● 1706 DIHYDROTESTOSTERONE (DHT) INHIBITS FETAL PULMONARY SURFACTANT PRODUCTION IN VIVO.

H.C. Nielsen, H.M. Zinman and J.S. Torday (Spon by H.W. Taeusch, Jr.), Harvard Medical School, Dept. Pediatrics, Boston, MA.

Pulmonary surfactant production, measured by the saturated phosphatidylcholine/sphingomyelin (SPC/S) ratio, is delayed in male rabbit fetuses at 26 to 28 days' gestation (Nielsen and Torday, Ped Res 14:459, 1979). We have observed that the SPC/S ratio in lung lavage (LL) of female fetuses is quantitatively related to the number of neighboring male fetuses, suggesting that the sex difference is hormone-dependent. Therefore, we administered DHT to pregnant rabbit does daily from the 12th postconceptional day. Doses of 25mg, 10mg and 1mg/day were used to show a dose/response relationship. The fetuses were delivered on the 26th day. The fetal lungs were lavaged with 5 x 0.5ml aliquots of iced saline. Fetal sex was determined by inspection of the gonads. Phospholipids were extracted from LL, chromatographed and then measured by spectrodensitometry. All DHT doses eliminated the sex difference in the LL SPC/S ratio. Increasing doses of DHT correlated significantly with lower mean SPC/S ratios ($p<.05$). The DHT effect was apparently organ-specific since there was significant inhibition of fetal lung alkaline phosphatase activity with no detectable effect on fetal duodenal alkaline phosphatase activity. This is the first evidence of a steroid hormone delaying pulmonary surfactant production. These findings suggest a hormonal basis for the known male disadvantage in the Respiratory Distress Syndrome of the newborn.

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1707 SURFACE TENSION HYSTERESIS IN LUNG SURFACTANT FILMS: ETIOLOGY AND PHYSIOLOGIC CONSEQUENCE.

Robert H. Notter and Richard D. Mavis (Spon. by Donald L. Shapiro) U.of Roch. School of Med., Strong Mem. Hosp., Dept. of Peds., Roch., NY

Far more effort has been applied to the measurement of minimum surface tension (σ_{min}) in lung surfactant films than to the identification of specific surfactant components responsible for surface tension-area (σ-A) hysteresis, or to the possible physiologic consequences of particular hysteresis characteristics. In this work we show that saturated phospholipids (primarily dipalmitoyl phosphatidylcholine, DPPC), not only act to allow the generation of low σ_{min} as known previously, but also confer on lung surfactant the particular σ-A hysteresis characteristic of an abrupt surface tension rise over a small area increment at the start of film expansion. This rapid rise in σ can be shown to exist even if a surface excess of surfactant is present at the interface during film compression, and results from the constrained surface re-entry properties of DPPC. This large, rapid surface tension increase should be of basic import for the recruitment of different sized alveoli during inspiration, and hence for the uniform expansion of the alveolar network. Consideration of σ-A hysteresis characteristics in combination with the development of low σ_{min} allows a view of lung surfactant function in vivo that is consistent with clinical findings in neonatal RDS, and with recent views of alveolar network stability on expiration and alveolar shape changes on inspiration. This implies that characterization of lung surfactant activity by σ_{min} or "Stability Index" criteria alone may be misleading, for these variables do not account for any hysteresis effects (Supp. by HL-25170)

1708 INTERACTIONS OF UNCONJUGATED BILIRUBIN WITH PHOSPHOLIPID COMPONENTS OF LUNG SURFACTANT.

Robert H. Notter, Donald L. Shapiro and Richard D. Taubold. U. of Roch. School of Med., Strong Mem. Hosp., Dept. of Peds., Rochester, NY.

This work examines the surface tension-area (σ-A) behavior of mixed films of unconjugated bilirubin with dipalmitoyl phosphatidylcholine (DPPC) and 9:1 DPPC:di-oleoyl phosphatidylcholine (DOPC) at 22°C on 0.15M NaCl and buffered phosphate subphases (pH=5.5, 7.4 and 8.0). Also pure films of unconjugated bilirubin spread from chloroform solution are studied under similar temperature and pH conditions. In pure films bilirubin is found to be a surprisingly surface active molecule able to reach minimum surface tension values of ~10 dynes/cm at pH5.5. In mixed films bilirubin exhibits interfacial interactions with DPPC and DPPC:DOPC in both high and low surface tension regimes. Most importantly bilirubin acts to increase respreading in films of DPPC and 9:1 DPPC:DOPC compressed past collapse, without any meaningful increase in the minimum surface tension achieved. Interactions in spread films of bilirubin-phospholipid are of greatest magnitude at low pH values (5.5), where bilirubin is constrained to remain at the interface by virtue of negligible subphase solubility. The interactions decrease as pH increases to physiologic values and beyond (7.4 and 8.0), consistent with concomitant increases in bilirubin solubility. Many infants with neonatal RDS also suffer hyperbilirubinemia with possible deposition of bilirubin in the alveoli (yellow hyaline membranes). Our results suggest that this bilirubin does not impair the activity of pulmonary surfactant in vivo, but further experiments with more complex films and subphases at body temperature would be required to make this definitive (Supp. by HL-25170)

1709 SURFACTANT CHOLESTEROL AS RELATED TO RESPIRATORY DISTRESS IN PREMATURE INFANTS.

Rosa M. Ortiz, M.Douglas Cunningham, Nirmala S. Desai, Dept. of Pediatrics, Univ. of Kentucky, Lexington (Spon. by Jacqueline A. Noonan).

The role of cholesterol in surfactant is poorly understood, but it is known to decrease lung surface-tension reducing properties in vitro. We studied lipid components of 24 tracheal aspirates from 16 mechanically ventilated infants, 29-36 wk gestation with respiratory distress (preterm A) and pharyngeal aspirates from 5 normal newborns. Mean airway pressure ($\bar{P}aw$) was used as an index of noncompliant lung disease. Cholesterol (Chol) and phospholipids were quantified by thin-layer chromatography and reflectance densitometry. Surfactant of preterm A and normal infants was not significantly different except for diminished phosphatidylglycerol (PG). However, a subgroup of preterm A (preterm B; n=7) had mature lecithin:sphingomyelin ratios (L:S), but reversed lecithin:chol ratios (L:C). The data (±SEM) are as follows:

	Normal	Preterm A	Preterm B	P
Lec	30.7 ± .3	30.7 ± 2.3	19.6 ± 2.2	<.01
Sph	6.4 ± .2	8.5 ± 1.4	6.9 ± 1.2	NS
PG	6.8 ± 2.4	Trace	0	
Chol	23.8 ± 3.1	30.4 ± 3.3	43.4 ± 6.1	<.05
L:S	7.1 ± 1.4	4.7 ± .7	3.4 ± .9	<.05
L:C	1.7 ± .1	1.5 ± .2	.5 ± .1	<.01

Preterm B infants required 17.3% greater $\bar{P}aw$ than preterm A infants (9.63 ± 1.6 SEM vs 7.96 ± .6 SEM). Despite a mature L:S, some preterm infants had added lung disease requiring increased $\bar{P}aw$ when the relationship of Lec to Chol was reversed.

1710 CYSTIC FIBROSIS AND PREGNANCY - PREDICTIVE FACTORS.

Judy Palmer, Cindy Dillon-Baker, Jan S Tecklin, Edward M Sewell, Loretta P Finnegan. Phila Regional Pediatric Pulmonary Disease Program. St Christopher's Hosp for Children, Hahnemann Medical College and Hosp, Thomas Jefferson Univ Hosp, Children's Hosp of Phila. Dept of Pediatrics. Phila.

With improved survival in cystic fibrosis (CF), women with CF are now seeking advice about the risk of pregnancy. To identify predictive factors, 8 pregnancies in 7 women, evaluated within 1 year prior to conception, were studied. Five pregnancies occurred in 4 women who did well (Group I) and 3 pregnancies occurred in 3 women who deteriorated and did not regain pregravid nutritional or pulmonary status post partum (Group II).

Pregravid Status	($\bar{x}$ ± SD)	{Group I}	{Group II}	{p Value}
Weight	(kg)	56 ± 7	44 ± 4	< 0.025
Vital Capacity	(% pred)	93 ± 6	62 ± 7	< 0.005
Residual Volume	(% pred)	108 ± 4	171 ± 16	< 0.005
FEV_1/FVC	(%)	78 ± 12	54 ± 9	< 0.025
FEF 25-75	(% pred)	59 ± 34	15 ± 5	< 0.05
Radiograph Score	(Brasfield)	22 ± 2	12 ± 5	< 0.005

The groups were similar in age and height. Group I had better weight gain during pregnancy, fewer hospitalizations, normal length gestation and normal birth weight infants. There were no deaths during pregnancy, however, 2 women in Group II died post partum. Although 2 infants of Group II mothers were premature, all infants survived and none had CF. These data suggest that comprehensive assessment of pulmonary and nutritional status is useful to predict the maternal outcome of pregnancy in CF.

1711 FETAL LUNG DEVELOPMENT IN THE SUBHUMAN PRIMATE (MACACCA MULATTA).

R.H. Perelman, M.J. Engle, J.W. Kemnitz, R.V. Kotas and P.M. Farrell, Univ.of Wisc., Madison, Wi.53792

Previous studies in subhuman primates have encompassed the entire third trimester to profile general patterns of fetal lung development(FLD); however, this work has not expanded the data base at key gestational ages(GA) to elucidate precise developmental changes. Accordingly, we have performed comprehensive pulmonary physiologic and biochemical analyses in 17 nonbreathing rhesus fetuses delivered by C-section at 4 gestational ages(term=165 days). Lung data including phosphatidylcholine(PC) and phosphatidylglycerol(PG) are presented in the table below(per gram wet wt) as mean±S.E. values. Marked changes in phospholipids were noted at

GA (N)	wt gms	PC µmole	DSPC µmole	PG nmole	Glycogen mg	DNA mg	V max cc
135(5)	325 ±46	5.4 ±.4	1.6 ±.3	17.3 ±9.7	6.2 ± 1	8.5 ±.6	1.3 ±.7
145(5)	390 ±19	4.9 ±.4	2.1 ±.2	19.8 ±6.7	4.0 ±.4	7.6 ±.4	1.9 ±.2
155(5)	460 ±38	8.1 ±.8	3.8 ±.6	74.5 ±50	3.2 ±.6	9.0 ±.6	2.0 ±.1
162(2)	561	11.2	5.5	208(1)	.89	6.9	3.3

155 days GA. Additionally, lung protein, wet weight, $\%V_{10}$ and selected fatty acids in PC increased with advancing GA. Although parallel increases occurred in lung PC, DSPC and PG, mature physiologic indices were obtained later in gestation. Furthermore, amniotic fluid analyses revealed no clear relationship between PG concentration and lung maturation.