in lymph nodes, spleen, lungs and skin consistent with graft versus host syndrome. A successful marrow graft in posthepatitis aplasia can be achieved.

- 131 *Liberal Versus Restricted Indications for Oxygen in RDS: A Controlled Trial.* ROBERT H. USHER, Royal Victoria Hosp. and McGill Univ., Montreal (introduced by Mary E. Avery).

Oxygen therapy for RDS may improve the course of the syndrome by increasing pulmonary perfusion, improving myocardial, renal and cerebral function, and by preventing lactic acidosis. Conversely, it may aggravate the disease by pulmonary toxicity. In an attempt to assess the balance between benefits and risk, oxygen therapy for RDS was given during the first 72 h of life according to liberal indications in 75 infants (for PaO_2 below 80 or PcapO_2 below 55 mm Hg), and according to more restricted indications in 75 others (for PaO_2 below 40 or PcapO_2 below 35 mm Hg). The 2 groups were well matched and had a similar severity of RDS at 1 h of age. Concentrations of oxygen exceeding 60% ambient were required in 50% of liberal and 10% of restricted oxygen cases.

Mortality was similar among the 45 infants weighing 500–1,250 g (68% liberal vs. 69% restricted). Infants weighing more than 1,250 g had a higher mortality when treated with liberal than with restricted oxygen (2% of 51 vs. 9% of 54). The liberal group developed more severe respiratory distress, more rales, faster respirations and more severe x-ray changes. Their pCO_2 and lactic acid rose to higher levels and they required 30% more bicarbonate to maintain a blood pH of 7.35. Liberal oxygen as defined therefore, conferred no apparent benefit and caused significant pulmonary oxygen toxicity.

- 132 *Pulmonary Pathology in Lambs with Hyaline Membrane Disease Ventilated with Air and 100% O_2 .* J. R. RAYE, R. L. GUTBERLET, G. FAXELIUS, S. SWANSTRÖM, V. S. LEQUIRE and M. T. STAHLMAN, Vanderbilt Med. Sch., Dept. of Ped. and Path., Nashville, Tenn.

There has been increasing controversy over the role of oxygen in the clinical and pathological picture of severe HMD assisted with positive pressure ventilation. For this reason a control study of the effects of 100% O_2 versus room air administered by IPPV to premature lambs with induced HMD was initiated. Ewes of 132–136 days gestation were made hypotensive with pentolinium and delivered 24 h later by cesarean section. Such lambs have previously been shown to develop the pathological sequence characteristic of HMD. Singleton lambs were immediately intubated, suctioned and ventilated with room air. A tracheostomy was performed and the RLL isolated with a Foley balloon catheter. The isolated lobe and remaining lung were ventilated separately with Bird respirators on either O_2 or room air. Twin lambs were intubated and ventilated either with room air or O_2 . Catheters were placed in Ao, SVC and, when feasible, PA and LA. Twin lambs were monitored until one died; the other was then sacrificed (1 ½ to 11 h). Lambs ventilated with 100% O_2 had a striking PAO_2 to PaO_2 gradient, metabolic acidosis, and lower PA pressures. All portions of lung examined showed some slough of alveolar duct and respiratory bronchiolar epithelium, pulmonary edema and arteriolar constriction. Portions of lung ventilated with 100% O_2 showed more advanced cellular slough, further advanced membrane formation

and more alveolar fluid. These findings suggest that, in severe HMD when cellular slough is already occurring, high PAO_2 may cause further direct damage to pulmonary epithelium, as well as increasing exudation of fluid from damaged capillaries by promoting $\text{L} \rightarrow \text{R}$ shunting, resulting in more extensive hyaline membrane formation.

- 133 *The Special Relation Between Oxygen and Nitrogen in Pulmonary Injury.* D. R. SHANKLIN, Pritzker Sch. of Med. Univ. of Chicago, Depts. of Obstet. and Path., Chicago, IL.

The lungs of post-vagotomy newborn rabbits show the lesion of hyaline membrane disease in extent directly proportional to the percentage of oxygen in polybaric (0.2–3.0 Atm. Abs.) mixtures [Lab. Invest. 21: 439, 1969]. At 7% O_2 lesions do not form, but all vagotomized animals die. Comparative gas studies show the direct proportionality to be related to nitrogen itself, probably through physical interaction at the pulmonary interface [South. med. J. 61: 1338, 1968; Fed. Proc. 28: 654, 1969]. In 3% O_2 (1 Atm.) further dissociation between mortality and pulmonary lesion is seen. 3% O_2 in nitrogen is 100% lethal without vagotomy over a time course (0.3–27.0 h) questionably longer ($0.02 > p > 0.01$), but otherwise similar to vagotomy effects. Minimal lesions are seen in both (2–3% extent). 3% O_2 in helium with or without vagotomy shows moderate lesions (19–32% extent); without vagotomy only 7% die by 24 and 40% by 48 h. 3% O_2 in sulfur hexafluoride shows moderate lesions (7–15% extent) after vagotomy; without vagotomy only 15% die by 24 and 26% by 48 h. The protective effect of SF_6 after vagotomy [South. med. J., *ibid*] is thus seen only at 20% + O_2 . The difference in survival without vagotomy between N_2 , He and SF_6 is highly significant ($p < 0.001$), and probably due to better uptake of oxygen. These data suggest a special relation between O_2 and N_2 , enhancing the importance of physical attributes, molecular size, shape, etc. They also suggest a further mediation of blocking by N_2 through physicochemical interaction which is not shown by He or SF_6 in relation to O_2 . The limit of 'hypoxic' tolerance ($> 3\% \text{O}_2$) described by G. AVERY [Pediatrics 32: 801, 1963], *inter alia*, is thus an effect of specific interaction of oxygen and nitrogen. (Supported by the John A. Hartford Foundation, New York.)

- 134 *Continuous Positive Airway Pressure with Spontaneous Respiration: A New Method of Increasing Arterial Oxygenation in the Respiratory Distress Syndrome.* GEORGE A. GREGORY, JOSEPH A. KITTERMAN, RODERIC H. PHIBBS, WILLIAM H. TOOLEY and WILLIAM K. HAMILTON, Univ. of California, San Francisco Med. Center, Depts. of Anesth., Ped. and Cardiovasc. Res. Inst.

Seven infants < 12 hours of age, weighing 1.1–2.8 kg and severely ill with idiopathic respiratory distress syndrome (IRDS) were allowed to breathe spontaneously against a continuous positive airway pressure (CPAP). Before CPAP they were unable to maintain an O_2 tension in the descending aorta (PaO_2) > 50 mm Hg in 100% O_2 , were candidates for mechanical ventilation and had probabilities of survival from 0–0.3 [STAHLMAN *et al.*, New Engl. J. Med. 276: 303, 1967]. After application of CPAP up to 12 mm Hg, PaO_2 rose at once in all. In 6/7 adequate oxygenation was maintained by CPAP until recovery; 1 died of IRDS despite use of CPAP and subsequent mechanical ventilation.

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 ($\bar{P}_{ao}$) but resulted in a rise in $\bar{P}_{ao}$ 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 Pre-term 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 $\frac{1}{2}$ –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 $149 \pm 35\%$ (percent of standard serum) and 132 ± 37 mg%, respectively; in maternal serum $139 \pm 43\%$ and 262 ± 48 mg%; and in adult control serum $152 \pm 34\%$ 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).