the cats shows the effect of DPH on the clotting factors reversible with Vit. K, prenatal treatment of mothers on DPH with Vit. K may be indicated.

Antihemophilic globulin (AHG) response to exercise for the detection of hemophilia A carriers. KOON-HUNG LUKE, ALAN TAYLOR, JACK HIRSH, and ALVIN ZIPURSKY. *McMaster Univ. and St. Joseph's Hosp., Hamilton, Ont., Canada.*

Plasma antihemophilic globulin (AHG) activity normally increases after vigorous exercise. Eleven normal women and nine mothers of patients with hemophilia A were studied before and immediately after a 10 minute, standardized and strenuous exercise load. In the normal group pre-exercise AHG levels ranged from 48–112% with a mean of 88%; after exercise the mean value was 168% with a range of 100–400%. In the hemophilic carriers the mean pre-exercise level was 49% with a range of 27–79%; after exercise the mean value was 68% with a range of 50–100%.

In 10/11 controls post-exercise AHG levels exceeded 120% whereas in 8/9 carriers the post-exercise levels were less than 80%. Three carriers had AHG levels in the normal range, 66%, 69% and 79%; following exercise values found were 78%, 68% and 100% respectively. Three controls had similar pre-exercise levels of 78%, 78% and 48%; however, following exercise these rose to 128%, 128% and 180% respectively, values significantly greater than the carrier group.

These data suggest that the mothers of patients with hemophilia A have a limited AHG response to exercise, a finding which may be of value in the detection of the hemophilia A carrier state.

Paradoxic changes in chronic intravascular coagulation. H. A. COOPER, C. A. OWEN, JR., P. DIDISHEIM, and E. J. W. BOWIE (Intr. by Gunnar B. Stickler). *Mayo Clinic and Mayo Foundation, Rochester, Minn.*

Paradoxic changes in platelet and fibrinogen levels were found in chronic intravascular coagulation induced in dogs. After preexperiment base-line values were obtained with saline alone, thromboplastin (acetone-dried dog-brain emulsion in saline, clarified by centrifugation) was given by continuous intravenous infusion at 2.5 ml/hr for 5 to 7 days. With undiluted thromboplastin, fibrinogen and platelet levels steadily fell and then stabilized at 50–100 mg/100 ml of plasma for fibrinogen and 5–10 $\times$ 10^3/mm^3 for platelets. Fibrinogen decreased more rapidly than platelets. Infusion of a 10-fold dilution of thromboplastin paradoxically increased fibrinogen to 550–650 mg/100 ml but with contemporaneous decrease of platelets to 20–40 $\times$ 10^3/mm^3. With 100-fold dilution of thromboplastin the fibrinogen also increased, to more than 500 mg/100 ml, while the platelets remained in the normal range. Whenever the thromboplastin infusion was stopped, platelets and fibrinogen levels increased, exceeding the preinfusion level and remaining high for 2 to 3 weeks. These data suggest that, in chronic intravascular coagulation in the dog, the liver is better able to compensate in the synthesis of fibrinogen than the marrow can in the synthesis of platelets. When intravascular coagulation is not too profound, fibrinogen or platelets may be normal or increased, as we have found in some patients who had evidence of intravascular coagulation without hypofibrinogenemia and thrombocytopenia.

Platelet transfusion as a diagnostic and therapeutic aid in the newborn. FRANCES M. GILL and ELIAS SCHWARTZ (Intr. by Robert L. Brent). *Jefferson Med. Coll., Cardeza Found., Philadelphia, Pa.*

Although platelet transfusions are commonly given to children and adults as treatment for bleeding due to thrombocytopenia, their use as a diagnostic tool in newborn infants is infrequent. We have infused platelets into 4 infants with marked thrombocytopenia at birth in an attempt to obtain information of diagnostic value and to prevent or treat bleeding. Platelets were obtained from a liter of whole blood by plasmapheresis of a single donor. The platelets were infused in a small volume of plasma and peripheral counts were monitored.

An infant with cytomegalic inclusion disease and one with absent radii had only rare marrow megakaryocytes. In both there was an excellent response to platelet transfusions with normal platelet survival. Two other infants with numerous megakaryocytes on bone marrow examination did not respond to random donor platelets. The mother of one child was subsequently found to have chronic idiopathic thrombocytopenia, presumably causing the observed random platelet destruction in her infant. In the other child maternal platelets produced an excellent response, while paternal platelets did not, indicating specific immune destruction.

Platelet transfusions are of value in differentiating peripheral destruction from decreased production in the newborn. In addition, platelet transfusions may be used safely at this age to treat and prevent life-threatening hemorrhage.

Thrombocytopenia in murine cytomegalovirus infection. JUNE E. OSBORN and NASROLLAH T. SHAHIDI. *Univ. of Wisconsin Med. Sch., Madison, Wis.*

The pathogenesis of cytomegalovirus-induced thrombocytopenia in neonatal cytomegalic inclusion disease is obscure, and the phenomenon has not previously been described in cytomegalovirus infections of other species. In these studies, 4-week-old female HA-ICR mice were infected i.p. with $10^{5.0}$ plaque-forming units of murine cytomegalovirus (MCMV) and their hemograms were serially determined over the succeeding 14 days. Mice infected similarly were sacrificed on appropriate days for histopathologic and fluorescent microscopic study of their spleens. Significant thrombocytopenia occurred uniformly on the 4th day of infection. This was correlated with distinctive histopathologic changes in megakaryocytes which included decrease in ratio of cytoplasm to nucleus, vacuolization of the nucleus, and appearance of markedly basophilic megakaryocytes suggesting increased turnover. Direct immunofluorescent staining for MCMV antigen, using hyperimmune anti-MCMV mouse serum, revealed positive megakaryocytic intranuclear fluorescence on days 4 and 5 of infection. These pathologic alterations gradually reverted to normal between days 7 and 14, concomitant with a return to normal control levels of circulating platelets. MCMV-induced megakaryocyte destruction is suggested as a useful model for exploration of the pathogenesis of human virus-induced thrombocytopenia.

Age lability of normal and variant methemoglobin reductase. STEPHEN A. FEIG, DAVID G. NATHAN, and HAROLD A. ZARKOWSKY. *Children's Hosp. Med. Ctr. and Harvard Med. Sch., Boston, Mass.*

The concentration of methemoglobin increases as red cells age in normals and in patients with congenital methemoglobinemia (CMHb), yet the activity of NADH diaphorase (ND) (Scott assay) does not decrease with age. A specific assay for methemoglobin reductase (MHR) (J. Lab. Clin. Med. 72:339, 1968) permits reassessment of this phenomenon. Red cells were separated by centrifugation at 100,000 g for 1 hour. The top and bottom 10% were harvested and mean ages determined by glutamic oxaloacetic transaminase (GOT) activity. The age stability of ND activity was confirmed. The MHR activity of old cells (bottom layer) was 15% lower than that of younger (top layer) cells in normal individuals. In one family with CMHb and two fast migrating isoenzyme variants of ND, the activity was only slightly reduced (12%) whereas MHR activity was markedly reduced (40 to 90%) in the old cells compared to young cells. An unrelated female with CMHb and a slow migrating variant of ND was previously reported to have "pseudo-mosaicism" on the basis of heterogeneous distribution of methemoglobin between her younger and older cells (NEJM 275:397, 1966). Her older cells actually had greater activity of ND than did her younger cells. In contrast, the MHR activity of her older cells was only 10% of her younger cells. Thus, the normal age-lability of MHR can account for the accumulation of methemoglobin as erythrocytes mature. Exaggeration of this tendency due to structural modifications in the enzyme molecules may account for methemoglobinemia in patients carrying variant isoenzymes.

Relationship between erythropoietin (EP) and erythropoiesis in chronic inflammation. JOHN LUKENS. *Univ. of Missouri, Columbia, Mo.* (Intr. by Calvin Woodruff).

The anemia associated with chronic inflammation results from failure of the erythroid marrow to increase its production sufficiently to compensate for a modest shortening of red cell survival. This defect in erythropoiesis was characterized by examining the quantitative relationship between EP production and erythropoietic response in rats with adjuvant-induced polyarthritis. EP production was measured by exposing rats to 0.5 atm. for 6, 9, 12, or 15 hours. The immediate post-hypoxic EP levels (assayed in post-hypoxic polycythemic mice and expressed as percent RBC ^{59}Fe incorporation per ml. plasma) was as follows for groups of 5 rats:

	0 Hr	6 Hr	9 Hr	12 Hr	15 Hr
Control	1.5 ± 0.7 ($\bar{x}$ ± SEM)	9.3 ± 3.7	9.8 ± 2.5	10.4 ± 3.1	12.8 ± 2.2
Adj. disease	0.6 ± 0.04	5.8 ± 1.6	3.5 ± 0.9	3.1 ± 1.2	3.4 ± 1.6
"p"	>0.2	>0.4	<0.05	<0.05	<0.01

That the decrease of biologically active EP in adjuvant disease (AD) plasma was not due to an EP inhibitor was demonstrated by failure of AD plasma, 1) to compromise the biologic activity of sheep EP, or 2) to suppress the erythropoietic response of exhypoxic mice to 10 hours of hypoxia. Finally, the responsiveness of the marrow to EP was quantitated in rats in whom endogenous EP was suppressed. Exogenous EP elicited a linear dose-response curve which did not differ for control and AD rats. These data suggest that the disturbance of erythroid homeostasis in chronic disease results from a relative insensitivity of EP elaboration to erythropoietic stimuli.

Toxic effect of lead on erythrocyte membranes. D. GRANT GALL, PATRICIA USHER, and ROBERT KLEIN. *Boston Univ. Sch. of Med., Boston, Mass.*

Lead has been reported to poison many enzyme systems including the Na+K dependent ATPase essential to maintaining normal membrane potentials. The present study was designed to measure the toxic effects of lead on membrane transport in human erythrocytes resulting from possible changes in ATPase activity. Na flux and membrane Na+K dependent ATPase were measured in erythrocytes of patients with lead poisoning and in normal erythrocytes exposed in vitro to lead in concentrations of 50–200 micrograms/100 ml. We have not been able to confirm the presence of decreased ATPase activity in patients with mild lead poisoning (i.e. no encephalopathy and blood concentrations of lead between 60 and 90 micrograms/100 ml.). However, we have demonstrated a markedly increased passive Na leak in both erythrocyte ghosts and intact cells. Active outward Na transport was also increased perhaps as a compensatory mechanism. In vitro exposure of intact red cells to lead has produced similar increases in membrane permeability to Na. In addition, when lead is incorporated in vitro into erythrocyte ghosts inhibition of active transport can be demonstrated. The mechanisms producing the two different effects of lead on membrane transport are separable and may be dose dependent. Thus lead affects the membrane in addition to any possible enzyme injury.

Autoradiographic and electron microscopic studies of marrow in congenital dyserythropoietic anemia. K. Y. WONG, GEORGE HUG, and BEATRICE C. LAMPKIN. *Univ. Cincinnati, and Children's Hosp. Research Found., Cincinnati, Ohio.*

A 12 year old Caucasian girl with congenital anemia and episodic jaundice was studied. Hemolysis was not present as evidenced by a normal Cr^{51} red cell survival time. Congenital dyserythropoietic anemia type II (Heimpel) was diagnosed after finding a positive acidified serum test of the circulating red cells and marked erythroid hyperplasia with erythroblastic multinuclearity in a bone marrow aspirate. A bone marrow specimen was labeled with H_3T in vitro and autoradiographs prepared. Electron microscopy was also done on the same specimen. The percent of uninucleated normoblasts labeling with H_3T indicated normal DNA synthesis. However, only 2% of the binucleated and none of the multinucleated polychromatophilic normoblasts labeled with H_3T, indicating decreased DNA synthesis in these forms. By electron microscopy, excessive membrane structures forming invaginations or cisternae and encompassing the circumference of the cell in varying degrees were seen in the majority of the normoblasts. The nuclear membrane appeared normal. Despite the abnormality, nuclear extrusion was noted in these cells. Small cisternae were also found at the periphery of the cell in about 1–2% of the mature erythrocytes. These findings are suggestive that the cells with more severe structural abnormalities and/or decreased DNA synthesis are destroyed intramedullarly and the circulating red cells are derived from a less abnormal portion of precursors.

Erythrocyte membrane alterations in experimental biliary obstruction. ROBERT C. NEERHOUT. *UCLA Sch. of Med., Los Angeles, Calif.*

To further clarify the erythrocyte abnormalities reported in patients with biliary atresia, a study was performed utilizing the bile duct ligated rabbit as a model. Hematologic parameters, membrane and plasma lipid determinations and P^{32} phospho-