637 VENO-OCCLUSIVE DISEASE (VOD): A NEWLY RECOGNIZED FORM OF DRUG-INDUCED LIVER DISEASE IN ACUTE MYELOCYTIC LEUKEMIA (AML). J. Lawrence Naiman, Robert S. Wimmer, Dale S. Huff, and H. Theodore Harcke. Temple U. Sch. of Med., Depts. of Pediatrics, Pathology and Radiology, St. Christopher's Hospital for Children, Philadelphia, Pa.

We have recently observed 3 children with AML treated with daunorubicin (DNR), ara-c and thioguanine (TG) who during remission developed marked hepatomegaly (H) in the absence of jaundice or significant transaminasemia. Liver scans revealed diffuse non-homogeneous reduction in uptake suggesting leukemic infiltration. Liver biopsies showed no significant infiltration, but instead thickening of the walls of the central veins, and intense centrilobular congestion and hemorrhage, a pattern resembling VOD caused by plant alkaloid poisoning. One child had a large R. pleural effusion requiring chest drainage for 1 month. All 3 children have been since maintained only on TG. H and abnormal liver scans have improved but remain abnormal 8-10 months later. One child in relapse was re-treated with all 3 drugs and developed an exacerbation of the liver disease and pleural effusion. The above reactions all occurred within a 2 month period in 1976 and had not been seen previously in other children receiving the same drug regimen. Etiologic considerations include an altered lot of DNR, enhanced toxicity of DNR by TG-induced hepatic dysfunction, or other complex interactions. Recognition of this type of liver disease is important in the diagnosis of acute hepatomegaly in such children. Further elucidation of its pathogenesis may enable safer usage of these potent drug combinations.

638 PULMONARY FIBROSIS, A DELAYED COMPLICATION OF CYCLOPHOSPHAMIDE. Arthur J. Newman, Carlos Alvarado, Samuel Gross. Case Western Reserve University, University Hospitals, Department of Pediatrics, Cleveland, Ohio.

Prolonged survival of patients with previously fatal malignancies has led to the identification of late appearing toxic manifestations of therapeutic agents. This report presents two children with late onset pulmoanry fibrosis believed secondary to remote cyclophosphamide administration. A 4 1/2 yr. old white female with acute lymphoblastic leukemia received 70 gm of cyclophosphamide over a 34 month period. Four years later she developed progressive pulmonary fibrosis with pleural thickening and effusions, bilateral apical pneumothorax, reduced AP diameter of chest and cor pulmonale. Over the next three years pulmonary function tests showed progressively decreasing function and she expired with hypoxia and hypercapnea. Autopsy revealed interstitial pulmonary fibrosis. A 3 1/2 year old male with Hodgkin's disease (lymphocytic predominence) received mantle x-ray therapy (2200R) followed by cyclophosphamide, 42 gm in fifty-one months. Six years later he developed cough, tachypnea, reduced exercise tolerance and weight loss. Chest x-ray revealed decreased AP diameter, interstitial fibrosis and pleural thickening. Pulmonary function tests revealed marked restrictive lung disease with severely diminished vital capacity. There was also EKG evidence of cor pulmonale. Microscopical examination of transbronchial lung biopsy showed interstitial fibrosis. Pulmonary function has decreased over subsequent two years and his vital capacity is now 24% of expected values.

639 IRON BURDEN IN SICKLE CELL ANEMIA. Richard T. O'Brien (Spon. by Howard A. Pearson) Yale-New Haven Medical Center, Dept. of Pediatrics, New Haven.

Hypertransfusion programs are being increasingly used in sickle cell anemia (SS dis.). A potential risk of such therapy is transfusional hemosiderosis. It has been assumed that patients with SS dis. acquire large iron burdens from increased GI absorption and sporadic transfusions. There are few data concerning the acquisition of an iron burden in SS dis. Total body iron burden was estimated by 2 indirect methods: 24 hour urinary iron excretion following a 10 mg/Kg IM dose of desferrioxamine (DFO) and the serum ferritin (SF). Serum iron and TIBC were also measured. 20 patients with SS dis. from 3 to 34 years of age were studied. These data were compared with that obtained from patients with thal. major on hypertransfusion programs and thal. intermedia not on regular transfusions. Serum iron and TIBC were normal for all SS dis. patients. DFO-induced urinary iron excretion correlated directly with age, but was normal or only minimally elevated in patients under 20 years of age. Those over 20 had modest increases, but only 2 exceeded 5 mg per day. SF did not correlate with age and were normal in almost half the patients. Elevations in SF were moderate and only rarely exceeded 1000 ng/ml. Patients with thal. major acquire massive iron burdens at an early age as indicated by SF in excess of 2000 ng/ml and very high DFO-induced urinary iron excretions. These data indicate that patients with SS dis. managed by conventional means do not acquire a large total body iron burden through early adult life.

640 METABOLIC CHARACTERISTICS OF CORD BLOOD ERYTHROCYTES STUDIED AT REDUCED OXYGEN TENSION. Frank A. Oski and Rosemarie Cittadino. SUNY, Upstate Medical Center, Syracuse, New York.

The erythrocytes of the newborn infant possess a variety of metabolic characteristics that serve to distinguish them from the red cells of normal adults. In an attempt to define the functional significance of some of these differences the red cells of newborn infants were studied at reduced oxygen tensions rather than in room air, in order to more closely mimic the intrauterine environment. Red cells from 10 adults and 10 infants were incubated for 3 hours in room air, 5% O_2, 2% O_2, and in nitrogen, and measurements of glycolysis, glycolytic intermediates, and response to menadione (7.5 µg/ml) were performed. Glucose consumption and pyruvate and lactate production rose in a similar fashion in both groups. In the adults the increase in glucose consumption was associated with an increase in the levels of triose phosphates and 2,3-DPG, while in the newborns both these compounds decreased. The fall in glutathione of 65.5% that occurred in room air became an increase of 1.1% when the cells of the newborn were incubated in an atmosphere of 5% O_2. These studies indicate that the normal activation of phosphofructokinase that occurs at low oxygen tensions is not as marked in the red cells of the newborn. Of more importance is the fact that these cells are not as prone to oxidant injury when incubated under conditions that simulate the intrauterine environment.

641 HISTOLOGIC MATURATION IN BILATERAL WILMS' TUMOR. J. Douglas Pinney, Brett B. Cantrell, John J. White, and Herbert Kaizer. The Johns Hopkins University School of Medicine, The Oncology Center, Baltimore, Maryland 21205. Sponsored by Brigid G. Leventhal.

The phenomenon of maturation of a malignant to a benign neoplasm is definitely known to occur in only one pediatric tumor, namely neuroblastoma. In Wilms' tumor there is evidence of variation in the relative histopathologic make-up of the malignancy; however, there has been no description of maturation of Wilms' to a benign tumor, either with or without treatment. In our series of sixty-eight Wilms' tumors seen since 1956 we have nine patients with bilateral involvement. All were treated similarly, with surgical resection of the more involved kidney, radiation therapy to the resected kidney bed and contralateral tumor, and variable courses of vincristine, actinomycin D and adriamycin. Six of these patients are alive and well. In two of these six bilateral cases we have evidence of histologic transition to a benign rhabdomyoma in the residual mass. A third patient, dying as a result of concomitant progressive nephritis, showed autopsy evidence of residual rhabdomyoma. The capacity for maturation of bilateral Wilms' may have played a role in the favorable courses we have observed in our patients with bilateral disease. Further therapeutic research should explore the possible use of agents promoting maturation of transformed cells.

642 AUTONOMOUS PRODUCTION OF PARATHORMONE BY LYMPHOBLASTIC LEUKEMIA CELLS IN CULTURE. Norma K.C. Ramsay, William Krivit, Mark E. Nesbit, Raymond Yip and David M. Brown. University of Minnesota School of Medicine and Hospitals, Department of Pediatrics, Minneapolis.

A 16 year old girl developed hypercalcemia (14.4 mgm/dl) at the time of exacerbation of acute lymphoblastic leukemia which required intensive therapy, including mithramycin, to reduce calcium levels. Parathormone (PTH) was inappropriately elevated to 82 µlEq/ml with a calcium level of 13.7 mgm/dl.

To determine if ectopic PTH production by leukemic cells was occurring in this patient, bone marrow (95% lymphoblasts) was cultured in vitro in a liquid culture system containing 15% fetal calf serum. No measurable PTH was present at 0 time or at 20 hours, however, 247 µlEq/ml PTH was measured at 68 hours. PTH levels increased in the culture system with levels of 349 µlEq/ml at 10 days and 533 µlEq/ml at 13 days. PTH was undetectable when no viable cells remained in culture at 17 days. PTH production was similar when the cells were cultured in media with calcium levels ranging from 2.7 - 5.9 mgm/dl. This is the initial demonstration of autonomous PTH production in culture of lymphoblastic leukemia cells, and is another example of a non-endocrine cell producing a biologically active polypeptide hormone. Autonomous production of PTH should be considered in the etiology of hypercalcemia in acute lymphoblastic leukemia.