ disappearance) are shown below: * = p<0.05, N vs Y; † = p<0.05, Y vs A; ‡ = p<0.05, A vs N; (n) = number of animals.

	PG syn		PG deg	
(n)	Cortex	Medulla	Cortex	Medulla
N (5)	$5.0 \pm 0.2^*$	$4.7 \pm .2^*$	$41.7 \pm 0.9^*$	$27.4 \pm 1.3^*$
Y (6)	$2.5 \pm 0.2^†$	$8.8 \pm .7^†$	$21.5 \pm 4.4^†$	$12.2 \pm 4.7^†$
A (6)	$1.1 \pm 0.1^‡$	$12.3 \pm .4^‡$	$5.5 \pm 2.6^‡$	11.0 ± 3.4

PG syn in C microsomes is highest in N rats and decreases with age; in contrast M PG syn is lowest in N rats and increases with age. Both C and M PG deg are highest in N rats and decrease with age. These studies demonstrate for the first time that significant age dependent differences in regional PG syn and deg exist in the developing rat kidney. The elevated synthesis of vasodilating PG's in the cortex may play a causal role in the increases in renal perfusion and glomerular filtration typical of the developing kidney.

- **279** INCREASED UPTAKE OF SO₄ BY CARTILAGE OF FETAL SHEEP PERFUSED WITH SO₄ COMPARED TO THEIR TWINS. Frank H. Morriss, Jr., Brian Fitzgerald, and Lavon Riddle.

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To test the hypothesis that fetal skeletal growth decreases in late gestation because the reported decline in serum sulfate conc ([SO₄]) limits SO₄ for incorporation into glycosaminoglycans by cartilage, 6 fetal sheep were perfused with Na₂SO₄ 2.2 g/h i.v. for 7 d. As controls, the twin of each fetus was perfused with equimolar NaCl. Costal cartilage was harvested at x GA=134 d and assayed in vitro for ³⁵SO₄ uptake (QSO₄, μ g/24h/mg cartilage adjusted per mg SO₄/tube) in the presence of 0, 10% and 20% normal human serum (NHS). Sera sampled before and during perfusion were assayed for [SO₄].

Results:	QSO ₄ @ 0%	QSO ₄ @ 10%	QSO ₄ @ 20%	Final [SO ₄]
SO ₄ -perf	6.24 ± 0.81	13.09 ± 1.85	18.69 ± 2.61	34.48 ± 4.02
Control	5.25 ± 1.03	9.64 ± 1.77	15.01 ± 2.39	12.20 ± 2.17
p (pr'd t)	<0.025	<0.025	<0.05	<0.005

Pairwise comparison of twin fetuses reveals SO₄-perfusion produces a 34-47% increase in QSO₄ independent of [NHS], compared to the ~300% increase in QSO₄ produced by 20% NHS. Fetal wt, length, and sex were not different between groups. These results demonstrate that although late fetal cartilage in vitro QSO₄ may be increased by elevating the fetal serum [SO₄], other serum factors are more important determinants of fetal cartilage metabolic activity. The decrease in [SO₄] observed from mid-gestation to term likely represents depletion of the SO₄ pool by fetal growth processes rather than a decreased availability of SO₄ that restricts growth.

- 280** EXPRESSION OF A COMMON ANTIGEN BY FETAL CEREBELLAR NEURONS AND ASTROCYTES. Thomas J. Moss and Robert C. Seeger, Department of Pediatrics, UCLA, Los Angeles.

Nervous system markers can provide information on maturation, differentiation, and intercellular interactions. Monoclonal antibody 459 (ab 459), was previously found to react strongly with fetal brain, and moderately with adult brain. The objective of this study was to determine which neural cells express the antigen (ag 459) defined by ab 459. Brains obtained within 12 hours postmortem from adults and a 22 week fetus were frozen and sectioned with a cryostat. They were fixed with acetone, incubated with ab 459, followed by biotinylated anti-mouse immunoglobulin, and then avidin-biotin-peroxidase complexes. Ag 459 is expressed by fetal neurons in the external granular layer of cerebellum; these same cells were negative for glial fibrillary acidic protein and neuron specific enolase (NSE). Ab 459 also labelled morphologically mature fetal neurons, which were NSE positive, in a cerebellar nucleus. Adult cerebellar neurons of the granular layer, which are derived from fetal external granular layer, and all adult cortical neurons did not display ag 459. Both adult and fetal astrocytes expressed ag 459. Ag 459 is the first antigenic determinant to be defined on human fetal neurons in the external granular layer of the cerebellum. The expression of this determinant on these cells, but not their mature derivatives, suggests that ag 459 is a stage specific marker for cerebellar neuron development. Astrocytes assist in migration of cerebellar fetal neurons in vivo, and the presence of ag 459 on fetal astrocytes and fetal neurons raise the possibility that this marker may be involved in the migration process.

- 281** COMBINED HORMONAL THERAPY MAY DECREASE THE TIME NEEDED FOR INDUCTION OF LUNG SURFACTANT PRODUCTION. Fernando Moya, Ian Gross. Yale Univ Sch of Med, Department of Pediatrics, New Haven, CT.

Failure to induce fetal lung maturation and prevent RDS after maternal administration of corticosteroids, is sometimes due to delivery of the fetus before 48 h have elapsed after maternal injection. Recent evidence suggests that combinations of hormones such as corticosteroids and thyroid hormones have an additive effect on the induction of pulmonary phosphatidylcholine (PC) synthesis. The aim of this investigation was to determine whether the use of combined therapy with betamethasone (beta) and triiodothyronine (T₃) would elicit a faster induction of surfactant production in the fetal rat.

Timed pregnant Sprague-Dawley rats were injected with betamethasone (1 mg/kg), T₃ (7 mg/kg) or both, at 6, 12, 18, 24, 36, or 48 h prior to day 20 of gestation. These doses (administered to the mother), were previously shown to be optimal for stimulation of surfactant synthesis in the fetal rat. On day 20 all the fetuses were delivered, the lungs were removed and the rate of choline incorporation into PC was determined in lung minces.

The 36 h value obtained with beta alone was not significantly different from the control, whereas the T₃ + beta value was. At present, however, the difference between the 36 h combination and beta groups has not achieved statistical significance. After 48 h the difference between the 2 groups was greater (beta $26.0 \pm 10.9\%$ stimulation, T₃ + beta $56.0 \pm 9.6\%$).

The use of combined hormonal therapy may decrease the time required for induction of lung surfactant production.

- 282** ACETAMINOPHEN ACCUMULATION IN PEDIATRIC PATIENTS AFTER REPEATED THERAPEUTIC DOSES. Milap C. Nahata, Dwight A. Powell, Diane E. Durrell, Marcia A. Miller, Ohio State University Colleges of Medicine and Pharmacy, Children's Hospital, Department of Pediatrics, Columbus, Ohio.

Acetaminophen is commonly used to control fever but little is known about its kinetics in infants and children after repeated doses. Twenty-one patients (age 0.5-6.4 yrs) with fever received acetaminophen elixir at a dose of 72-90 mg/kg/day given in divided doses as 12-15 mg/kg every 4 hr or 24-30 mg/kg every 8 hr. Multiple blood samples were collected and analyzed by HPLC after the first dose and/or at steady-state (1-3 days of therapy). Maximum acetaminophen serum concentration ranged from 10.2-19.6 μ g/ml in patients on every 4 hr schedule and 13.9-40.1 μ g/ml in those on every 8 hr schedule. Area under the serum concentration-time curve (AUC) normalized for dose/kg averaged 0.209 (ml/min/kg)⁻¹ and elimination half-life averaged 2.3 hr. In 10 patients, total normalized AUC averaged 0.181 and 0.202 (ml/min/kg)⁻¹ after the first dose and at steady-state, respectively (p<0.05). Five patients showed a 13.2-43.5% increase and one had a 10.4% decrease in AUC; four had <6% change in the AUC. There was no evidence of hepatotoxicity. These data suggest that acetaminophen may accumulate after repeated therapeutic doses in children with fever.