

**INTERRUPTION OF MALIGNANCY-ASSOCIATED PLATELET CONSUMPTION WITH A COMBINATION OF RA233 AND SULFINPYRAZONE.** S. J. Slichter, P. L. Weiden, M. R. O'Donnell, and R. Storb. Puget Sound Blood Center, Fred Hutchinson Cancer Research Center, Seattle, WA. and Albany VA Hospital, Albany, N.Y.

Fifty-five dogs with spontaneous tumors of varied histology were evaluated by platelet counts and  $^{51}\text{Cr}$  labeled autologous platelet survivals to determine if platelet hemostasis was altered. None of the dogs received cancer-directed therapy during the course of these studies. In 12 dogs with local tumors, platelet counts were  $303,000/\text{ul} \pm 28,000$  (normal  $391,000/\text{ul} \pm 34,000$ ,  $p > 0.05$ ), and platelet survival was  $4.9 \text{ days} \pm 0.2$  (normal  $5.6 \text{ days} \pm 0.2$ ,  $p < 0.05$ ). In contrast, 23 dogs with metastatic tumor had platelet counts of  $268,000/\text{ul} \pm 26,000$  ( $p < 0.005$ ) and platelet survivals of  $3.4 \text{ days} \pm 0.3$  ( $p < 0.001$ ). When the platelet survival was less than 4 days, the platelet count was also depressed with a correlation coefficient of 0.60.

After baseline studies, 17 additional dogs with metastatic disease were treated with drugs (RA233 and sulfinpyrazone) that interfere with two different enzyme systems. Although there was some improvement in platelet survival in 6 of 9 dogs treated with RA233 or sulfinpyrazone alone ( $2.4 \text{ days} \pm 0.3$  baseline vs.  $3.5 \text{ days} \pm 0.4$  treated,  $p < 0.05$ ), platelet counts were not elevated ( $241,000/\text{ul} \pm 54,000$  baseline vs.  $201,000/\text{ul} \pm 46,000$  treated). However, when the two drugs were given in combination to 8 other dogs, all had increased platelet survivals ( $2.7 \text{ days} \pm 0.4$  baseline vs.  $4.4 \text{ days} \pm 0.6$  treated,  $p < 0.02$ ), and this was associated with improved platelet counts in 6 of 8 ( $259,000/\text{ul} \pm 46,000$  baseline vs.  $367,000/\text{ul} \pm 47,000$  treated,  $p < 0.05$ ). Five had completely normal platelet survivals.

This study indicates that metastatic tumors, regardless of histology, are associated with significant platelet consumption resulting in depressed platelet counts. This consumption can be modified and platelet counts increased by treatment with a combination of two platelet active drugs that may act synergistically. We plan to determine whether similar treatment programs would maintain platelet counts and/or improve the survival of transfused platelets in human subjects with malignant disorders.

**GENERATION OF PLATELET AGGREGATING ACTIVITY BY ADSORPTION OF LOW-MOLECULAR-WEIGHT FACTOR VIII-RELATED PROTEIN TO COLLOIDAL GOLD.** M. Furlan, \*M. Horisberger, B.A. Perret and E.A. Beck. Central Hematology Laboratory, Inselspital, Berne and \*Nestlé Products, Technical Assistance Co. Ltd., La Tour-de-Peilz, Switzerland.

Both the ristocetin cofactor (VIII:Rcof) and the platelet aggregating factor (PAF) are preferentially associated with the largest complexes of human and bovine factor VIII, respectively. It is not known whether the functional deficiency of smaller species of factor VIII is due to their size or quality. Binding of small oligomers of factor VIII-related protein, isolated by gel filtration from cryoprecipitates or prepared by disulfide reduction of multimeric factor VIII, onto gold granules (diameter 20-30 nm) generated platelet aggregating activity; on the other hand, adsorption of large factor VIII multimers onto gold particles impaired the initially high VIII:Rcof and PAF. Aggregation of human platelets by human factor VIII-coated gold particles required ristocetin and was not competitively inhibited by unbound low-molecular-weight factor VIII. We conclude that essential properties of factor VIII, necessary for its "von Willebrand activity", are present potentially in the smallest species recovered from plasma or even after disulfide reduction. Factor VIII-coated gold granules can be used as an electron-dense label for surface receptors for factor VIII on human platelets.