1712 A PRIMATE MODEL FOR THE STUDY OF FETAL LUNG DEVELOPMENT IN THE GLUCOSE INTOLERANT PREGNANCY.

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A procedure which reliably produces an insulin dependent state of glucose intolerance in Macaca mulatta is described, along with normal glucose disappearance rates(K) in adult female macaques and biochemical and physiologic indices of fetal lung development(FLD) in 3 diabetic progeny(IDM) and 5 matched controls. After an initial observation period and an IV glucose tolerance test, female monkeys received 47.5mg/kg of freshly mixed streptozotocin by rapid central intravenous injection. Subsequently the mean glucose disappearance rate was markedly decreased from 5.63±1.36% per min to 1.30±0.52% per min(P<.001) and no insulin response could be demonstrated. Fasting plasma glucose values averaged 245mg/dl and glycosylated hemoglobin levels were markedly elevated($\bar{x}$=14.7%). Urine volume was increased from 236±99ml/day to 1261±264ml/day(P<.001)and urine glucose from 10±3mg/dl/day to 4237±608mg/dl/day(P<.001). Lung biochemical analyses including phosphatidylcholine(PC) and phosphatidylglycerol(PG) are represented below(per gram wet wt) for fetuses delivered by C-section at 145 days gestation(term =165±3days). PG was not demonstrable in any of the 7 amniotic

	PC(µmole)	PG(nmole)	DSPC(µmole)	Glycogen(mg)	DNA(mg)
Controls(N=5)	4.94±.38	19.8±6.7	2.10±0.19	4.01±.35	7.63±42
IDM-LGA(N=2)	4.66	10.1	1.85	5.37	8.82
IDM-SGA(N=1)	6.97	576	3.34	3.80	7.99

fluid samples analyzed and other lung indices (Te $\%V_{10}$, Vmax,Vmin) did not vary significantly from controls. Weights for IDM were strikingly abnormal at 629, 529 and 341 gms vs 390±19 gms for controls. Mean maternal/fetal plasma glucose values at birth were 203/147 mg/dl for diabetics and 45/39 mg/dl for controls. In this pilot study, fetal animals with somatic features of IDM and altered FLD compared to controls were obtained. Therefore, this model provides an apt homologue for human diabetes.

● 1713 INCREASED MONOCYTE CHEMILUMINESCENCE IN CYSTIC FIBROSIS PATIENTS AND OBLIGATE CARRIERS.

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Because cultured fibroblasts from patients with cystic fibrosis (CF) and their obligate carriers (CR) have been shown to have increased oxygen uptake, we reasoned that purified peripheral blood monocytes from CF and CR might show increased radical formation compared to age and sex-matched controls (CT). Monocytes were purified, counted and placed in media containing 10^{-6} M luminol. Chemiluminescence after stimulation 1) by opsonized zymosan particles or 2) by adherence to glass liquid scintilation vials was measured by a liquid scintilation counter and expressed as peak CPM/monocyte. When maximally stimulated with pre-opsonized zymosan particles monocytes from CF, CR and CT generated essentially equivalent amounts of chemiluminescence. However, after stimulation by adherence to glass scintillation vials, monocytes from both CF (n = 5) and CR (n = 5) generated significantly greater amounts of chemiluminescence than their respective controls (CF: 3.5 ± 0.5 vs CT: 1.2 ± 0.6, p = .001; CR: 2.7 ± 0.8 vs CT: 1.3 ± 0.5, p = .01). Moreover, peak chemiluminescence produced by CF monocytes after adherence was significantly higher than CR monocytes (p < .05).

Thus the monocytes from both obligate carriers and patients with CF respond to membrane stimulation triggered by attachment to glass with increased oxygen radical formation as measured by chemiluminescence. This assay may be useful for detecting the carrier state of cystic fibrosis.

1714 UPPER AIRWAY OBSTRUCTION IN THE SUDDEN INFANT DEATH SYNDROME (SIDS).

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Acute airway obstruction in the pharynx or larynx causing asphyxia is a proposed cause of SIDS and "near miss" SIDS. Documentation of these events in such cases is rare. We studied 2 infants at high risk for SIDS in whom absent respiratory efforts alternating with obstructed respiratory efforts (i.e., mixed apnea) produced episodes of asphyxia. Infant A (28wk gestation) had apnea and bradycardia spells through the first month of life. In polygraphic studies at 5days of age (heart rate, abdominal excursion, nasal and oral airflow, $TcPO_2$), we identified 9 mixed apnea spells causing hypoxemia ($TcPO_2$ as low as 29Torr) and bradycardia (as low as 33bpm). This infant died at home of SIDS (autopsy diagnosis) at 14wks of age. Infant B, a thriving 32wk gestation infant, had a family history of SIDS (half sibling) but no history of apnea or bradycardia until 4wks when he required resuscitation for sudden cardio-respiratory arrest (i.e., "near miss SIDS"). Spells of apnea, cyanosis and bradycardia recurred for 4wks in this otherwise healthy infant. We monitored 4 episodes of mixed apnea, each causing hypoxemia ($TcPO_2$ as low as 36Torr) and bradycardia (as low as 70bpm). In infant B we found the site of obstruction to be above the larynx by using a pharyngeal catheter which detected transmission of thoracic pressure during obstructed breaths. Documentation of mixed apnea causing asphyxial spells in these at risk and subsequent SIDS infants supports the concept that mixed apnea with pharyngeal obstruction could be a cause of the fatal SIDS event. (NIH grant#HD 10993)

● 1715 EFFECT OF INSULIN (I) AND ISOXSUPRINE (X) ON LUNG SURFACTANT PRODUCTION IN THE FETAL RHESUS MONKEY.

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We examined the effect of chronic hyperinsulinemia on lung lavage phospholipid (PL) content and composition. I (19 U/d for 20 d) was administered to fetal rhesus monkeys with an Alzet minipump implanted in the hind leg (Diabetes 28: 1058, 1979). Sham- and non-operated animals were used as controls (C). X (5-10 mg/d for 20 d) was administered to additional mothers. Fetuses were delivered by cesarean section at 134-147 d (term is 165 d). I levels were 49±14 and 4470±780 µU/ml and glucose levels were 43±6 and 21±6 mg/dl in the C and I-treated groups respectively. Results are shown in the table. Hyperinsulinemia did not inhibit surfactant production. This suggests that the increased incidence of RDS in infants of diabetic mothers may not be due to hyperinsulinemia but rather possibly to the concomitant hyperglycemia. X increased surfactant production. X may be useful in the prevention of RDS in humans.

Group (number of fetuses)	C (5)	I (3)	X (3)
PL content (µg P/g lung dry wt)	65±14	104±50	327±144*
Phosphatidylcholine (PC) content	43±14	62±30	272±188*
PC/sphingomyelin ratio	10± 2	16± 3	55± 17**

Significantly different from control: *P<0.05, **P<0.02

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1716 USE OF SUPEROXIDE DISMUTASE IN NEONATES WITH SEVERE RESPIRATORY DISTRESS SYNDROME.

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Bronchopulmonary Dysplasia (BPD) may be related to deficiency of the enzyme, superoxide dismutase (SOD), in the lung. SOD detoxifies O_2^- and may thereby prevent lung destruction and BPD. A preliminary study in human neonates with severe IRDS evaluated the safety and pharmacokinetics of parenterally administered SOD (Orgotein (R), Diagnostic Data, Inc., Mountain View, California).

19 prematures with severe IRDS with $\bar{m}$ b.wt. 1179gm and $\bar{m}$ G.A. 28.9 wks on ventilators with $FiO_2 > .70$ at 24hrs of age were included. SOD was given as a test dose .1mg/kg ID followed in 1hr by .25mg/kg q12h SQ. No adverse (cutaneous or systemic) affects were associated with SOD administration. No abnormalities occurred in electrolytes, SGPT, SGOT, coagulation profile, white cell, platelet or reticulocyte counts. Serum creatinine and urine output were unaffected. SOD plasma levels, undetectable prior to therapy, were measurable in 8/13 patients 1hr after test dose and in all within 1hr following the therapeutic dose. In patients > 28wks $\bar{m}$ levels rose to .2-.9mcg/ml and remained in this range for the 12hr interval and with subsequent doses. Higher levels generally occurred in patients ≤28wks for the entire 12hr period and attained peak levels as high as 2.0mcg/ml with subsequent doses. These results suggest that SOD may be safely administered to newborns severely ill with IRDS and provide a preliminary guide to dosage and frequency of injection.

1717 MITOCHONDRIAL RESPIRATORY ACTIVITY: RESPONSE TO INCREASED CARBOXYHEMOGLOBIN (COHb) IN BRAIN AND HEART OF GUINEA PIGS.

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Previous studies show that mitochondria adapt to changes of arterial PO_2. The present study investigates heart and brain mitochondrial respiratory rate (RR) in 23 guinea pigs at varying blood COHb levels. Blood gases and [COHb] were recorded in all animals. Brain and heart mitochondria were isolated. State 4 RR, state 3RR with glutamate-malate substrate, expressed as nm O_2/min/nm cytochrome $a+a_3$, respiratory control ratio(RCR) (state 3/state 4), and Ca^{++} uptake were measured. All preparations were well coupled with RCR 10.7+1.9 for heart and 8.3±1.2 for brain mitochondria. State 3 RR increased from 225 at 0% COHb to 500 at 40% COHb in the heart (r=.8) and from 260 at 0% COHb to 628 at 80% COHb in the brain (r=.7). There was an inverse correlation of state 3 RR and arterial O_2 content. Mitochondrial activity increased from 190-525 as arterial O_2 content decreased from 19-9 ml/dl (r=.9) and from 340 to 580 as arterial O_2 content decreased from 16-4 ml/dl (r=.6) in heart and brain respectively. Ca^{++} uptake in heart and brain increased with increasing [COHb]. Blood flow was not measured but presumably circulatory adjustment failed to compensate for the decreased arterial O_2 content, thus impairing O_2 delivery to the tissues. These data suggest that increased mitochondrial activity with increased [COHb] and decreased O_2 content, occurring in the presence of normal PaO_2, represent an adaptive response to tissue hypoxia comparable to the changes reported during acute and chronic hypoxemia.