ANTI-INFLAMMATORY AGENTS WHICH DO NOT INHIBIT PLATELET PROSTAGLANDIN SYNTHESIS. I. Cerskus and R.B. Philp. University of Western Ontario, London, Ontario N6A 5C1, Canada.

There is overwhelming evidence to support the theory that non-steroidal anti-inflammatory drugs (NSAID) act by interfering with production of prostaglandins (PG). Since PG intermediates are intimately involved in platelet aggregation, NSAID such as aspirin (ASA) also have adverse effects on platelet function. In the present study three compounds bearing structural resemblance to ASA were investigated for effects on platelet aggregation, PG synthesis and carrageenin-induced rat paw oedema.

ASA was more potent than 3-methylphthalide (3-MP) in inhibiting platelet aggregation in response to ADP and collagen. 2-Acetylbenzoic acid (ABA) inhibited aggregation only at very high doses (150 mM), whilst 3-propionyloxybenzoic acid (PBA) significantly potentiated aggregation. Neither ABA nor PBA, up to 5mM final concentration, affected PG synthesis from labelled precursor in platelet lysates, and 3-MP inhibited PG synthesis by only 20% at 1mM, at which concentration aggregation was virtually abolished. However, 3-MP was slightly more potent than ASA in suppressing carrageenin-induced rat paw oedema, whilst ABA and ASA were of approximately equal potency. PBA had no effect.

These results indicate that anti-inflammatory activity may be separated from effects on platelet function, and that the PG synthetase of platelets may differ from that involved in PG elaboration in an acute inflammatory response. The possibility that ABA and 3-MP may be selective inhibitors of the latter enzyme, cannot be excluded.

PROSTAGLANDIN-ENDOPEROXIDES AND CYCLIC 3'-5'-AMP IN PLATELETS OF PATIENTS WITH UREMIA. F.R. Matthias and W. Palinski. Dept. of Int. Medicine, Justus Liebig University, Giessen, Germany.

In platelets of normal donors and of patients with chronic renal failure the following determinations were performed: 1. prostaglandin-endoperoxide-formation after *N*-ethylmaleimide stimulation measured as malondialdehyde; 2. the c-AMP level according to the Gilman-method; 3. the adenylate-cyclase activity in response to prostaglandin E_1 ; 4. aggregation in response to collagen.

In comparison to normal donors the prostaglandin-endoperoxide production was reduced in uremic patients. Plasma of uremics depresses the endoperoxide formation of normal platelets. The basal c-AMP level of platelets of patients with renal failure was not significantly changed, whereas the plasma c-AMP level was increased; the activation of the platelets adenylate-cyclase was impaired. The adenylate-cyclase activity of platelets from normal donors was reduced by uremic plasma. The results are of interest as to the explanation of the bleeding tendency of uremic patients.

THE ROLE OF CYCLIC NUCLEOTIDES AND PROSTAGLANDINS IN THE MECHANISMS OF AGGREGATION OF THROMBOCYTES. S.V.ANDREEV, A.A.KUBATIEV, Ya.D.MAMEDOV. The USSR Academy of Medical Sciences, Moscow, USSR.

In a comparative study into the mechanisms of aggregation of thrombocytes under the influence of various agents, two types of reactions were established, one realized through the system of cyclic 3'-5'-AMP and the other, through the system of cyclic 3'-5'-GMP. The former type of reaction was observed when ADP and thrombin were used as aggregation inductors; the latter was induced by serotonin. The initial link in the development of aggregation of thrombocytes induced by ATP and thrombin was an increase in the level of prostaglandin E_1 (by 32%), under the effect of which the activity of adenyl cyclase rose more than by 41%, and the amount of 3'-5'-cAMP increased by almost 180% as compared with the initial level. Unlike ADP and thrombin, stimulation of thrombocytes with serotonin brought about, as a rule, an increase in the level of prostaglandins F_2 (by 60%), which subsequently led to activation of guanyl cyclase and marked augmentation in the content of 3'-5'-cGMP (by 300%). The application of proteolytic enzymes with thrombolytically oriented properties caused inhibition of biosynthesis of prostaglandins and cyclic nucleotides with a clearcut disaggregating effect.