● 403 STIMULATION OF NEONATAL HEPATIC UDP-GLUCURONYLTRANSFERASE ACTIVITY WITH PRENATAL THYROID ANALOG THERAPY.

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Unconjugated hyperbilirubinemia is often observed in congenital hypothyroidism, due to impaired activity of the bilirubin-conjugating enzyme UDP-glucuronyl transferase (UDPGT-ase). This enzyme is tighly membrane bound and is dependent on membrane physical state, which varies with thyroid status and maturation. We examined the effects of maternal treatment with the non-halogenated thyroid analog, 3,5-dimethyl, 3'- isopropyl thyronine (DIMIT,0.5 ug/100gm/d) to rats whose fetuses had been rendered hypothyroid (HYPO-Tx) by maternal propylthiouracil. Neonatal pups were sacrificed and liver microsomes prepared for assessment of UDPGT-ase activity (nM/mg/min). Membrane fluidity was determined by fluorescence polarizaton (FP)

	CONTROL	HYPO-Tx	HYPO-Tx+DIMIT
UDPGT-ase	2.65+.33*	1.42+.11	6.4+.21**
FP @25°C	.169+.027*	.179+.020	.165+.006

* = p<0.02, **p<0.001 vs.HYPO-Tx

Neonatal HYPO-TX was associated with reduction of UDPGT-ase activity, in comparison to euthyroid controls. Prenatal treatment with DIMIT stimulated the suppressed enzyme activity in HYPO-Tx. There was an inverse correlation between membrane fluidity (FP) and enzyme activity (r=-.51, n=23, p<0.05). Conclusion: Impaired conjugation of bilirubin in congenital hypothyroidism is the direct result of reduced membrane fluidity. Both of these defects can be reversed by prenatal treatment with DIMIT, a thyroid analog which readily crosses the placenta.

● 404 COMPARATIVE EFFECTS OF ACUTE HYPOXEMIA (H) ON CARDIOVASCULAR RESPONSES TO DOPAMINE (Dp), DOBUTAMINE (Db) AND ISOPROTERENOL (Ip) IN NEONATAL SWINE.

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Two week old piglets were anesthetized and ventilated; the ductus arteriosus was ligated. ECG, aortic (AO) and LV pressures (P), LV dP/dt max, and phasic pulmonary (cardiac output, CO), mesenteric (Mes) and renal (Ren) flows (F) were recorded. Sequential 10 min infusions of Ip (n=8) 0.05, 0.1, 0.2 mcg/kg/min, Dp (n=6) 2, 5, 15 or Db (n=7) 2, 5, 15 mcg/kg/min were given during normoxemia (NO; PO_2 103±4 mmHg) and repeated during H (PO_2 39±1 mm Hg). In 8 age-matched controls saline was infused and no significant (NS) changes observed. Mean percent change ± SE ($p \leq 0.05$) to the highest doses are presented.

	Dp		Db		Ip	
	NO	H	NO	H	NO	H
LV dP/dt max	114±31	93±21	56±15	30±12	42±8	NS
CO	25±9	26±10	13±3	20±5	21±8	NS
HR	42±7	25±4	43±8	14±4	26±5	9±3
AoP	20±4	NS	NS	NS	NS	NS
TaR*	NS	NS	NS	NS	-14±6	NS
MesR	-27±10	NS	NS	NS	-13±4	NS
RenR	27±9	NS	NS	NS	NS	NS

*Ta = total arterial; R = resistance

Conclusion: 1) Dp maintained increments in LV inotropy and CO during H, while Ip did not. Db increased CO, but increases in inotropy were attenuated during H. 2) Chronotropic effects of all three drugs were attenuated by H. 3) Peripheral vascular effects during NO were not sustained during H by any drug. 4) The data suggest that Dp is most, and Ip is least effective in eliciting beneficial cardiac responses in hypoxic newborns.

† 405 POSTNATAL β-ADRENERGIC THERAPY AUGMENTS SURFACTANT RELEASE IN PREMATURELY DELIVERED RABBITS.

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Prenatal exposure to β-adrenergic agonists, such as terbutaline (T), augments surfactant release in rabbit fetuses. The impact of postnatal (T) administration to prematurely delivered rabbit pups, however, remains largely unexplored. We postulated that surfactant release would also occur with postnatal (T). To explore this, premature rabbit pups of known gestation (28-30d) were randomized at delivery into (T) or placebo (P) groups. (T) (5.8-8.8 mg/kg) or (P) was injected i.p. within 5 min of delivery. Thirty min after injection, pups were sacrificed and evaluated for total lung capacity (TLC), lung deflation stability, and lung lavage disaturated phosphatidyl choline (DSPC). (T) and (P) pups had similar birthweights, survival characteristics, TLC, and dry lung weights (DLW). 28d (T) pups demonstrated improved deflation stability at 7 & 5cmH_2O and increased DSPC. Data: 28d pups (2 litters: 4 pups/group/litter)

GROUP	DEFLATION STABILITY (%TLC) 7cmH_2O	5cmH_2O	DSPC(ug/gm DLW)
(T) X±SEM	63±5	49±4	194±14
(P)	55±5	41±6	139±22

Additionally, 29 and 30d (T) demonstrated increased DSPC despite "mature" deflation stability indistinguishable from (P). Our results suggest that postnatal (T) augments surfactant release in prematurely delivered rabbits, and may suggest a future role for early β-adrenergic therapy of hyaline membrane disease.

† 406 PROPHYLACTIC INDOMETHACIN: EFFECTS ON RENAL FUNCTION.

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This controlled, double-blind, study assessed the renal impact of early (< 12 hr postnatal age) indomethacin [I], for prevention of patent ductus arteriosus (PDA), in O_2 dependent inborn infants with birth weights (BW)≤1300 gm. Fifty infants randomly received 3 IV doses of [I] or placebo [P] at 12 hr intervals. Dose$_1$ (D_1) was 0.2 mg/kg;D_2 and D_3 were 0.1 mg/kg each. Fluid balance, serum sodium (Na), potassium (K), creatinine (Cr), blood urea nitrogen (BUN) and fractional Na excretion (FE_{Na}) were evaluated pre-D_1, 6-12 hr post-D_1, 12-36 hr post-D_3, and 1 wk post-D_3. Timed urine specimens were used to derive Cr clearance (C_{Cr}) post-D_3 and 1 wk post-D_3. The 25 infants in each group were comparable in BW, gestational age, APGARs, pH and base excess at study entry. [I]-treated infants had reduced urine output (UO) in the 12 hr period following D_1 that was no longer evident post-D_3. Fluid intake, Na, K, BUN, Cr, FE_{Na}, and C_{Cr} were similar throughout the study. Renal data (x±SEM) revealed:

		6-12 hr post-D_1	12-36 hr post-D_3	1 wk post-D_3
UO (% intake)	[I]	39.6 ± 6.2]*	70.9 ± 4.8	61.0 ± 3.2
	[P]	61.2 ± 6.2	74.3 ± 7.2	59.6 ± 3.6
FE_{Na}(%)	[I]	3.5 ± 1.1	4.9 ± 0.8	5.1 ± 1.4
	[P]	2.8 ± 0.7	5.2 ± 0.8	3.2 ± 0.4
C_{Cr} (ml/min/kg)	[I]	----------	0.49 ± 0.09	0.77 ± 0.13
	[P]	----------	0.51 ± 0.11	0.48 ± 0.07

* represents p<0.05 between [I] and [P]

In contrast to reports of renal dysfunction induced by indomethacin therapy for symptomatic PDA, early [I] appears to alter renal function minimally in prematures without significant PDA.

† 407 ONTOGENY OF RAT LIVER MICROSOMAL UDP-GLUCURONOSYL TRANSFERASE (UDP-GT) ACTIVITY TOWARD FUROSEMIDE(F)

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Disposition of F depends on its renal tubular secretion and its metabolic conjugation with glucuronic acid. It has been suggested that decreased F clearance in the neonatal period is due to immaturity of these dispositional pathways. The development of UDP-GT activity in the perinatal period falls into two substrate specific groups: a "late fetal" group of activities that attain adult levels just before term and an "early neonatal" group that shows minimal activity during pregnancy but increases rapidly after birth. The "late fetal" group correlates with activities that are induced by 3-methylcholanthrene (3MC) type inducers while the "early neonatal" group correlates with phenobarbital (Pb) induction in adult rats. We have studied the ontogeny and inducibility of UDP-GT activity toward F (F-UDP-GT) in fully activated rat liver microsomal preparations. During days 18 and 20 of gestation and third and sixth postnatal days, liver F-UDP-GT activities were 3%, 9%, 57% and 80% of adult activity (373±21 pmoles/mg protein/min), respectively. After treatment of adult rats with F, Pb, 3MC or pregnenolone-16-alpha-carbonitrile (PCN), F-UDP-GT activity was 310±24; 617±84; 864±185 and 1010±73 pmoles/mg protein/min respectively. It is concluded that F-UDP-GT activity develops in the early neonatal period, and is inducible by not only Pb, but even more so by 3MC and PCN.

408 VITAMIN E CONTENT OF TISSUES OBTAINED FROM HUMAN INFANTS GIVEN PHARMACOLOGIC DOSES OF TOCOPHEROL OR TOCOPHERYL ACETATE INTRAVENOUSLY.

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Tissues obtained from infants who had received varying doses of vitamin E were analyzed for tocopherol (T) and tocopheryl acetate (TA) content by HPLC. IV administration of TA (27-48 U/kg/day for 9-42 days) resulted in liver TA levels from 30-500 ug/g and T levels from 0-4135 ug/g. TA and T levels in kidney tissue ranged from 0-36 ug/g and 0-189 ug/g, respectively. The method of tissue preservation employed (type of fixative, storage temperature) may account for the lower range of TA and T values observed in these tissues. Lower IV doses of TA (3-6 U/day for 21-52 days) resulted in levels of TA in liver of 0-27 ug/g and T levels of 12-30 ug/g. One infant given a single 20 mg/kg IV dose of T 3 hrs prior to death had 382 ug/g of T in the liver and no TA. Infants given only nutritional amounts of T or TA orally (2-25 U/day) have T levels of less than 20 ug/g in the liver, kidney, and lung.

These results indicate that the amounts of T and TA are significantly increased in tissues, particularly the liver, in infants receiving pharmacologic doses of TA intravenously. The significance of T and TA tissue levels relative to efficacy or toxicity of vitamin E therapy in infants remains to be established.