HEMOGLOBIN DEVELOPMENT IN RAT FETUSES. Hernan Sabio, Virgil F. Fairbanks, Gerald S. Gilchrist, and E. Omer Burgert, Jr. Mayo Clinic and Mayo Foundation, Rochester, MN.

A model was established for studying the effect of various drugs on the maturation of rat hemoglobin from fetal to adult types. To elucidate further the regulatory mechanisms in the ontogenic development of mammalian hemoglobins, agents were studied which are believed to influence hemoglobin development in the rat fetus. We confirmed that adult rats have 5 and occasionally 6 hemoglobin types, which we designated hemoglobins 1, 2, 3, 4, 5, and 6 (in order of increasing anodal electrophoretic mobility at alkaline pH). Fetuses of 11-12 days of gestational age possess only hemoglobins 3 and 4. At 14-15 days, hemoglobins 2 and 5 appear. Between 16 and 18 days, hemoglobin 1 becomes detectable, hemoglobin 3 decreases, and hemoglobin 5 predominates. The adult pattern is present in newborns (21-22 days of gestational age). Changes in red cell morphology were correlated with hemoglobin development. Phenobarbital, progesterone, or cortisone acetate was administered in various dosages to rats at different times during pregnancy to determine whether any alteration in the rate of appearance of the adult pattern of hemoglobin could be achieved. No significant changes in hemoglobin pattern in the fetuses were observed with any of the three drugs. The model provides a useful tool for the study of the effect of other agents on the ontogenic development of hemoglobins.

INDUCTION OF ORNITHINE TRANSCARBAMYLASE ACTIVITY IN FETAL RAT LIVER BY THE BY-PRODUCTS OF PROTEIN METABOLISM. Kenneth E. Schuit, Department of Anatomy, (Intr. by Robert M. Blizzard), University of Virginia, Charlottesville.

A congenital, sex-linked disorder characterized by low or absent levels of the urea-cycle enzyme, ornithine transcarbamylase has been reported in a number of families. Activity of this enzyme in the liver of fetal and neonatal rats was studied in an effort to elucidate the factors which control its synthesis. Detectable amounts of ornithine transcarbamylase appear in fetal liver during the final third of gestation, reaching a peak immediately prior to birth, dropping sharply after birth and remaining low for 3 days. Subsequently, enzyme activity again rises, reaching adult levels by the 15th day after birth. These data suggest that ornithine transcarbamylase is represented before birth and in the neonatal period by distinct isozymes, sensitive perhaps, to different inductive influences.

In order to identify the stimulus for the induction of ornithine transcarbamylase activity, three of the constituents of the urea cycle were injected into newborn rats and the levels of ornithine transcarbamylase were measured. Whereas administration of ornithine and arginine (which act as nitrogen carriers in the urea cycle) did not affect enzyme activity, carbamyl phosphate, (one of the sources of nitrogen atoms for urea synthesis) greatly stimulated enzyme activity. Thus, the activity of ornithine transcarbamylase is related to the concentration of the end products of protein catabolism, an example of substrate induction.

A NEW SYNDROME OF FAMILIAL PANCREATIC AGENESIS: THE ROLE OF INSULIN AND GLUCAGON IN SOMATIC AND CELL GROWTH. William C. Sherwood, Graham W. Chance, and Donald E. Hill. Research Institute and Department of Paediatrics, Hospital for Sick Children, Toronto, Canada. (Intr. by Donald Fraser).

Two sibs of a consanguineous union were born with severe intrauterine growth retardation and agenesis of the pancreas confirmed at autopsy. We report the association between the growth failure and absence of fetal insulin and glucagon, and some of the changes in somatic and cell growth occurring in one of the infants at age 6 weeks. Birth weight 1280 gm at term; length 37 cm; head circ. 29 cm; (all <3rd centile). The brain weighed 214 gm (<3rd centile), and the liver weighed 95.7 gm (<25th centile). All other visceral organs were extremely small, particularly the adrenals whose combined weight of 1 gm was less than that of a 24-week old fetus. The total DNA in the cerebrum was 172 mg (N=258), in the cerebellum 95.6 mg (N=120), and in the liver 200 mg (N=320), respectively, indicating a reduction in the cell number in each of these organs. Protein/DNA ratio was normal or increased in brain and liver indicating a relatively greater reduction in DNA content than in protein. In muscle, the total DNA was reduced as calculated from muscle mass and the protein/DNA ratio of 58 was extremely low (N=100). The results in brain and muscle were similar to those seen in infants with severe postnatal marasmus, and suggest that insulin and glucagon are key hormones for normal fetal growth.

PULMONARY ALVEOLAR MACROPHAGES IN PRE-AND POST-NATAL RABBITS. Lance Sieger and Marc A. Beaudry (Intr. by Jerry Z. Finklestein). U.C.L.A. School of Medicine, Harbor General Hospital, Dept. of Pediatrics, Torrance, Ca.

Pulmonary alveolar macrophages (PAM) are the most important phagocytic cells in the lung. We have studied a fetal rabbit model to show whether functioning PAM are present in normal numbers in the fetus or whether air breathing is required for their formation and/or migration to the lung. Broncho-pulmonary washings, with 37°C. normal saline, were examined from a). 30 day fetal rabbits delivered by hysterotomy with tracheas ligated prior to first breath, b). spontaneously breathing neonatal rabbits born normally, and c). adult rabbits. The cells contained in all the washings were >99% PAM and the PAM from all rabbits appeared to be similar when stained with Wrights and α-napthol acetate. There were no significant differences in the total numbers of PAM per rabbit when corrected for wet lung weights. The PAM from all the rabbits phagocytized P. aeruginosa and S. aureus equally well. These findings indicate that functioning PAM are present in equivalent numbers in intra- and extra-uterine life. The susceptibility of neonates to serious pulmonary infections may be due to factors other than diminished numbers of functioning PAM.

GLUCONEOGENIC ENZYMES IN FETAL SHEEP LIVER AND KIDNEY. Roger E. Stevenson, Eugene W. Adcock, Frank H. Morriss, and R. Rodney Howell. University of Texas Medical School at Houston, Program in Pediatrics, Houston.

Recent studies of fetal sheep metabolism in unstressed preparations have suggested that amino acids (AA) may furnish up to 25% of the substrate for fetal aerobic metabolism after 125 days gestational age (GA). This investigation was performed to determine throughout gestation the activities in fetal sheep liver and kidney of key enzymes for gluconeogenesis. Tissue specimens from 10 fetuses of well-nourished ewes at 44-145 d. GA were assayed by spectrophotometric methods. Results: (1) After 125 d. GA substantial activities were found in both liver and kidney for glucose-6-p'tase (G6P), fructose-1,6-dip'tase (F1,6DP), pyruvate carboxylase, PEP carboxykinase, aspartate aminotransferase (asp AT), and alanine aminotransferase (ala AT). The activity in kidney for each enzyme except asp AT was comparable to or greater than the activity in liver. (2) Activities of 2 enzymes increased with gestation:

Enzyme	< 125 d.	> 125 d.	p
G6P (liver)	6.1 ± 0.9	36.8 ± 3.8	< .005
F1,6DP (kidney)	24.7 ± 2.3	36.3 ± 2.5	< .005

Conclusion: Significant activities of these enzymes in late gestation support the theories of fetal utilization of AA (a) as substrate for aerobic metabolism, and (b) for gluconeogenesis. Speculations: (1) Increasing capability for gluconeogenesis may occur as gestation proceeds. (2) The role of the kidney in overall fetal metabolism may be substantial.

(* μM Pi produced/min/g. protein; x ± SEM)

GESTATIONAL CHANGES IN CELL TYPES WITHIN THE OVINE PLACENTA. François Teasdale, Giacomo Meschia, and Frederick C. Battaglia. Division of Perinatal Medicine, University of Colorado Medical Center, Denver.

A recent study in our laboratory on the DNA content and permeability of the sheep placenta showed that in the last third of gestation, although there is a decrease in placental weight, the total placental DNA tends to remain constant, and the placental urea permeability per gram of DNA rises logarithmically. In an attempt to clarify these data we have studied the morphometric changes on 6 placentas of known gestational age, ranging from 40 to 145 days. A microscopic point-counting technique was applied to determine the numerical density (N_V) and the pattern of distribution of 7 types of nuclei in each placenta. The study of this morphometric parameter along gestation has revealed a stable concentration of the columnar and cryptal epitheliums, a fall in the binucleate giant cells and in the fetal mesenchyme from 11.9% to 2.1% and from 17.5% to 6.4%, as compared to a rise from 9% to 21.2% for the fetal and maternal capillary endotheliums. The mean N_V for all types of nuclei from early gestation to term did not change significantly, in agreement with the DNA data. These results indicate 1) the reliability of DNA measurements in determining the total number of nuclei in the placenta, and 2) that different patterns of cell growth in the placenta may underlie a stable DNA, a fall in placental weight, and a progression in functional capacity.