●758 APPLICATION OF DNA ANALYSIS TO DETERMINE CARRIER STATUS (CS) OF HEMOPHILIA A. Robert L. Janco*, John Phillips III*, Pamela J. Orlando*, Martha J. Woodard*, and Richard M. Lawn†. *Vanderbilt Univ., Dept. of Peds, Nashville, TN & †Genentech, Inc., Dept. of Molecular Biology, S. San Francisco, CA.

Hemophilia A is an X-linked disorder caused by absent or dysfunctional factor VIII:C. Because of therapy-induced complications: hepatitis, inhibitor formation, and infection with Human Immunodeficiency Virus, CS determination is often requested. CS by analysis of factor VIII:C levels and pedigree-derived probabilities has limited utility and significant risk for error. We evaluated the utility of 3 intragenic restriction fragment length polymorphisms (RFLPs) (Intron 18, 22 and 25) and the closely-linked extragenic RFLP (ST14) to provide CS through genotype assignment. Using standard Southern blots we found that 38/93 (41%), 25/43 (58%), 14/44 (32%) and 103/106 (97%) of female relatives were heterozygous for the Intron 18, 22, 25 and ST14 RFLPs. Utility of Intron 18 and 25 in combination was limited by strong linkage disequilibrium (27/27 females homozygous for Intron 18 were also homozygous for Intron 25). In contrast of 38 females homozygous for the Intron 18 RFLP 20/38 (53%) were heterozygous for Intron 22. Our data indicate that analysis of the Intron 18 and 22 RFLPs could provide highly accurate information for 68% of females at risk for being carriers and the closely-linked ST14 RFLPs would be informative for the remaining 32%.

759 PROSPECTIVE NEURODEVELOPMENTAL STUDIES OF FOUR INFANTS TREATED WITH CHEMOTHERAPY, TOTAL BODY IRRADIATION, AND BONE MARROW TRANSPLANTATION. Thomas A. Kaleita, W. Donald Shields, Stephen A. Feig, UCLA School of Medicine, Department of Pediatrics, Los Angeles, CA.

Bone marrow transplantation (BMT) is being used increasingly for the treatment of pediatric malignancies and aplastic anemia. Conditioning regimens used prior to BMT may cause neurotoxicity, especially to the developing nervous system. We report results of serial neurodevelopmental assessments of four patients transplanted during infancy for acute leukemia (AL) or aplastic anemia (AA).

Four consecutively studied children, all less than 18 months old at the time of BMT, were studied with the Gesell Developmental Schedules (GDS), and, later, with the Stanford-Binet (S-B) or Wechsler (WISC-R) intelligence tests and other standardized tests of language, perception, and motor coordination.

All four children obtained average developmental quotient scores on the GDS at the time of BMT. Two patients with AL and one with AA, who received total body irradiation, now show at least average intelligence (SB IQ = 107 and 138, and WISC-R IQ = 128 respectively) more than five years after BMT. The other AA patient, 7 months old at BMT, obtained an SB IQ of 121, 23 months after BMT. All four children show no abnormalities in perception, language, and motor coordination.

The post BMT development of these patients is contrary to expectations that lethal chemoradiotherapy would likely produce neurologic disability in very young children and suggests that future therapeutic studies of infants and very young children using BMT and intensive conditioning regimens are not contraindicated by the expectations of debilitating CNS sequelae.

760 METABOLIC IMPLICATIONS OF CATALASE-BOUND NADPH. Henry N. Kirkman. Univ. of N.C. School of Medicine, Dept. of Pediatrics, Chapel Hill, N.C.

Renewed interest in the metabolism of O_2 radicals and H_2O_2 stems from awareness of their roles, for example, in BPD, WBC function, and certain hemolytic anemias. Two means for disposal of H_2O_2 are: (a) catalase and (b) the glucose-6-phosphate dehydrogenase (G6PD), NADPH, glutathione reductase/peroxidase pathway. As reflected in the present study by initial rates in the spectrophotometric assay of Aebi, purified catalase from human red cells and bovine liver underwent partial inactivation when diluted to nanomolar concentrations at pH 7. Inactivation occurred despite the presence of bovine albumin and the use of plastic containers. The inactivation was prevented, but not promptly reversed, by the addition of NADPH. This effect seems to be a second type of protection of catalase by NADPH. Kirkman & Gaetani recently found that catalase contains tightly bound NADPH, which is slowly oxidized in the process of preventing and reversing the inactivation (formation of compound II) of catalase by its own substrate, H_2O_2 (J. Biol. Chem. 262, in press, 1987). Human catalase came to be regarded as a "fossil enzyme" as a result of the relatively benign nature of acatalasemia and the known sensitivity to drug- induced peroxidative stress of G6PD-deficient red cells, a deficiency affecting over 100 million people. Knowledge of catalase-NADPH interaction, however, allows re-interpretation of earlier studies and leads to the conclusion that human catalase and pathway (b) are both responsible for H_2O_2 removal. Both are dependent on NADPH, which explains the particular susceptibility of G6PD-deficient red cells to peroxidative stress.

761 ELEVATED SERUM IRON LEVELS FOLLOWING ADMINISTRATION OF CISPLATINUM Gad Kletter, Bruce R. Parks, Arati Bhatnagar, Rathi V. Iyer University of Mississippi Medical Center, Department of Pediatrics, Jackson, MS

An increase in serum iron levels and a decrease in serum unsaturated iron binding capacity (uIBC) were noted following the administration of cisplatinum to 9 children with malignancies. The mean serum iron concentration increased from a pretreatment level of 75.7±30.5 ug/ml to a post treatment level of 162.1±65.3 ug/ml with the first cisplatinum treatment course($p<0.004$). The uIBC concomittantly decreased from 181.9±33.7 ug/ml to 86.4±44.6 ug/ml($p<0.0005$). Cummulative effect was noted following subsequent courses. The levels returned to baseline values within 2-4 months following cessation of therapy in 6 children in whom follow up data was available. It is possible that this reversal of the iron/uIBC ratio is the result of cisplatinum competition for iron binding sites to proteins.

●762 *DDAVP (1-DESAMINO-8-D-ARGININE VASOPRESSIN) DECREASES OPERATIVE BLOOD LOSS IN PATIENTS UNDERGOING HARRINGTON ROD SPINAL FUSION SURGERY.* *Nathan L. Kobrinsky, R. Mervin Letts, Leena R. Patel, Esther D. Israels, Ronald C. Monson, Nora Schwetz, Mary S. Cheang. Faculty of Medicine, University of Manitoba, Dept. of Pediatrics and Child Health, Winnipeg, Manitoba, Can. R3E 0V9*

To evaluate the effect of 1-desamino-8-D-arginine vasopressin (DDAVP) on surgical blood loss, 35 hemostatically-normal subjects received 10 μg/M² DDAVP or placebo by randomized double-blind assignment prior to Harrington rod spinal fusion. On preoperative testing, DDAVP increased factor VIII coagulant activity, von Willebrand antigen, platelet adhesiveness and prothrombin consumption and decreased the partial thromboplastin time and the bleeding time ($p<.0003$). At surgery, the drug reduced blood loss by 32.3% (1681 ± 901 ml in the placebo group vs. 1134 ± 593 ml in the treated group, $p=.03$) and similarly, reduced the requirement for concentrated red cell transfusions by 26.5% (3.36 ± 1.64 units in the placebo group vs. 2.50 ± 0.97 units in the treated group, $p=.04$). Post-operatively, the drug reduced the duration of analgesia from 201.5 ± 83.0 hours in the placebo group to 149.0 ± 64.0 hours in the treated group ($p=.01$), presumably by decreasing bleeding into the surgical wound. By multivariate regression analysis, the best three predictors of surgical blood loss ($p=.024$) and transfusion requirements ($p=.008$) were the bleeding time, platelet adhesiveness and the use of DDAVP. In conclusion, DDAVP shortens the bleeding time and decreases operative blood loss in hemostatically normal subjects.

763 *INCREASED NAUSEA AND VOMITING INDUCED BY NALOXONE IN PATIENTS RECEIVING CANCER CHEMOTHERAPY.* *Nathan L. Kobrinsky, Patricia B. Pruden, Mary S. Cheang, Martin Levitt, Agnes J. Bishop, and Milton Tenenbein. Faculty of Medicine, University of Manitoba, Department of Pediatrics and Child Health, Winnipeg, Manitoba, Canada, R3E 0V9.*

To evaluate the role of endogenous opiates in chemotherapy-induced nausea and vomiting, the narcotic-antagonist naloxone was administered to six pediatric patients receiving cancer chemotherapy. Naloxone was administered by continuous intravenous infusion after randomized, double-blind controlled assignment at a dose of 0, 10 or 40 μg/kg/hour for 12 hours. Each patient was studied for four consecutive and identical courses of chemotherapy (eight courses for each naloxone dose, or 24 courses in all). A dose-related increase in nausea (nausea score 2.5 ± 2.24, 3.83 ± 2.73 and 5.75 ± 2.86 per 12 hours, $p=.003$), vomiting (emetic events 6.0 ± 7.50, 8.08 ± 6.71 and 10.3 ± 8.91 per 12 hours, $p=.035$) and patient aversion (course preference rank 1.5 ± 0.45, 2.83 ± 1.17 and 3.25 ± 0.42 per four courses, $p=.014$) was observed. The infusion of naloxone in the absence of chemotherapy was without effect. These results support a role for endogenous opiates in regulating chemotherapy-induced nausea and vomiting, and further, suggest that narcotic agents may be effective anti-emetics in this setting.