and lysis of in vitro and in vivo fibrins encourages the use of in vitro systems to help understand the initiation and progression of clinical thrombosis.

E. Genton, J. Ellis and P. Steele (Denver Veterans Administration Hospital, University of Colorado Medical Center, Denver, Colorado): **Comparative Effects of Platelet Suppressant Drugs on Platelet Survival Time. (164)**

The important role of platelets in thrombosis makes inhibitors of their reactivity potentially useful therapeutically. A number of laboratory tests have been identified which measure platelet reactivity, but it is not clear which test and which drug effect will correlate with thrombosis and thrombosis prevention. Platelet survival (SURV) correlates with thromboembolism in patients with valvular heart disease and is shortened in several other diseases. Therefore, it is of interest to identify drugs which prolong shortened SURV. Patients with arterial and venous thromboembolism and shortened SURV (^{51}Chromium) were treated with platelet suppressants and restudied after 12 weeks. Sulfinpyrazone prolonged SURV ($2.4 \pm .04$ to $3.1 \pm .06$ days; $p < 0.001$; $n = 94$; average $\pm$ SEM; normal, $3.7 \pm .04$ days) and 68 (72%) had some prolongation and 39 (42%) had normalization (> 3.3 days). Dipyridamole (100 mg qd) combined with aspirin (1200 mg qd) prolonged SURV ($2.6 \pm .11$ to 3.2 ± 0.12 days; $p < 0.001$; $n = 13$) and 9 of 13 (69%) had prolongation and 6 (46%) had normalization. Clofibrate altered SURV ($2.6 \pm .09$ to $3.4 \pm .14$ days; $p < 0.001$; $n = 12$) and 10 of 12 (83%) had prolongation and normalization occurred in 6 (50%). Aspirin (1200 mg qd), cryproheptadine (32 mg qd) and propranolol (160 mg qd) failed to alter SURV.

Thus, of drugs which alter in vitro tests of platelet reactivity, only sulfinpyrazone, dipyridamole and clofibrate improve shortened SURV.

M. Buchanan and J. Hirsh (McMaster University, Hamilton, Canada): **Comparison of in Vivo and in Vitro Effects of Platelet Function Suppressing Drugs. (165)**

Comparison of in vivo and in vitro platelet function tests to assess the antithrombotic efficacy of drugs which suppress platelet function have been contradictory. For example, aspirin (ASA) has a potent effect in vitro but little effect when tested on platelet survival in prosthetic heart valve replacements whereas dipyridamole (DIP) has little or no effect in vitro but a marked effect on platelet survival. We have compared in parallel the in vivo and in vitro effects of a number of drugs which suppress platelet function in an animal model. Rabbits were infused with homologous ^{51}Cr-labelled platelets and then given either ASA (10–200 mg/kg), DIP (1–20 mg/kg) or sulfinpyrazone (SUF) (30–200 mg/kg) intravenously. One hour later PRP from each rabbit was tested by ADP and collagen-induced aggregation. Then each rabbit was infused with an identical final concentration of collagen and the subsequent recovery of ^{51}Cr platelet radioactivity was monitored. In untreated rabbits collagen infusion produced 30% reduction of ^{51}Cr platelets which returned to within 85% of a precollagen level by 5 min. ASA ($\geqslant$ 10 mg/kg) inhibited in vitro collagen-induced aggregation while a dose of 100 mg/kg of ASA was necessary to achieve the same inhibitory effect in vivo. On the other hand, DIP (1–20 mg/kg) had no inhibitory effect on in vitro platelet aggregation whereas it inhibited aggregation in vivo. The results of SUF were similar in vitro and in vivo. These results suggest that the effectiveness of drugs on platelet function may be affected by centrifugation, addition of anticoagulant or removal of red cells. This may explain the discrepancies reported between the in vivo and in vitro effectiveness of such drugs.

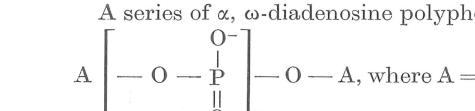
K. Subbarao, B. Rucinski and S. Niewiarowski (Specialized Center on Thrombosis Research, Temple Univ., Health Sciences Center, Philadelphia, Pa. 19140): **Binding of (^{14}C) Dipyradamole (RA 8) to Platelets and Inhibition of ADP Induced Platelet Aggregation. (166)**

RA 8 (conc. 10^{-5}–10^{-6} M) strongly inhibits ADP induced aggregation of washed platelets but has no similar effect if platelets are suspended in the plasma medium. α, Acid glyco-

protein (GP) of human plasma has been found to complex RA 8 and to block its antiplatelet aggregation activity (Niewiarowski, S. et al. J. Lab. Clin. Med. 1975, in press). Incubation of washed platelets of human or rabbit with (^{14}C) RA 8 (conc. 10^{-6} M) resulted in a binding of 20–30% radioactivity to platelets reaching a maximum within 1 minute incubation at 37° C and remaining constant for the length of time. Addition of human or rabbit plasma and α, GP inhibited binding of RA 8 whereas other fractions such as fibrinogen, Cohn fraction II, IV and albumin did not show any effect. The binding of RA 8 to platelets correlated with the inhibition of ADP induced aggregation. The binding was independent of temperature at the range of 4–50° C and of pH at the range of 6.0–8.0. Intravenous injection of (^{14}C) dipyradamole to rabbits at a dose of 25 mg/kg and 10 mg/kg weight resulted in a 32.6% and 6.0% (respectively) inhibition of ADP induced aggregation in platelet rich plasma (PRP). In both instances 3.0% of the total radioactivity recovered in PRP was associated with platelets. It can be suggested that α, GP present in blood may also inhibit binding of drug to platelets in vivo and interfere with its antiplatelet aggregation activity. Large doses of RA 8 are needed to overcome this effect.

R. Brossmer, M. J. Harrison and R. S. Goody (Institut für Biochemie II (Med. Fak.), 69 Heidelberg, Im Neuenheimer Feld 328 and Max-Planck-Institut für Medizinische Forschung, 69 Heidelberg, German Federal Republic): **α, ω-Diadenosine Polyphosphates, a New Class of Substances, and ADP-Methylester Inhibit Platelet Aggregation and the Release Reaction. (167)**

A series of α, ω-diadenosine polyphosphates, which may be represented by the formula



A — O — P(O⁻) — O — A, where A = adenosine and n = the number of phosphate groups, were studied for their effect on the aggregation and release reaction of human platelets. The adenosine derivatives inhibit ADP-induced aggregation in the same order of efficiency as they inhibit the enzyme activity of adenylate kinase i.e. up to n = 5 the more phosphate groups, the more inhibitory the activity. Double reciprocal plots suggest that these adenosine derivatives act competitively with ADP. AP_5A and AP_4A inhibit the release reaction in washed platelets but AP_3A and AP_2A do so only in high concentrations. In platelet-rich plasma the AP_nA derivatives inhibit the ADP release reaction with diminished strength as n decreases from 5 ($55 \pm 13\%$ inhibition) to 2 ($4 \pm 4\%$ inhibition). The adenosine polyphosphates also inhibit the aggregation of washed platelets by thrombin and dextran sulphate but do not affect DEAE-Dextran aggregation.

The ADP-methylester does not cause aggregation of platelets but inhibits ADP-induced aggregation and release in a manner suggestive of competitive inhibition.

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A. M. White and K. D. Butler (Horsham Research Centre, CIBA Laboratories, Horsham, West Sussex RH12 4AB, U.K.): **The Effect of Sulphinpyrazone (Anturan®) on Immunologically Derived Thrombocytopenia and on Platelet Survival. (168)**

Thrombocytopenia was produced in rabbits by means of the Arthus reaction. Animals were challenged by intradermal administration of ovalbumin (1 mg or 10 μg) on each of six sites in the back, six weeks after the first immunisation (1.0 mg alum precipitated ovalbumin) and four weeks after a subcutaneous boost (0.5 mg). Fifteen minutes after the 1 mg and 10 μg challenges there was an 83% and 26% fall, respectively, in the platelet count. This was confirmed by measurements of radioactivity in whole blood from animals which had received ^{51}Cr-labelled platelets. Sulphinpyrazone (50, 30, 10 mg/kg) administered 1 hour before the 10 μg antigen challenge inhibited the immediate thrombocytopenia completely. Significant, but only partial inhibition was achieved with 50 mg/kg given