The effect of CPAP on PaO_2 was measured in the 7 infants and on 30/31 occasions PaO_2 rose 10–300 mm Hg within 5 min. There were no consistent changes in arterial CO_2 tension or pH. Aortic blood pressure was measured in all infants. Application of CPAP never caused narrowing of pulse pressure or fall in mean aortic pressure ($\overline{P}_{ao}$) but resulted in a rise in $\overline{P}_{ao}$ in 8/20 occasions. In 3 infants serial measurements of the effects of CPAP on heart and respiratory rates, tidal volume, esophageal pressure and dynamic compliance, made on 9 occasions, showed no consistent changes. Less than 20% of the CPAP was transmitted to the intrathoracic space (by esophageal pressure). CPAP results in improved oxygenation in severe IRDS without mechanical ventilation, and without adverse effects on arterial CO_2 tension, acid base or cardiovascular status or survival. (Supported in part by HEO 6285.)

135 *Early Correction of Neonatal Acidemia in the Preterm Low Birth Weight Infant.* C. J. Hobel, W. Oh, M. A. Hyvarinen, G. C. Emmanouilides and G. Klyman, Harbor Gen. Hosp., UCLA Sch. of Med., Torrance, CA.

The effects of early correction of acidemia in the newborn period was evaluated in 43 pre-term infants. Criteria for inclusion into the study was a pH of less than 7.25 either from fetal scalp blood, cord arterial blood or from umbilical arterial blood up to 20 min after birth. The infants were placed at random into: Group A, birth weight < 1,500 g, early treatment (Rx.), Group B < 1,500 g late Rx., Group C 1,501–2,250 g early Rx., and Group D 1,501–2,250 g late Rx. Infants in the early Rx. groups were given intravenous sodium bicarbonate within 30 min of age. The late Rx. groups were given bicarbonate at 2–3 h of age. All infants were otherwise similarly managed. Predetermined clinical parameters were used to make the diagnosis and to grade the severity of respiratory distress syndrome (RDS) at designated intervals. No significant difference was observed in arterial blood pH, PO_2, PCO_2 and base deficits between groups during the first 30 min of life. The arterial blood pH were significantly higher during the first 12 h following early correction of acidemia. Group A has significantly higher PaO_2 than Group B during the first 12 h. The arterial $PaCO_2$ was similar in early vs. late Rx. groups, but the base deficit was significantly lower in early Rx. infants at ½–12 h. The incidence of RDS between groups was similar. However, the degree of severity of RDS was less in the early Rx. group. Four of 21 early Rx. and 6 of 22 Rx. infants died during the first 10 days of life. These preliminary data suggest that early correction of acidemia in low birth weight infants improves acid base and blood gas status as well as the clinical course of RDS.

136 *Developmental Changes in the Oxygen Equilibrium Curve of Infants as Related to the 'Functioning DPG Fraction' and Its Alteration with Disease.* Maria Delivoria-Papadopoulos and Frank A. Oski, Dept. of Ped., Univ. of Pennsylvania Sch. of Med. and The Children's Hosp., Philadelphia, PA.

The red cell organic phosphate 2,3-diphosphoglycerate (DPG) has been shown to bind to adult hemoglobin and decrease its affinity for oxygen while it has little effect on altering the oxygen equilibrium curve of fetal hemoglobin. Sequential studies of the P^{50} (partial pressure of oxygen at which hemoglobin is 50% saturated), fetal hemoglobin and red cell DPG were performed in 31 term and 28 premature infants. In term infants the P^{50} averaged 19.4 mm Hg on day 1; 20.6 on day 5; 26.6 at 3–4 months, and 28.0 at 6 months (normal adults 27.5±0.8). The initial P^{50} of the premature infants was lower and its change with age more gradual. The P^{50} did not correlate precisely with the percent fetal hemoglobin alone or the DPG alone but correlated significantly with the product of the percent adult hemoglobin times the DPG content ('functioning DPG fraction'). Calculations indicate that the term infant at age 3 months with a hemoglobin of 11.0 g% is delivering more oxygen to his tissues at a mean venous PO_2 of 40 mm Hg than is the newborn with a hemoglobin of 17.0 g%. Sick infants were found to have low P^{50}'s and DPG levels. Infants given either simple or exchange transfusions of fresh adult blood showed an increased 'functioning DPG fraction', a shift of the oxygen equilibrium curve to the right and their oxygen unloading capacity reached that of a 6-month infant. Such treatment appears useful in the sick infant because it facilitates peripheral oxygen delivery to the tissues.

137 *Development of Fibrinolytic Proteins in Health and Disease.* Marcia Hyvarinen, Stanley N. Graven and E. Richard Stiehm, Dept. of Ped., Univ. of Wisconsin Med. Center, Madison.

Because of the propensity of newborns, especially low birth weight (LBW) infants, to bleeding and thrombosis, and the possibility of a fibrinolytic defect in the respiratory distress syndrome (RDS), serum proteins of the fibrinolytic system were measured in healthy term and LBW infants and compared to maternal levels and levels in sick LBW infants with and without RDS. Levels of plasminogen (PLM), two antiplasmins, alpha-2-macroglobulin (α 2-MC) and alpha-1-antitrypsin (α 1-AT) and albumin and IgG globulin were measured by radial immunodiffusion on paired maternal-cord serums of 45 term newborns, 37 LBW well newborns, 28 LBW infants with RDS, 24 sick LBW infants without RDS, and 9 immature (< 0.8 kg) infants. Term infants had PLM levels of 45±14 (1 standard deviation) mg/100 ml, compared to maternal levels of 90±18 mg% and adult controls of 70±7 mg%. Levels of α 2-MC and α 1-AT in term infant serum were 149±35% (percent of standard serum) and 132±37 mg%, respectively; in maternal serum 139±43% and 262±48 mg%; and in adult control serum 152±34% and 133±22 mg%. There were significant ($p < 0.01$) reductions of levels of α 2-MC and PLM with decreasing birth weight; no such relationship was noted for α 1-AT. Significant correlation existed between maternal and cord levels of albumin, IgG, PLM, α 1-AT and α 2-MC, suggesting transplacental passage of these proteins. No differences were noted in levels of PLM, α 2-MC and α 1-AT in the RDS or other ill LBW infants.

The relatively high levels of antiplasmins compared to plasminogen levels suggest impaired fibrinolysis at birth. These studies do not correlate well with prior functional studies of the fibrinolytic system, suggesting that poorly characterized activators and inhibitors play a major role in the regulation of fibrinolysis.

138 *Angiocardiographic and Metabolic Studies in Immersed Lamb Fetuses Perfused Through an Artificial Placenta.* Warren M. Zapol, Theodor Kolobow, John Doppman, Joseph E. Pierce, Gerald G. Vurek and Robert L. Bowman, NHLI, NIH, Bethesda, MD (introduced by Gordon Avery).

Using angiocardiography we studied twelve premature lambs of 130–145 days gestation (2.3–4.0 kg) obtained at caesarian section and maintained in a filtered and thermoregulated bath of synthetic amniotic fluid. By selectively varying the oxygen concentration in the gas compartment of the membrane lung we were able to control the level of blood oxygen tension independent of pH, PCO_2, and placental flow. Within 20 min after raising fetal umbilical pO_2 from 13–20 to 40–60 mm Hg there was almost total conversion of the fetal circulatory pattern to that of the newborn. The I.D. of the ductus arteriosus constricted from 4.1 mm to less than 1.0 mm; pulmonary circulation time decreased from more than 18.4 to 2.4 sec. These findings were not affected by metabolic or respiratory acidosis. Inferior vena cava injections illustrated complete closure of the foramen ovale; no opacification of the left atrium occurring at pO_2 from 40–60 mm Hg with a constricted ductus arteriosus. Oxygen consumption of fetuses paralyzed with succinylcholine measured continuously by spirometry averaged 6–7 ½ cm^3/kg/min while carbon dioxide production was measured continuously by infrared analysis of effluent gas at 7–8.5 cm^3/kg/min. Respiratory quotients consistently greater than one were observed with blood glucose levels above 100 mg%. Four fetuses were delivered following angiocardiographic study; two are long-term survivors.

139 *Effects of Compression of the Umbilical Cord on the Unanesthetized Fetal Goat.* MOLLY E. TOWELL and HERMINIA S. SALVADOR, Dept. of Obstet. and Gynaecol., Univ. of British Columbia, Vancouver, B.C. (introduced by Sydney Segal).

Compression of the umbilical cord has previously been studied under acute experimental conditions but it is not known to what extent the effects are modified by anesthesia or the operative procedure. The purpose of these experiments was to investigate the effects of umbilical cord compression under relatively undisturbed conditions *in utero*. Seven fetal goats were prepared with intravascular catheters, subcutaneous electrodes and a device for compressing the umbilical cord with an inflatable balloon, by an operative procedure under halothane anesthesia. The fetus was replaced in the uterine cavity and the mother permitted to recover. Observations were made on heart rate (FHR), arterial pressure (FAP) and respiration of the fetus during and after cord compression. Arterial blood samples were analyzed at intervals for pH, PCO_2, PO_2 and O_2 saturation. During anesthesia and in the first few hours post-operatively, compression of the cord led to persistent bradycardia and elevation of FAP. After recovery from anesthesia cord compression was associated with a rise in FHR following bradycardia. Continued compression of the cord for more than 5 min led to a gradual fall in both FHR and FAP and severe fetal acidosis (arterial pH < 7.1). Respiratory movements *in utero* were induced by partial or total compression of the cord and were also seen during the recovery phase for as long as 60 min after release of the cord. It is concluded that halothane anesthesia may alter the response of the FHR to cord compression and that fetal respiration can occur *in utero* not only during intrauterine asphyxia but in the recovery phase as well.

140 *Glucose Oxygen Uptakes Across Umbilical and Cerebral Circulations of the Fetus.* NICHOLAS G. TSOULOS, JAMES R. COLWILL, JACK M. SCHNEIDER, EDGAR L. MAKOWSKI, GIACOMO MESCHIA and FREDERICK C. BATTAGLIA, Depts. of Ped., Obst.-Gynecol. and Physiol., Univ. of Colorado Med. Center, Denver, Colo.

Glucose has been considered the principal metabolic fuel of the mammalian fetus, but sound experimental evidence is lacking. In this study, the relative contribution of glucose to aerobic metabolism across the umbilical and cerebral circulations of fetal lambs was evaluated. The fetal vessels catheterized were: femoral artery and vein, umbilical vein, subclavian artery and periorbital vein. The arteriovenous differences in glucose and oxygen contents (Δ glucose and Δ oxygen) were determined from simultaneous samples across both circulations. The Δ glucose was expressed as the O_2 stoichiometrically required to metabolize glucose to CO_2 and H_2O. In six chronic, unstressed, unanesthetized animals, the Δ glucose/Δ oxygen ratio across the umbilical circulation during control periods was 0.47 ± 0.04 (mean$\pm$s.e.m.). Fetal infusions of porcine insulin increased the ratio by 90%.

We have attempted to compare metabolism in a single organ of the fetus, the brain, with that of the whole fetus (i.e. umbilical circulation) in acute experiments in seven fetuses. The ratio across the cerebral circulation was 1.5 ± 0.03 and across the umbilical circulation was 0.38 ± 0.03. These data indicate that (a) under normal conditions, glucose supplies a maximum of 50% of the metabolic fuel of the fetal lamb, (b) exogenous insulin does affect fetal glucose uptake, and (c) in the acute preparation, the fetal brain utilizes more glucose than can be accounted for by aerobic metabolism.

141 *Inhibition of Mixed-function Oxidations by Pregnanolone: A Possible Basis for Impaired Drug Metabolism During Infancy.* LESTER F. SOYKA and LASZLO GYERMEK, Stanford Univ. Sch. of Med.

The presence of inhibitor(s) to explain impaired drug metabolizing capacity in the newborn remains an attractive, but unproven hypothesis. In the rat, by 3 days after birth, the endoplasmic reticulum assumes a mature appearance, but drug metabolism remains depressed until after weaning. Studies to date have failed to identify a particularly depressed component of the mixed-function oxidase system during the neonatal period. Progestational steroids are reasonable candidates for the role of physiologic inhibitors since their high levels late in pregnancy coincide with decreased drug metabolism of the mother and absent activity in the fetal liver. Moreover, inhibition of glucuronide conjugation reactions of liver microsomes by several steroids including progesterone, pregnanediol, and pregnanolone, has been reported. Pregnanolone (3α-ol 5β-pregnane-20-one) has been found in the human fetus after progesterone infusion and in the serum of newborn infants. Pregnanolone was a potent, noncompetitive inhibitor of aniline hydroxylation and p-nitroanisole demethylation, typical reactions of the mixed-function oxidase system in rat microsomes. At saturating concentrations of substrate, inhitition by pregnanolone (5×10^{-4} M) was 20–40%. Duration of hypnosis in rats after hexobarbital and pentobarbital administration was prolonged by pretreatment with a non-hypnotic dose of pregnanolone. These results permit speculation on a possible role for pregnanolone and/or related steroids in the well-established decreased ability of newborns of many species to metabolize drugs. (Supported in part by USPHS Grant HD-03063.)