

925 EFFECT OF ASPIRIN ON ALPHA₂-RECEPTORS ON HUMAN PLATELETS. Paulette Mehta and Jawahar Mehta,

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Aspirin decreases epinephrine-induced platelet aggregation and release reaction. Activation by epinephrine is mediated through interaction with alpha₂-adrenoceptors on platelet membrane. We evaluated specific binding of alpha₂-antagonist ³H-yohimbine to determine the maximal number of binding sites (B_{max}) and the dissociation constant (K_D) of alpha₂-receptors. Platelet alpha₂-receptor B_{max} and K_D were quantitated in four normal subjects before and 24 hours after aspirin 650 mg ingestion. In these subjects, B_{max} increased from 166±40 to 281±30 fmol/mg protein (P<0.05) and K_D from 2.95±0.52 to 5.91±0.92 nM (P<0.05). To determine if these effects were direct, isolated human platelet membranes were studied before and after in vitro incubation with aspirin (90µg/ml) for 30 minutes. In three experiments, alpha₂-adrenoceptor B_{max} increased significantly (P<0.05) from 135±34 to 236±42 fmol/mg protein, K_D also increased from 2.52±0.42 to 9.42±1.12 nM (P<0.05).

These studies indicate that aspirin causes an increase in the number of alpha₂-adrenoceptors on platelets, and increase in K_D, representing a decrease in affinity. Decreased affinity may be a mechanism for diminished responsiveness of platelets to epinephrine after aspirin.

926 LONG TERM ENDOCRINE SEQUELAE IN MEDULLOBLASTOMA PATIENTS. Sharon Oberfield, Lenore Levine, Maria New, Jeffrey Allen.

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Over 50% of pts. with medulloblastoma who receive conventional therapy with craniospinal irradiation will be alive and free of disease five yrs. from diagnosis. Endocrine evaluation was performed in 22 pts. aged 2½-23½ yrs. at time of diagnosis, status post treatment for medulloblastoma. Evaluations were performed 2 mos. to 6 3/4 yrs. after diagnosis. The pts. received either 12 mos. of chemotherapy and/or radiation therapy. The mean radiation dose to the neuraxis and hypothalamus was 3600 rads. Three pts. had completed their growth prior to onset of disease. Post-treatment, decreased growth rates were observed in 13 pts. Only 3 of 10 pts. tested had deficient GH response to stimulation. Elevated TSH levels were noted in 15 pts. with abnormal TSH responses to TRH in 13 of 13 tested. Compensated thyroidal hypothyroidism was observed in 13 pts., 1 patient each had thyroidal hypothyroidism, or hypothalamic hypothyroidism. We conclude that an abnormal growth rate associated with a normal GH response to standard stimuli, postulated to be caused by growth hormone neurosecretory dysfunction, and compensated hypothyroidism are frequent complications of therapy for medulloblastoma. Further, standard provocative tests of GH reserve are inadequate to define neurosecretory growth dysfunction; a trial of GH treatment may be indicated in children with poor growth rates. In addition, treatment with thyroid hormone of patients with compensated hypothyroidism should be considered. These therapies may allow achievement of normal growth and development and thus, decrease survivor's morbidity.

927 LONG TERM RESULTS AFTER CNS RELAPSE IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA (ALL). Jorge A. Ortega, Mark E. Nesbit, Harland N. Sather, Leslie L. Robison, Carolyn Level, Giulio J. D'Angio, G. Denman Hammond.

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The status of children with ALL treated on studies CCG-101/143 who developed CNS disease was investigated. Presymptomatic CNS therapy consisted of craniospinal radiation (CRT), cranial CRT plus IT MTX x6, or only IT MTX x6. Of the 791 pts who achieved remission, 63 (7.9%) developed CNS disease as the first evidence of relapse with no subsequent CNS episodes. The median time to isolated CNS relapse was 385 days. Of these 63 pts 41 relapsed subsequently in the bone marrow (BM) and 38 died. Survivors had their initial relapse late (median: 457 days). Of the 63 pts with 1 isolated CNS relapse, 38 received presymptomatic CNS treatment with IT MTX alone; however, their disease-free (DF) survival was no different from the other 2 groups (p=0.1). Twenty-six pts (3.3%) developed 2 isolated CNS episodes and 20 of these pts subsequently relapsed in the BM. Only 3 pts survived, none of whom had any other relapses besides the 2 CNS relapses. Twenty-four pts (3%) had multiple CNS relapses (3 to 9 separate episodes); 20 died. The 4 survivors in this group have had no BM relapses, but have shown a pattern of chronic CNS disease. The DF survival at 84 mo for pts with 1 or more isolated CNS relapses was 16% and 8.4%, respectively. Time to the initial CNS relapse was found to be the most important factor for predicting outcome (p<0.0001). The data show that a CNS relapse is an indicator of poor prognosis. These pts require new therapeutic strategies to improve prevention and salvage.

928 EFFECTIVE TREATMENT OF METASTATIC CANCER WITH IN VITRO IMMUNIZED AUTOLOGOUS LYMPHOCYTES AND CIMETIDINE.

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We report results of a Phase I study of a novel immunotherapy we developed based on our described technique for in vitro primary immunization of human peripheral blood mononuclear cells (PBM) (Biotechniques 1:30, 1983). Twenty patients with metastatic cancer were enrolled in this prospective study (15 renal cell and 1 each of breast carcinoma, glioblastoma, rhabdomyosarcoma, melanoma and transitional cell carcinoma). Patient PBM were depleted of suppressor T-cells and immunized in vitro against autologous tumor antigen. The immunized PBM were then re-infused. Patients received 3 infusions, each of 50-100 x 10⁶ cells. In addition, patients received cimetidine to block suppressor T-cell activation (Lancet I:636, 1981). The only toxicity was fever of 102° in 1 patient following the second infusion. At this time, 10 patients are available for analysis with regard to therapeutic efficacy. This excludes 5 patients who died prior to their first efficacy evaluation timepoint (3 months) and 5 others who have not yet reached that timepoint. Five of these 10 evaluable patients had an objective clinical response, as evidenced by clinical examination or radiographic study. There was a significant correlation (p<.05) between clinical response and the level of specific anti-tumor antibody that could be measured in patient sera following treatment. We are encouraged by these results, since toxicity appears minimal, and we saw objective evidence of therapeutic efficacy in patients with end-stage metastatic disease.

929 THE RED CELL VOLUME DISTRIBUTION WIDTH (RDW) AND THE DIAGNOSIS OF IRON DEFICIENCY. Frank A. Osk, P. David Sadowitz and Brenda Helu.

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The distribution of red cell volume now is displayed in histogram form on many commercial hematology instruments. Measured as coefficient of variation, and reported as RDW, the heterogeneity of distribution of red cell size (anisocytosis) has become a useful means of classifying anemias in adults. Norms for the RDW, and its diagnostic utility, have not been established in the pediatric population.

Hemoglobin (Hb), red cell indices (RDW), and erythrocyte protoporphyrin (EP) were obtained in infants 6 mos, 9 mos and 12 mos of age. In children with a Hb >11.0, an MCV of >72 fl and an EP of <30 µg/dl the RDW's were:

Age	RDW
6 mos	14.05 ± 1.05
9 mos	14.98 ± 0.92
12 mos	14.44 ± 1.14

In contrast, in 12 month old infants with EP of more than 30 µg/dl, hemoglobins 10.2-13.5 g/dl, the RDW was significantly higher, averaging 17.32. The increase in RDW correlated with the increase in EP (r = 0.81) and identified patients with iron deficiency while the hemoglobin or the MCV was still within the normal range.

The RDW is a useful means of identifying patients with iron deficiency and distinguishing patients with microcytosis due to thalassemia trait from those with iron deficiency.

930 LOW RISK OF HEPATITIS B IN THALASSEMIA MAJOR: IMPLICATIONS FOR THE USE OF HEPATITIS B VACCINE IN CONNECTICUT. Howard A. Pearson, Warren A. Andiman, Linda Rink, Joseph R. Bove.

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Active immunization with the HB vaccine is advocated for patients receiving frequent transfusions of blood or blood products, including hemophiliacs and thalassemics. We have diagnosed HB in our hemophiliacs who receive pooled plasma concentrates but not in thal major patients who receive 15ml/kg of washed, leukocyte-poor RBC every 3-5 weeks. Blood from 25 thal major patients was tested for HB_s Ag, anti-HB_s, anti-HB_c, and also for EBV-VCA and CMV-CF. All bloods were negative for HB_s Ag. Two of 25 had anti-HB. One of these was an immigrant Greek boy who had anti-HB when he came to CT. The other patient converted between 1981-82 but had no symptoms of hepatitis. The percent positive and range of titers against CMV and EBV were similar to normals. These patients receive 800 units of RBC every year and have been exposed to about 10,000 units of blood during the past 17 years. Thus the risk of developing anti-HB (= exposure) in CT appears to be of the order of 1/10,000 units transfused. The probability of developing clinical HB is much less. Reasons for this very low risk include: 1. Use of wholly volunteer blood in CT for 20 years. 2. Routine screening of all blood for HB_s Ag for 9 years. 3. Use of washed, leukocyte-poor blood. Because of the low risk of HB exposure, the need for HB immunization of thal major patients in CT is dubious. Similar procedures should be effective in reducing the risk of other transfusion related diseases, including non-A, non-B hepatitis and HTLV III related AIDS.