

**Thursday, July 16, 1981**

## **Oral Presentations**

### **Thrombosis, Clinical – X**

#### **Arterial Disease**

**08:00–09:30 h**

#### **Platelets – XX**

#### **Density, Size, Heterogeneity**

**09:45–11:00 h**

**Grand Ballroom Centre**

**0613**

**08:00 h**

**ABNORMAL ARACHIDONIC ACID METABOLISM IN DIABETES: EFFECT OF NORMALISATION WITH DRUGS.** M. Johnson, A. H. Reece and H. E. Harrison. Department of Bioscience, ICI Pharmaceuticals Division, Macclesfield, England.

Patients with diabetes mellitus develop microvascular complications and have an increased susceptibility to both atherosclerosis and arterial thrombosis. We have demonstrated an imbalance in arachidonic acid metabolism in diabetes, vascular prostacyclin ( $\text{PGI}_2$ ) being reduced and platelet thromboxane ( $\text{TxA}_2$ ) being elevated. Platelet aggregation in response to ADP and arachidonic acid is also increased, and platelet survival is decreased. Treatment of diabetic rats with a specific thromboxane synthetase inhibitor, 1-nonyl-imidazole (50mg/Kg), for 7 days significantly ( $p < 0.05$ ) inhibited platelet aggregation and  $\text{TxA}_2$  synthesis. Aortic  $\text{PGI}_2$  production was increased and there was now no difference between treated animals ( $0.39 \pm 0.05 \text{ ng/mg}$ ) and non-diabetic controls ( $0.41 \pm 0.04 \text{ ng/mg}$ ). "Low dose" aspirin (2.5mg/Kg) further decreased  $\text{PGI}_2$  levels. Chronic treatment of diabetic animals for 3 months with 1-nonyl-imidazole restored both  $\text{TxA}_2$  and  $\text{PGI}_2$  production to normal, and significantly reduced the incidence and severity of microvascular lesions. If an imbalance in arachidonic acid metabolism plays a role in the vascular complications of diabetes, then the apparent beneficial effect of some drugs has important implications for therapy.

**0614**

**08:15 h**

**ANTI-PLATELET THERAPY IN DIABETIC PATIENTS WITH RETINOPATHY.** H. Tindall, R.C. Paton and G.P. McNicol. University Department of Medicine, The General Infirmary, Leeds LS1 3EX, U.K.

The effect of a combination of aspirin at 2 dosage levels (330mg/day and 1gm/day) and dipyridamole 225mg/day on platelet lifespan and some haemostatic variables was investigated in 30 insulin-dependent diabetic patients with retinopathy. Platelet regeneration time using a modification of the Stuart technique was measured in 40 normal controls and all patients before therapy commenced. Treatment was then allocated in a double-blind manner using a Latin square design and haemostatic variables were measured at the end of each treatment period. Platelet survival by the standard  $\text{Na}^{51}\text{Cr}$  radioisotopic technique was performed twice during treatment. The post-aspirin platelet regeneration time in normal subjects was  $9.98 \pm 0.22$  days (mean  $\pm$  SEM) and in diabetic patients was significantly ( $p < 0.001$ ) shorter at  $7.16 \pm 0.18$  days. A similar result of  $7.37 \pm 0.20$  days was obtained in the diabetic patients by  $\text{Na}^{51}\text{Cr}$  platelet survival (analysed by  $\gamma$  function). The aspirin/dipyridamole combination (330mg/75mg tds) resulted in significant ( $p < 0.001$ ) lengthening of platelet survival to  $8.46 \pm 0.13$  days (as estimated by  $\text{Na}^{51}\text{Cr}$  method). The post-aspirin platelet regeneration time was significantly prolonged ( $p < 0.01$ ) in this group ( $9.75 \pm 0.52$  days). Although the lower dose aspirin - dipyridamole combination (110mg/75mg tds) caused a prolongation in regeneration time ( $8.29 \pm 0.45$  days) this time was not significantly different from placebo, and was significantly ( $p < 0.01$ ) shorter than the time taken on the higher aspirin dosage. No significant changes in haemostatic function were observed. These results support the hypothesis that platelets may be involved in the microvascular complications of diabetes mellitus. Treatment with 1gm aspirin + 225mg dipyridamole/day significantly lengthened platelet survival suggesting that long term trials at this aspirin dosage level are justified.

**0615**

**08:30 h**

**THE INFLUENCE OF CYCLOOXYGENASE INHIBITORS ON PERIPHERAL BLOOD FLOW IN MAN.** J.E. Tooke and H. Tindall. University Department of Medicine, The General Infirmary, Leeds LS1 3EX, U.K.

Previous work has shown that inhibition of cyclooxygenase with indomethacin and flurbiprofen blunts post-occlusive reactive hyperaemia in man. Patients with diabetes mellitus exhibit a similar control-related impairment in vascular response due to their underlying disease. We were therefore concerned that the use of cyclooxygenase inhibitors in these patients might further impair vascular reactivity. We studied nine insulin-dependent diabetics with retinopathy who were given either aspirin 330mg + dipyridamole 75mg tds or placebo according to a randomised double-blind cross-over protocol. Calf and digital perfusion were measured using an ECG-triggered mercury strain gauge plethysmograph (Janssen, Periflow) which provided a semi-continuous computerized calculation of blood flow. Rest flow (RF) was measured following full acclimatization in a constant temperature room. Peak flow (PF) was assessed from the reactive hyperaemia following a four minute period of arterial occlusion. The aspirin-dipyridamole combination caused a significant reduction in mean PF : RF ratio (9.2: 7.2,  $p < 0.01$ ) measured in the calf, and a significant prolongation of the mean time for 50% decay of peak flow (19.7 to 26.0 seconds,  $p < 0.02$ ). A significant reduction also occurred in digital PF : RF ratio following aspirin-dipyridamole (5.0: 3.7,  $p < 0.05$ ). These results suggest that moderate doses of cyclooxygenase inhibitors prescribed for their platelet-inhibiting action may have profound effects on vascular reactivity. In diabetic patients the effects may add to a pre-existent abnormality.