836 USE OF THE FACTOR VIII HALF-TIME FOR DESIGNING CONTINUOUS FACTOR VIII INFUSION IN CLASSIC HEMOPHILIA. Campbell W. McMillan and Walter B. Greene. University of North Carolina School of Medicine, Department of Pediatrics and Division of Orthopaedic Surgery, Chapel Hill, N. C.

In studies on continuous infusion of factor VIII for treatment of patients with classic hemophilia, the following regression equation was derived for patients with a factor VIII half-time (T/2) of 13.4 hr± 0.6: Y = (3.1±1.8) + (23.4±0.7)X, where Y is plasma factor VIII units/dl and X is factor VIII dose-rate in units/kg/hr; or, essentially Y = 23.4X. Preliminary studies suggested that the plasma factor VIII level could be correlated with dose-rate for any T/2 as follows: if Y = 23.4X for T/2 of 13.4 hr, then Y = (1.75)(13.4)X where 1.75 is an empiric constant; therefore, Y = (1.75)(T/2)X where T/2 may be any measured plasma factor VIII half-time after a single infusion. The validity of this equation and its application to design of continuous infusion of factor VIII were supported in studies during orthopaedic and dental surgical episodes of three hemophilic patients with factor VIII half-times ranging from 0.7 to 6 hrs. For example, following synovectomy and radial head excision of the left elbow in a child with T/2 of 4 hrs, a plasma factor VIII level of 76 to 86 units/dl was observed during continuous infusion of 9.4 factor VIII units/kg/hr; for this dose-rate and T/2, the expected factor VIII level is 66 units/dl, i.e., 1.75 x 4 x 9.4. This approach is not applicable to design of therapy for patients with potent factor VIII inhibitors (above 20 Bethesda units/ml) in whom T/2 may not be measurable.

837 INCREASED PLASMA THROMBOXANE LEVELS IN SICKLE CELL DISEASE, Paulette Mehta (Sponsored by James Talbert), Department of Pediatrics, University of Florida College of Medicine, Gainesville.

Platelet function abnormalities, i.e., increased circulating platelet aggregates and decreased platelet aggregation, have been observed in sickle cell disease patients. To determine the mechanism of these abnormalities, we studied 13 patients with sickle cell disease and 10 normal subjects. Peripheral venous blood samples were collected for plasma thromboxane B_2 (TXB_2) (stable metabolite of TXA_2) determinations by radioimmunoassay. In addition, platelets were stimulated with sodium arachidonate (1 mM) and thrombin (10 units/ml), and platelet TXB_2 generation quantitated. In 11 patients in steady state, plasma TXB_2 levels were increased compared to normal subjects (480 ± 41 vs 252 ± 37 pg/ml, P<0.01). In contrast, platelet TXB_2 generation in response to sodium arachidonate was lower in patients with sickle cell disease (44 ± 10 vs 103 ± 32 pg/10^8 platelets, P<0.01). Similarly, thrombin-induced platelet TXB_2 generation was decreased (186 ± 45 vs 801 ± 320 pg/10^8 platelets, P<0.01). In 2 patients with acute vaso-occlusion, plasma TXB_2 levels were extremely high (1650 and 1350 pg/ml), but platelet TXB_2 generation was similar to those in steady state. Increased plasma TXB_2 levels in sickle cell disease patients imply continuous platelet activation and may be a mechanism of increase in circulating platelet aggregates. Decrease in platelet TXB_2 generation suggests either substrate or enzyme deficiency due to persistent platelet activation, and may be the cause of decreased platelet aggregation.

● **838** INCREASED ERYTHROCYTIC CALMODULIN IN HEREDITARY XEROCYTOSIS. Carlos M. Monzon, E. Omer Burgert, Jr., Virgil F. Fairbanks, John J. Penniston, and James Jones. Mayo Graduate School of Medicine, Mayo Clinic, Department of Pediatrics, Rochester, Minnesota.

Previous studies of the red blood cells of patients with xerocytosis have shown a membrane abnormality with increased permeability to cations with a greater efflux of potassium than of sodium. Consequently these erythrocytes lose potasssium in excess of sodium gained with a decrease in the total cation content in the cells. Osmotically resistant xerocytes are thus formed and are readily identified.

Two patients in one family demonstrated abnormal erythrocytic cation content and elevation of calmodulin activity.

Patient	Na (meq/L)	K (meq/L)	Total (meq/L)
1	19.7	79.4	99.1
2	29.0	76.1	105.1
Normal	14 (6.2-19.9)	99 (95.2-105)	113.5 (109-123)

In these patients calmodulin activity as estimated by stimulation of cyclic nucleotide phosphodiesterase activity was elevated 3 x above that of normal control erythrocytes and significantly above that found in patients with G-6 PD deficiency.

Calmodulin	Normal range	Xerocytosis
(ng/ug Hgb)	0.0789-0.1289	0.3333

This implies an enhanced exchange of Ca^{++} between the cytosal and membrane associated sites. Calmodulin controls the location and amount of membrane Ca^{++}-K^+ efflux and such a pertubation in Ca^{++} handling would lead to the type of K^+ loss observed in xerocytosis and the resultant morphologic aberrations.

839 CASEIN INHIBITION OF NEUTROPHIL PHAGOCYTOSIS. Linda L. Moore, James R. Humbert, Carel J. van Oss. State Univ. of New York and Children's Hospital of Buffalo, Departments of Pediatrics and Microbiology, Buffalo.

Peritoneal irritation with casein is widely used to obtain neutrophil (PMNs) from rodents for investigations. Since casein forms aggregates, its phagocytosis could produce "fatigued" PMNs whose subsequent behavior might not reflect basic experimental conditions. We therefore studied the effect of casein upon yeast phagocytosis by human and rat PMNs, using a cytochemical method. Results are reported as means only, with corresponding P values. Following in vitro exposure to 8% sodium caseinate(9 experiments) human PMNs phagocytized less yeasts/100 cells than control PMNs (130 vs 410, $P < 0.005$); the number of phagocytic PMNs was also decreased (61% vs 96%, $P < 0.005$). With rat PMNs, 7 experiments yielded similar results (120 vs 270 yeasts/100 PMNs; 65.5% vs 96.0% phagocytic PMNs, $P < 0.005$). Elimination of casein aggregates by micro-filtration followed by reconcentration of the casein to 8% by ultrafiltration (4 experiments), partly corrected the phagocytosis inhibition (yeasts/100 PMNs with unfiltered 8% casein: 53; with filtered/reconcentrated 8% casein: 267; in controls: 471). Casein suspensions used to obtain peritoneal PMNs in rodents lead to significant cell fatigue as evidenced by a pronounced phagocytic defect. This dysfunction can be minimized by preventing casein aggregates through filtration and reconcentration of the casein suspension. Cell fatigue caused by particulate matter must be anticipated in studies of rodent phagocytes obtained from peritoneal exudates.

840 XANTHINE OXIDASE (XO) DEFICIENCY IN A PATIENT WITH ACUTE LYMPHOCYTIC LEUKEMIA (ALL). Elaine R. Morgan, George R. Honig and Donald J.Nelson. Children's Memorial Hospital, Division of Hematology, Chicago; and Wellcome Research Laboratories, Research Triangle Park, North Carolina.

XO catalyzes the oxidation of xanthine and hypoxanthine to uric acid (UA), as well as the conversion of 6-mercaptopurine (6-MP) to the inactive products 6-thioxanthine and 6-thiouric acid. A child with XO deficiency and ALL provided an opportunity to examine the role of XO as a mediator of 6-MP toxicity and metabolism. A 16 y/o girl presented with a leukocyte count (WBC) of 310,000/µl with >90% lymphoblasts in her blood and bone marrow. Her WBC fell to 9,500/µl after 3 days of chemotherapy, and she achieved complete remission after 4 wks. Her initial UA level was 0.7 mg/dl, and the level did not increase during treatment. Her maintenance chemotherapy included daily 6-MP, and subsequently high-dose intermittent 6-MP (500 mg/m^2/day x 5), which she tolerated without apparent toxicity. On an unrestricted diet she excreted 28.5 mg of UA/24 hr (N=300-600) and 2,955µ mol of oxypurines (N=70-155). Assays of XO activity indicated <1% of normal enzyme activity, confirming the diagnosis of XO deficiency. HPLC assays of the patient's urine showed that 47% of administered 6-MP was excreted unchanged (N=5-7%) with 6-thiouric acid representing <1% (N=25-30). The absence of unusual toxicity from 6-MP in this child indicated that in leukemia patients with XO deficiency, either congenital or due to allopurinol, major reductions in 6-MP dosage, which could compromise antileukemic therapy, may not be necessary or appropriate.

841 INTENSIVE PLASMA EXCHANGE (PE) IN REFRACTORY ACUTE AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA). J. Lawrence Naiman, Mark L. Bernstein, Barbara K. Schneider. Temple U. School of Medicine, St. Christopher's Hospital for Children, Dept. of Pediatrics, Philadelphia, Pa.

Idiopathic AIHA in childhood is usually an acute self-limited disease, responding well to steroids and transfusion. In severe refractory cases, immunosuppressive agents may be of help, but the slow onset of effect (usually weeks) limits their usefulness. Presented with a 17 year-old boy with severe acute AIHA unresponsive to prednisone (10 mg/kg/d), exchange transfusion & splenectomy, we performed PE using the IBM model 2997 Blood Cell Separator. Before PE he required 20 u PRBC over 14 days to keep his Hb > 4 g/dl. Post-PE his Hb remained stable for 5 days. Azathioprine was begun, but when his Hb fell 2 days later a 2nd PE was performed. Again there was abrupt stabilization of Hb levels followed by return to normal over the next 3 weeks, without further transfusion. Total volumes of blood processed in the 2 PE were 8500 & 8250 ml, representing 4240 & 4140 ml plasma (incl. extracellular fluid). Transient coagulation defects were observed, but were corrected by fresh frozen plasma infused post-PE; no bleeding problems developed. Our observations in this case suggest that antibody removal by PE enabled prompt control of severe hemolysis, 'buying time' until the immunosuppressive effect of azathioprine took place. Further trial of this combined therapy seems warranted in cases of acute disease refractory to large doses of steroids, and perhaps in younger children with chronic drug-dependent disease prior to consideration of splenectomy.