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THE USE OF ONTOGENY AND MUTATION TOGETHER TO DEFINE THREE RENAL TRANSPORT SYSTEMS FOR PROLINE AND GLYCINE IN MAN. L. Lasley and C.R. Scriver. McGill Univ.-

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Renal hyperiminoglycinuria with impaired net tubular reabsorption of proline (pro), hydroxyproline and glycine (gly) occurs permanently in mutant homozygotes with benign familial renal iminoglycinuria and transiently up to six mos after birth, in the normal human infant. We studied seven infants (4 Ashkenazim, 2 Fr.Can., 1 Greek) with massive iminoglycinuria detected by newborn screening. Family studies defined two types of homozygotes and one genetic compound in the group. Sequential quantitative renal clearance studies (endogenous creatinine and amino acids) under a standardized protocol were performed in the first year of life. A profound defect in net reabsorption of pro and gly was found in each proband in early infancy; fractional excretion (FE) of pro and gly approached 1.0 (no net reabsorption) in some. Mean $FE_{pro} = 0.60$ and mean $FE_{gly} = 0.64$ for the group in early infancy compared with normal values, <0.05 and <0.20 respectively. Pro reabsorption matures by 3 mos and gly reabsorption by 6 mos in normal infants; regression analysis of FE_{pro} and FE_{gly} vs age in the proband group revealed reabsorption capacities maturing on a delayed but analogous schedule. These findings indicate three carriers for tubular transport of pro and gly: a shared carrier for pro and gly detected by the mutation; and independent pro-prefering and gly-prefering carriers each with their own schedule of postnatal maturation. The mutant homozygous newborn lacks all three carriers at birth.

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THE EFFECT OF INTRAUTERINE GROWTH RETARDATION (IUGR) ON SMALL INTESTINAL ENZYMES. E. Leberthal, B. Chrzanoska, J. Krasner, M. Nitzan, D. Branski, T. Hatch,

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Fetal malnutrition and growth retardation can be related, in part, to poor placental blood supply. Experimental IUGR was induced on the 18th day of gestation in pregnant rats by ligating the uterine horn, while leaving the opposite horn intact as a control. On the 22nd day of gestation, the weight of the fetal, small intestine parallels the decrease of body weight. The weight loss is related to a significant reduction in DNA content and in cell number, and to a lesser extent, to a decrease in cell size.

	#	L	M	AP	EK
Control	(23)	78 ± 14	35.5 ± 16	135 ± 22	2551 ± 1403
IUGR	(28)	64 ± 15	36.7 ± 16	111 ± 28	2579 ± 1219

In contrast to maltase (M), alkaline phosphatase (AP), and enterokinase (EK), only lactase (L) activity is significantly decreased in fetuses paired from same mothers. These results suggest, that in addition to the decreases in small intestinal cell number and enzyme content in IUGR, there is a proportionally greater decrease in L activity. This can be explained by either a selective effect of IUGR on a critical developmental period for lactase, or that lactase is more vulnerable to insult.

(*Units \pm S.D. = μ mole/gm protein/min.)

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OXIDATIVE METABOLISM AND UPTAKE OF KETONE BODIES BY THE CEREBRAL CORTEX OF THE BABOON NEONATE. Lyone L. Levitsky, John B. Paton, David E. Fisher, and

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Net cerebral uptake of energy substrates was measured by repetitive arteriovenous sampling in 9 baboon neonates in the first 3 days of life. Catheters were placed in the aorta, left ventricular outflow tract, and in the superior sagittal sinus. Cardiac output and cerebral cortex blood flow were determined by the radioactive microsphere method. Glucose (G) uptake was $9.4 \pm 2.1 \mu\text{M}/\text{min}/\text{kg}$ body weight or $11.2 \pm 2.6 \mu\text{M}/\text{min}/100 \text{ g}$ cerebral cortex. Cerebral uptake of alanine was detected in 4/4 animals, and of lactate in 3/9 animals. There was no net lactate release and no net uptake or release of glycerol. Infusion of Na DL-3-hydroxybutyrate (βOHB) to steady state levels of 2-6 mM total KB (acetoacetate + D- βOHB) did not alter G, lactate, or O_2 uptake. However, KB uptake was correlated in a linear fashion with arterial KB to levels of 8 mM.

	G (mM)	KB (mM)	O_2 (mM)	G x 6/ O_2
Pre- βOHB Art.	$2.77 \pm .32$	$.393 \pm .096$	$8.02 \pm .35$	$.77 \pm .09$
A-V	$-.51 \pm .07$	$-.017 \pm .010$	$-3.90 \pm .36$	
Post- βOHB Art.	$2.89 \pm .92$	$3.810 \pm .673$	$6.86 \pm .11$	$.77 \pm .04$
A-V	$-.47 \pm .04$	$-.268 \pm .107$	$-3.73 \pm .34$	

Although G/ O_2 ratios less than 1 suggest that substrates other than glucose are utilized by the brain of the baboon neonate, cerebral KB uptake does not necessarily reflect oxidative metabolism of acetoacetate and D- βOHB .

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SERIAL PLASMA CORTICOSTEROIDS IN THE FETAL GROWTH RETARDED LAMB (FGR) Anibal J. Llanos, Maria Seron-Perre, James R. Green, Abraham M. Rudolph, Robert K.

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Growth retarded fetuses are considered to be under chronic stress due to lack of oxygen and nutrients. Since FGR lambs have proportionally a large adrenal weight and a small thymus, both suggestive signs of increased adrenal activity, we measured the total corticosteroid levels in this syndrome. Growth retardation was produced in 7 chronically catheterized fetal lambs by embolization of the maternal uterine bed with non radioactive microspheres. Fetal femoral artery pH was (mean \pm SE) 7.38 ± 0.008 ; PO_2 18.41 ± 0.61 torr; PCO_2 46.62 ± 1.19 torr and hematocrit $36.64 \pm 0.68\%$. Total corticosteroid was measured by RIA serially in fetal femoral arterial plasmas from 113 to 141 days gestation. Mean corticosteroid concentration (ng/ml) in FGR lambs were 4.92 ± 1.0 (n=10), 7.44 ± 1.3 (n=11), 20.75 ± 5.42 (n=17) at 110-120, 121-130 and 131 to 141 days gestation respectively. These values are not significantly different from control animals, (5.21 ± 1.02 , n=10; 7.22 ± 0.75 , n=5; 13.75 ± 3.12 , n=4; respectively). These results indicate that placental embolization enough to cause fetal growth retardation is not a stimulus for enhanced fetal adrenal activity nor accelerates fetal adrenal maturation.

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APOLIPOPROTEINS (APOS) IN AMNIOTIC FLUID. W. J. McConathy, P. R. Blackett, R. Nordquist, R. Kling.

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Amniotic fluid (AF) obtained from 17 pregnant women with gestational ages 20 to 45 weeks contained apos A-I (1.29 ± 0.59 mg/dl) and A-II (0.44 ± 0.28 mg/dl) by electroimmunoassay (EIA). The other known serum apolipoproteins Apo B, C-I, C-II, C-III, Apo D and Apo E were not detected by double diffusion analyses (DDA). Lecithin: sphingomyelin (L/S) ratios ranged from 1.6 to 7.0. All samples (n=4) with L/S ratios ≥ 5.0 were past term and were deficient in or had trace amounts of A-II by EIA. By DDA, A-I and A-II were absent from a premature infant's urine and a postmortem saline lavage of neonatal lung. Lung and placental tissues were negative for A-I and A-II by fluorescent antibody staining. Pooled AF (400 ml) was passed through an immunosorbent specific for A-I. The retained fraction (R) reacted with anti-A-I and contained three major bands on basic polyacrylamide gel electrophoresis (PAGE) one of which had a mobility similar to A-I. After ultracentrifugation at density 1.23 g/ml , the unretained (U) fraction eluted as a single peak in the void volume (V_e) from sepharose-6B. Lipid analysis revealed lecithin, sphingomyelin, phosphatidyl inositol, triglyceride, cholesterol and cholesterol ester. By SDS PAGE analysis, the V_e peak contained 3 to 4 bands of m.w. 50-80,000 daltons and electron microscopy revealed homogenous spherical micelles with protein bubbles stained by phosphotungstic acid. We conclude that apolipoproteins A-I and A-II are present in amniotic fluid in addition to non-serum apolipoproteins which may have clinical significance for further studies on the composition of protein and lipid components of surfactant in AF.

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EFFECTS OF INSULIN AND THEOPHYLLINE ON GLYCOGEN CONTENT OF FETAL RAT LUNG IN ORGAN CULTURE. William M. Maniscalco, Christine M. Wilson and Ian Gross (Spon.

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Control of maturation of the fetal lung is poorly understood. Since fetal lung maturation is characterized by both accumulation of phosphatidylcholine (PC) and loss of glycogen in aveolar type II cells, control of these events may be effected by similar agents. Previous studies have indicated that insulin delays morphologic maturation and that theophylline stimulates PC synthesis in fetal rat lung in organ culture.

We have investigated the effects of insulin and theophylline on the glycogen content of 19 day fetal rat lung in organ culture. In explants cultured without added hormones, glycogen content decreased by 34% after 24 hrs in culture and 70% after 48 hrs. During this time there was morphologic and biochemical evidence of lung maturation. Treatment of the explants with insulin (0.1u/ml) for 24 hrs resulted in a 34% increase in the glycogen content compared to controls. Theophylline treatment (1.0mM) of the explants resulted in a 53% decrease in glycogen after 48 hrs. The glycogen content of fetal lung explants is affected by agents known to influence pulmonary maturation and PC synthesis. Supported by USPHS grant no HL19752.