(mean ± s.e. mean) 10 s after ADP (100 $\mu g\ kg^{-1}$; n = 22) administration. One minute later the drop was 21 ± 7 and the count returned to basal levels within 5-10 minutes. Higher doses of ATP (0.5-1 $mg\ kg^{-1}$) were required for similar effects. AA (500 $\mu g\ kg^{-1}$) decreased the number of platelets by 70% ± 4.4 (n = 11). Bronchoconstriction and the platelet decrease were suppressed by 10 $mg\ kg^{-1}$ of aspirin i.v. B (0.5-1 $\mu g/kg^{-1}$) had no effect on platelet counts. Platelet depletion resulted in suppression of ADP- and of ATP-induced bronchoconstriction, whereas the effect of B and of AA was maintained or only slightly reduced. Administration of propranolol (5 mg/kg^{-1} + 2 mg/kg^{-1} i.v.) restored responses to B demonstrating that the reduction of its effect was due to antagonism by released adrenaline and not to platelet depletion (Collier, 1966). B failed to aggregate guinea-pig platelets in presence of the kininase inhibitor BPP9A (250 $\mu g/ml^{-1}$), whereas ATP induced a marked aggregation, probably via conversion to ADP. In conclusion, agents likely to start the release reaction and thus to activate prostaglandin synthesis (Zucker & Peterson, 1968; Smith, Ingerman, Kocsis & Silver, 1974) with formation of bronchoconstrictor substances (Vargaftig & Dao Hai, 1972a) interact with different sites, all of them subject to blockade by aspirin. In the case of ADP and of ATP, this site is circulating platelets. Bradykinin probably induces formation of bronchoconstrictor substances by activating release of prostaglandin precursors directly from the lungs (Vargaftig & Dao Hai, 1972b).

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The effect of sulphinpyrazone, sodium aspirin and oxprenolol on the formation of arterial platelet thrombi

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Platelets play a major role in the formation of arterial thrombi (see Mustard, Kinlough-Rathbone & Packham, 1974). In an effort to study the reaction *in vivo*, various methods of injuring the microcirculation have been examined to produce platelet thrombosis (white body formation) (see Didisheim, 1972).

In the present study we have used the hamster cheek pouch as described by Duling, Berne & Born (1968) and perfused with a modified Krebs solution at 5 ml/min as described by Duling & Staples (1974). The following parameters were found to be optimal for producing white body formation. After a 30 min equilibration period, a glass micropipette with a 3 μm tip filled with 1 M KCl was placed in contact at approximately 90° with the wall of an arteriole of 40-60 μm

diameter. The solution in the micropipette was connected with a Ag/AgCl electrode via an external circuit to a reference Ag/AgCl electrode immersed in the outflow of the bathing solution. A Bell stimulator in conjunction with a Devices isolated stimulator (type 2533) provided positive square wave DC pulses to the micropipette at 10 Hz, 20 ms and a current of 100 μA which were monitored by an oscilloscope in the circuit.

The amount of white body formation was assessed by counting, at a magnification of 350. the total thrombi adhering during the first 4 min after stimulation. A graded response could be produced by varying the duration of stimulation. Stimulation for 1, 2 or 4 s produced (mean ± s.e. mean (*n*)), 2.91 ± 0.54 (12), 3.8 ± 0.33 (17), 5.25 ± 0.49 (8) white bodies respectively. n refers to the number of 1, 2 or 4 s stimulations in six hamsters. The difference between the responses to 1 and 4 s were statistically significant ($P < 0.001$).

The method has so far been used to study the effects of sulphinpyrazone and aspirin which are being currently assessed in man as anti-thrombotic agents (Barnett, 1973). In addition, oxprenolol has been examined since β-adrenoceptor blockers have been reported to inhibit platelet aggregation (Bucker & Stucki, 1969).

Groups of 4-7 male hamsters, 100-120 g were given orally 18 h and 1 h before injury, one of the following treatments: 3, 10, 20 or 65 mg/kg of sulphinpyrazone (0.5 ml/100 g); 1, 10, 30, 60, 100 or 200 mg/kg of sodium aspirin (0.5 ml/100 g); or oxprenolol, 0.1, 1 or 5 mg/kg (0.2 ml/100 g).

Significant reduction in white body formation was found with all three drugs. Sulphinpyrazone produced a significant reduction for all periods of stimulation ($P < 0.001$ and $P < 0.05$) at 20 and 65 mg/kg respectively, a small reduction at 10 mg/kg and no effect at 3 mg/kg. Oxprenolol produced a significant reduction ($P < 0.05$) at 5 mg/kg but not at 1 mg/kg. Aspirin behaved differently in producing a bell-shaped dose response curve. Whereas 10 and 30 mg/kg produced a significant reduction ($P < 0.005$), both a lower dose (1 mg/kg) and higher doses (60 and 100 mg/kg) produced no significant reduction, while 200 mg/kg enhanced white body formation.

These results support the view that sulphinpyrazone is an effective anti-thrombotic agent and suggest a similar action for oxprenolol. However, the effectiveness of aspirin is variable according to dosage.

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The effect of sulphinpyrazone on the thrombocytopenia occurring in the Arthus reaction

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Sulphinpyrazone is a uricosuric agent, which, *in vitro*, inhibits platelet aggregation and release caused by a large number of agents including collagen, ADP, antigen/antibody complexes, viruses and bacteria (Mustard & Packham, 1975). The drug has also shown, in a number of clinical trials, to have anti-thrombotic activity, and to reverse shortened platelet survival (Steele, Weily & Genton, 1973; Steele, Weily, Davies & Genton, 1974). However, some *in vitro* findings suggest that the *in vivo* effect of sulphinpyrazone may not be due to its direct interference with the aggregation of platelets (Mustard & Packham, 1975). In order to investigate further the problem of the mode of action of the drug, an examination of its influence on intravascular immune platelet