ues. Peripheral blood responses were generally consistent with previous ""macro" lymphocyte reports for similar leukemic patients. However, 12 of 30 patient marrows were nonresponsive to PHA on at least one occasion, and only 6 leukemic marrows were positive to the antigen battery—each only to a single antigen. Some immune and clinical correlates of these studies will be discussed.

Monocyte function in children with neutropenia. ROBERT L. BAEHNER, and RICHARD B. JOHNSTON, JR. *Children's Hosp. Med. Ctr., Harvard Med. Sch., Boston, Mass.*

It has been reported that normal monocytes kill *S. aureus* as effectively as do PMN but patients with congenital neutropenia (CN) have increased number of circulating monocytes in the presence of uncontrolled infection. Therefore, we have compared the metabolic and bactericidal responses of CN monocytes from 2 such patients, the monocytes from 2 patients with cyclic neutropenia, patients with chronic infection, to the PMN from normals and patients with acute infection. At a bacteria to phagocyte ratio of 2–3:1 in an *in vitro* system which measured the combined effect of uptake and intracellular killing of *S. aureus,* PMNs consistently killed about 95% of the inoculum during 2 hours. In contrast, monocytes from all patients failed to diminish the number of bacteria during the incubation. PMNs initiated ingestion sooner, took up *S. aureus* or zymosan particles faster, and ingested more bacteria or particles than did monocytes. Furthermore, despite a brisk respiratory burst, pentose shunt stimulation and hydrogen peroxide production by monocytes, there was less iodination of bacteria by monocytes than PMN. Granule myeloperoxidase was significantly less in monocytes (163 ± 47) from all patients compared to PMN (390 ± 10). Cell associated bactericidal activity by monocytes was markedly diminished compared to PMN. These studies show that monocytes from patients with neutropenic syndromes function similarly to monocytes from children with subacute infection. Such monocytes are less bactericidal than PMN because of the combination of decreased phagocytic capacity and lower activity of the intracellular mechanisms related to peroxidation of bacteria.

Successful treatment of inoperable embryonal rhabdomyosarcoma. JORDAN R. WILBUR, WATARU W. SUTOW, MARGARET P. SULLIVAN, JOSEPH R. CASTRO, HERBERT KAIZER, and H. GRANT TAYLOR. *M. D. Anderson Hospital and Tumor Institute, Houston, Tex.* (Intr. by Robert E. Greenberg).

Embryonal rhabdomyosarcoma, when inoperable or metastatic, has usually been a rapidly fatal cancer. Intensive combination chemotherapy (VAC) with Vincristine (VCR), Actinomycin-D (AMD) and Cyclophosphamide (CYT) in conjunction with radiotherapy is effective in the treatment of this tumor. Twenty-one children with inoperable or metastatic embryonal rhabdomyosarcoma, or undifferentiated sarcoma suggestive of embryonal rhabdomyosarcoma, were treated in the 3-year period 1967–1969. Sixteen of them (76%) are alive without evidence of disease 1–4 years after initiation of therapy. Therapy consisted of biopsy, Co^{60} radiation 5000–6000 rads tumor dose, and VAC chemotherapy. Surgery was subsequently utilized when feasible. The chemotherapy consisted of VCR 2 mg./M^2 IV weekly x12, AMD 75 mg./Kg. divided into 5–8 daily doses every 3 months for 5 or 6 courses, and CYT given either as 2.5 mg./Kg./day for 2 years or 10 mg./Kg./day for 7 days every 6 weeks. The type of CYT therapy was dependent on tumor location and extent.

"Total therapy" of childhood acute lymphocytic leukemia. DONALD P. PINKEL, JOSEPH V. SIMONE, H. OMAR HUSTU, and RHOMES J. AUR. *St. Jude Children's Res. Hosp., Memphis, Tenn.*

In 1962 studies were initiated to determine, first, whether a significant 5 year cure rate of childhood acute lymphocytic leukemia (ALL) was attainable with present therapeutic agents and secondly, how best this could be accomplished. The basic plan was (1) to induce complete remission promptly, (2) to administer multiple antileukemic drugs for 2–3 years with the purpose of eradicating all residual leukemia and (3) to prevent nervous system leukemia by "prophylactic" central nervous system (CNS) therapy early during remission. From early pilot studies with relatively few patients the program has evolved to more elaborate investigations involving large numbers of patients and comparisons of alternate treatment methods. Of 37 children who developed complete remission (CR) in studies I–III (1962–65) 7 survive in CR for 6 to 8 years and have been off all therapy for 3 to 5 years. Study IV (1965–67) demonstrated the superiority of full dosage over half dosage of combination chemotherapy. Of 31 patients entering CR in Study V (1967–68) 20 remain in continuous CR for 2½ to 3 years; therapy has been discontinued in the majority and will soon be terminated in the remainder. In Study VI (1968–70) 94 children in CR were randomized for craniospinal radiation (2400 R) or none. Of 45 who received craniospinal radiation only 2 developed initial relapse in the CNS and 35 remain in continuous CR for 8 months to 2½ years. Of 49 who did not receive radiation, 25 have developed CNS relapse. It is concluded that a significant 5 year cure rate is an attainable goal in ALL, that ALL can no longer be considered an incurable disease, that CNS therapy inhibits CNS relapse, and that palliation is no longer an acceptable approach to the management of this disease.

Diphenylhydantoin induced coagulation abnormalities. M. HILGARTNER, G. E. SOLOMON, and H. KUTT (Intr. by Carl H. Smith). *Cornell Med. Ctr. N. Y., N. Y.*

Bleeding within the first 24 hours of life has been reported in some infants whose mothers received anticonvulsants. This study was designed to evaluate the relationship between Diphenylhydantoin (DPH) and coagulation defects. Eight cats were given DPH intraperitoneally daily (two cats received 2.5mg./kilo, two cats 5mg./kilo, four 10mg./kilo). These animals were followed weekly for coagulation abnormalities, neurologic toxicity and DPH blood levels. Cats receiving 10mg./kilo, for 8 to 15 days showed a decrease in Factors I, II, V, VII and X plus ataxia. Cats receiving 2.5 and 5.0mg./kilo showed a decrease in the same factors to a lesser degree. After one week of treatment with DPH, Factors I, II, V, VII and X were decreased 50% in all animals. Vitamin K dependent Factors II, VII and X returned to normal in cats on low doses of DPH. These Factors continued to fall in cats receiving 10mg./kilo. Animals on low dosage of DPH appeared to adapt and no longer showed a coagulation abnormality. Factor V fell initially and then rose above base line values in all cats after one week suggesting transient liver dysfunction. Factor VIII remained normal in all the animals. To prove that the coagulation defect was dependent on Vit. K three cats were treated with 10mg./kilo DPH and 1mg. Vit. K daily. This combination prevented the clotting abnormalities without preventing neurologic signs of DPH toxicity. Cord blood levels of DPH have been found increased over mother's DPH blood levels suggesting a mechanism for infant toxicity. Since this study in

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.*