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Platelets and artificial surfaces: the effects of drugs

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[Plate 1]

Contact of blood with a foreign surface activates platelets and leads to their consumption. This property is shared by most non-biological materials, including air, but can be reduced by an optimal balance of hydrophobicity and hydrophilicity, minimal capacity for hydrogen bonding, avoidance of crystallinity, maintenance of polymer backbone mobility, and other manipulations of the chemistry of the polymer. None the less, no totally non-thrombogenic artificial surface has been developed. Attention has therefore turned to suppression of platelet–surface interaction by drugs that alter platelet function. Agents that block cyclo-oxygenase inhibit surface-induced secretion and aggregation but have no effect on platelet adhesion. Drugs that increase platelet cyclic AMP levels have a dose-related effect, which at high concentrations can eliminate adhesion to surfaces. The most successful agent, prostacyclin, has achieved total protection of platelets during cardiopulmonary bypass, with preservation of normal platelet number and function. Associated vasodilatation is a notable side effect, and hypotension may prove to be a significant problem in clinical practice. The development of more selective analogues with minimal vasodepressor activity is to be encouraged.

Blood–surface interactions

Exposure of the blood to artificial surfaces leads frequently to thromboembolic complications in patients with artificial heart valves, arterial grafts, and other prosthetic devices, and in patients undergoing extracorporeal circulation, including cardiopulmonary bypass and haemodialysis. Blood platelets are particularly susceptible to the effects of contact of blood with an artificial surface, which may result in altered platelet function, shortened platelet survival, thrombocytopenia, or gross thromboembolism. In spite of substantial efforts to develop thrombo-resistant surfaces, present-day biomaterials are not totally bland in contact with the blood. The widespread successful clinical use of artificial organs is therefore dependent on skilful engineering and appreciation of fluid mechanics and is in large part attributable to the patient's tolerance to microembolism and his capacity to compensate for increased consumption of haemostatic elements.

At its extreme, the situation is illustrated by the haematological effects of cardiopulmonary bypass (Bachmann *et al.* 1975; McKenna *et al.* 1975). Patients undergoing open-heart operations with the support of a pump oxygenator invariably develop a bleeding tendency characterized by thrombocytopenia, defective platelet function (manifested by a reduction in the aggregation response to ADP and other stimuli), evidence of platelet activation (demonstrated by increased

circulating levels of plasma thromboxane B_2 (Davies *et al.* 1980), platelet factor 4 (Hennessey *et al.* 1977) and other platelet products (Addonizio 1980), and incoagulability of the blood as a result of heparin anticoagulation.

The first event observed upon contact of the blood with an artificial surface is adsorption of plasma proteins on the surface (Baier & Dutton 1969). The small size and high concentration of plasma protein molecules compared with blood cells dictate that protein adsorption must occur before formed elements can diffuse to the surface (Salzman 1971). Thus, the platelet never encounters a bare surface but only a film of blood constituents deposited on it. It seems likely that the composition of the adsorbed protein coat and changes in configuration of protein molecules secondary to the adsorption process are critical in transmitting to blood elements a message regarding the nature of the underlying surface and thus in determining the subsequent events. The details of these interactions are not well understood.

Initial conditioning of the surface by the adsorbed film of plasma proteins is quickly followed by adhesion of platelets. The adsorbed platelets spread out on the surface, a gross distortion of platelet morphology that is analogous in many respects to the shape change that precedes the primary phase of platelet aggregation induced *in vitro* by ADP (Salzman *et al.* 1977). The formation of an aggregate of platelets on the surface subsequently occurs by accretion. The reaction may be augmented by secretion of platelet constituents such as ADP and serotonin by platelets adhering to the surface or to other platelets, and further aggregation of non-adherent platelets in the bulk fluid phase may ensue. The process has many features in common with formation of a haemostatic plug or intravascular thrombus but has a number of important distinctive features.

1. The intensity of the platelet response varies depending on the surface. Although there is evidence that platelets adhere to virtually all artificial surfaces (Friedman *et al.* 1970), platelet adhesion can be reduced or even prevented by manipulation of the adsorbed plasma protein film on the surface. Furthermore, the degree to which platelet–surface interaction leads to platelet aggregation and secretion varies with the nature of the surface, being influenced by features such as contour (i.e. roughness on a scale the size of a blood cell), crystallinity, hydrophobicity, hydrophilicity, capacity for hydrogen bonding, and possibly the flexibility of the molecular backbone, in polymers.

2. An artificial surface lacks the capacity of the natural endothelial cell for active inhibition of platelet interactions afforded by local production of prostacyclin and ADP-hydrolysing enzymes (Moncada *et al.* 1976).

Influence of the surface

We have studied the contribution of the nature of a surface to the events that follow its contact with blood in a model system *in vitro* (Lindon *et al.* 1978) in which whole blood anticoagulated with citrate is pumped from below through a column of beads composed of or coated with the material to be studied. The system has a very large surface/volume ratio (e.g. 1500 cm^2 for 3 ml of blood) and is thus a severe test of the compatibility of a material with the blood. Platelets are retained within the column by adhesion to the beads, followed by development of aggregates as further platelets adhere to the initial platelet layer. Comparison of the platelet count in effluent blood with the platelet count in blood before surface contact reflects both platelet adhesion and aggregation. The secretion of platelet constituents can also be measured.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

As an illustration of the importance of surface composition, consider the segmented polyurethanes, inhomogeneous block copolymers consisting of a continuous 'soft segment' phase composed of linear polyethers held together by partial crystallization of 'hard segment' areas containing the intensely hydrogen-bonding urea or urethane moieties.Such polymers are widely used for angiographic catheters and other clinical applications because of their favourable

TABLE 1. HYDROPHILICITY AND PLATELET REACTIVITY

polyurethane	*n*	a or c	percentage H_2O	p.r.i.†
PEO	46	a	64	0.95
PEO	28	a	33	0.88
PTMO	28	a	28	0.71
PTMO	56	c	5	0.45
HSA	5	c	±0	0.20

Abbreviations: a, amorphous; c, crystalline; PEO, polyethylene oxide soft segment; PTMO, polytetramethylene oxide soft segment; HSA, hard segment analogue; *n*, number of structural units.

† Platelet recovery index: ratio of platelets in effluent to platelets entering the bead columns. For a bland surface, p.r.i. = 1; for a surface that retains all platelets presented to it, p.r.i. = 0.

mechanical properties and relative blandness in contact with blood. In a series of polyurethanes varying in composition of the hard and soft segments, we observed (Sa da Costa *et al.* 1980) that reactivity with platelets increased as the fractional concentration of the hard segment phase at the blood contacting surface. The most successful polyurethanes in practical clinical use can be shown by electron spectroscopy for chemical analysis to lack nitrogen (an indicator of the hard segment) within 5 nm of the blood-contacting interface. Furthermore, a series of model polyurethanes that vary in composition of the soft segment have decreasing platelet reactivity as the capacity of the polymer to imbibe water increases (table 1).

Experiments such as these lead to the following generalization: for thromboresistance, the surface of a polyurethane destined to come in contact with the blood should be formed against a hydrophobic interface, such as air, which encourages phase separation and promotes the formation of a surface composed chiefly of the relatively hydrophobic soft segments, the highly reactive hard segment phases being buried below. The composition of the soft segment phase should be selected to be as hydrophilic as possible, short of actually having the capacity for hydrogen bonding or polar interactions.

The undesirable effects of surface hydrophobicity are not limited to polyurethanes. We studied (Brier-Russell *et al.* 1981) a series of alkyl acrylates and methacrylates whose alkyl side chains varied in length from one carbon (polymethylacrylate, polymethylmethacrylate) to 12 (polylaurylacrylate, polylauryl methacrylate). Platelet reactivity varied directly with the length of the alkyl side chains and thus with the capacity of the polymer for hydrophobic interactions (figure 1). Polymethylacrylate was one of the least reactive materials we have studied. While not hydrophilic, it is the least hydrophobic of the acrylate and methacrylate series. Its blandness is also demonstrable *in vivo*. To study platelet–surface interactions in living animals, we have measured (Lindon *et al.* 1980) the lifespan of ^{51}Cr-labelled or ^{111}In-labelled platelets in sheep bearing arteriovenous shunts in the form of tubing. The survival time of platelets in animals with a polymethylacrylate arterio-venous shunt 150 cm long is no shorter than in control animals.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Pharmacological control of platelet–surface interactions

Experiments such as the foregoing may lead to an increased understanding of a theoretical basis for the interaction of blood with artificial surfaces. However, until truly non-thrombogenic surfaces are available, the use of prosthetic devices in contact with the blood will of necessity be supplemented instead by anticoagulant drugs and agents that alter platelet function to prevent thromboembolic complications and consumption or alteration of blood elements.

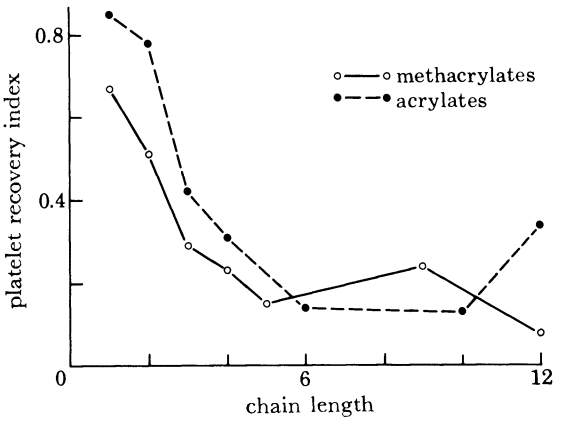

Figure 1. Platelet recovery after passage of citrated whole blood through a column of acrylate- or methacrylate-coated beads, in which the length of the alkyl side chain is varied from one (polymethylacrylate and polymethylmethacrylate) to 12 (polylaurylacrylate and polylaurylmethacrylate). From Brier-Russell *et al.* (1981).

Conventional anticoagulation has a limited ability to protect against the haematological consequences of blood–surface interaction, in which platelets play a predominant role. The administration of heparin during coronary angiography reduces thromboembolic complications, but the effects of cardiopulmonary bypass and haemodialysis on the blood occur despite the universal use of heparin with these procedures. In patients with prosthetic heart valves, anticoagulation with vitamin K antagonists reduces the frequency of thromboembolic events but does not totally eliminate them. Anticoagulants do not inhibit platelet reactions except those induced by thrombin; in fact, there is evidence (Salzman *et al.* 1980) that heparin actually enhances platelet reactivity, inducing the aggregation of platelets itself and augmenting the effects of other aggregating agents such as ADP.

In the resultant search for more effective pharmacological aids in the suppression of blood–surface interactions, drugs that alter platelet function have received increasing attention. A host of agents suppress platelet activity by various mechanisms, but for practical purposes at present the drugs available are those that either block the activity of platelet arachidonic acid cyclooxygenase or increase the platelet content of cyclic AMP. Decalcifying agents such as EDTA and 'membrane-stabilizing agents' such as local anaesthetics, which alter the calcium homoeostasis of the platelet, are highly effective *in vitro* but have limited application *in vivo* because of their lack of selectivity and their effects on other organs. Regional use of such drugs during haemodialysis in experimental animals has been reported (Scharschmidt *et al.* 1977), but does not appear to have been studied in man.

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

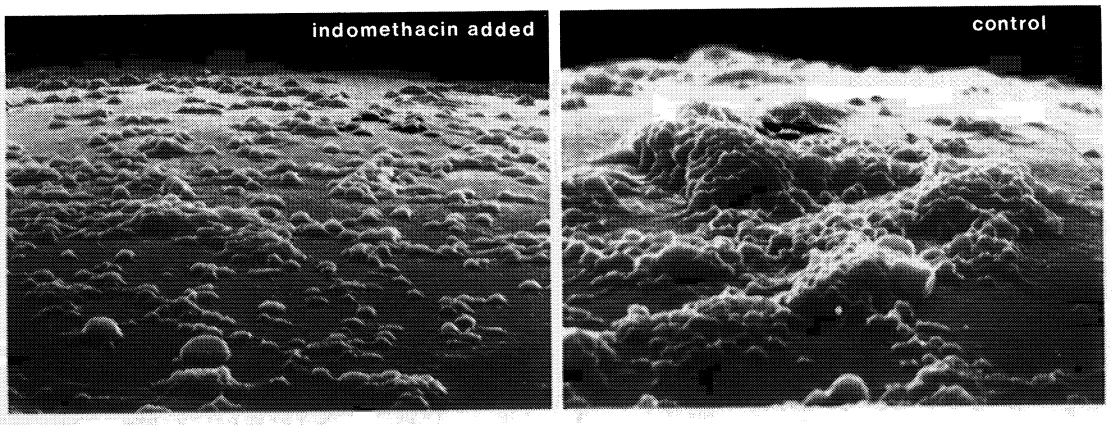

FIGURE 2. Suppression of platelet aggregation by 10^{-4} M indomethacin. Platelet adhesion to the bead surface is not inhibited. From Salzman *et al.* (1977).

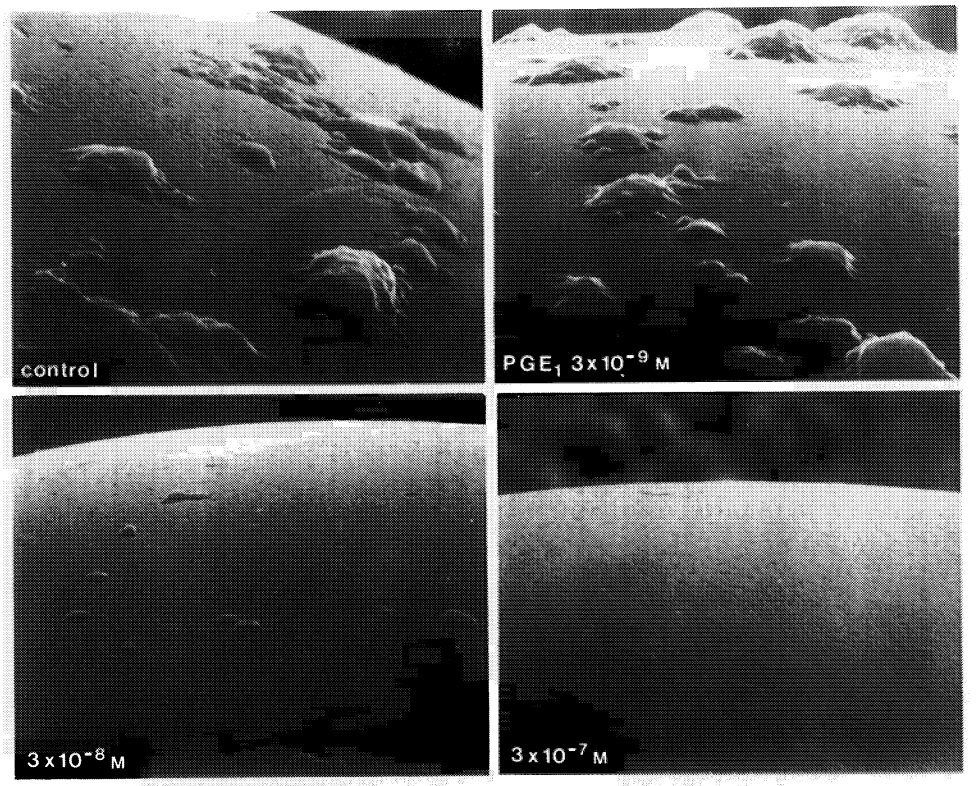

FIGURE 3. Effect of prostaglandin E_1 (3×10^{-9} M to 3×10^{-7} M) on platelet interaction with polystyrene beads.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

Inhibitors of platelet cyclo-oxygenase

Non-steroidal anti-inflammatory agents such as aspirin and indomethacin and the uricosuric drug sulphinpyrazone inhibit the generation of thromboxane A_2 by platelets and thus prevent platelet aggregation by this substance, which appears to mediate the effect of many platelet stimulants. Alternative pathways to platelet activation are available to thrombin and collagen, so drugs such as aspirin usually do not produce an intolerable interruption of haemostasis. The formation of platelet aggregates on artificial surfaces is markedly reduced, and secretion of platelet products is largely eliminated. The combination of oral anticoagulants with sulphinpyrazone or aspirin has proved to be more effective to prevent thromboembolism in patients with prosthetic heart valves then has Warfarin alone (Dale *et al.* 1977; Steele & Genton 1976). Lindsay *et al.* (1972) found reduced platelet consumption during haemodialysis in patients who received aspirin. Kaegi *et al.* (1975) reported that the occlusion of arterio-venous shunts employed for haemodialysis was prevented by the administration of sulphinpyrazone.

Unfortunately, these encouraging results must be tempered by the serious shortcomings of non-steroidal anti-inflammatory agents in extracorporeal circulation. Blood loss is significantly increased in patients who undergo cardiopulmonary bypass after the administration of aspirin (Torosian *et al.* 1978), and increased blood loss has also been observed during haemodialysis after aspirin ingestion. Aspirin and drugs that act similarly lack the property of prompt reversibility of action that is essential to the successful use of platelet-active agents during cardiopulmonary bypass. Otherwise the protection against platelet consumption afforded by paralysis of platelet function during extracorporeal circulation would be vitiated by the persistant bleeding tendency induced by the drug, whose effect must be reversed at the conclusion of bypass for haemostatic competence. Furthermore, inhibitors of platelet cyclo-oxygenase block platelet aggregation but do not prevent the adhesion of platelets to artificial surfaces (figure 2, plate 1). The vast surface areas of membrane oxygenators and dialysers may provide a capacious platelet sink even in the absence of platelet aggregation. Also, even without aggregation, the adhesion of individual platelets may seriously interfere with the function of a device designed for transfer of gases or solutes by compromising the area available for diffusion.

Drugs that raise platelet cyclic AMP levels

The inhibition of platelet activity by elevation of cyclic AMP may be brought about by the activation of adenylate cyclase or the inhibition of phosphodiesterase or more directly by the incubation of platelets with a cyclic AMP derivative, such as dibutyryl cyclic AMP, able to cross the cell membrane. *In vitro*, the platelet response to cyclic AMP elevation is dose-dependent. With increasing concentrations of inhibitor, there is at first suppression of platelet secretion and reduction in the size of aggregates, then elimination of aggregation with persistance of adhesion, and finally prevention of adhesion of solitary platelets to the surface (figure 3, plate 1). The mechanism of these reactions is not completely understood. It is known that cyclic AMP can activate a calcium pump mechanism in platelets (Käser-Glanzmann *et al.* 1977) and presumably through this action can lower cytoplasmic calcium levels. Such an action would inhibit the activity of the calcium-dependent enzymes phospholipase A_2 and phospholipase C and arachidonic acid cyclo-oxygenase, thus blocking the production of thromboxane A_2. That there are other important effects of cyclic AMP is suggested (Steer & Salzman 1980) by the fact

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

that increased cyclic AMP inhibits platelet reactions that do not appear to require metabolism of arachidonic acid, such as the action of the thromboxane A_2 itself or its synthetic analogues, the 'primary phase' of platelet aggregation induced by ADP, and the adhesion of platelets to artificial surfaces. There is evidence (Hathaway *et al.* 1980) that cyclic AMP is required for the phosphorylation of myosin light chain kinase, which could account for a direct effect of elevated cyclic AMP levels on the contractile activity of the platelet.

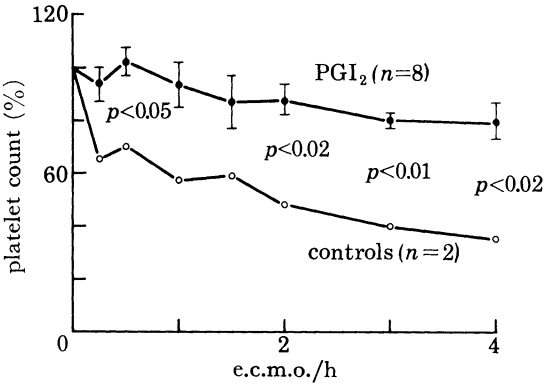

FIGURE 4. Effect of prostacyclin (PGI_2) on consumption of platelets during veno-venous bypass for extracorporeal membrane oxygenation (e.c.m.o.) in lambs. Platelet counts expressed as a percentage of pre-e.c.m.o. levels. From Coppe *et al.* (1979).

The phosphodiesterase inhibitor dipyridamole has been extensively studied as an anti-thrombotic drug, most effectively when administered in conjunction with aspirin, and has been found to offer some protection against prosthetic valve-associated thromboembolism (Sullivan *et al.* 1968) and platelet consumption during cardiopulmonary bypass or haemodialysis (Becker *et al.* 1972; Nuutinen *et al.* 1977). It has been suggested (Whittle 1978) that the action of dipyridamole is based on its ability to enhance the elevation of platelet cyclic AMP induced by natural or exogenous stimulants to adenylate cyclase, such as the prostaglandins.

There are several reported studies of the use of prostaglandin E_1 in *ex vivo* models of cardio-pulmonary bypass and in animals, and a more limited experience in patients has been described. In monkeys, PGE_1 (0.2–5 μg kg^{-1} min^{-1}) significantly reduced consumption of platelets during cardiopulmonary bypass, ameliorated the defect in platelet aggregation that otherwise occurred, and maintained a normal bleeding time (Addonizio *et al.* 1978). However, administration of PGE_1 to patients during bypass was unsatisfactory because of profound vasodilatation and hypotension that made it impossible to give enough of the drug to prevent platelet consumption (van den Dungen *et al.* 1980; Ellison *et al.* 1980). Administration of PGE_1 (0.1 μg kg^{-1} min^{-1}) did not significantly affect platelet number or function, compared with a control group receiving no prostaglandin. There was no difference in post-operative blood loss in the two groups of patients.

Exploration of the use of prostacyclin (PGI_2) in extracorporeal circulation has been more encouraging. Several authors (Coppe *et al.* 1979, 1981; Addonizio *et al.* 1979; Longmore *et al.* 1979; Plachetka *et al.* 1980) have reported reduction of platelet consumption *in vitro* and during veno-venous bypass or total cardiopulmonary bypass in lambs and dogs (figure 4), and similar observations have been reported with haemodialysis (Turney *et al.* 1980) and charcoal haemo-perfusion (Gimson *et al.* 1980). A defect in platelet aggregation is regularly induced by cardio-

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

pulmonary bypass and is attributed (Beurling-Harbury *et al.* 1978) to continued circulation of platelets that had previously been partly activated and thus partly exhausted by contact with the extracorporeal circuit. This functional defect was reduced or in some cases totally eliminated by infusion of prostacyclin (figure 5). The dose required in lambs was around 1 μg kg^{-1} min^{-1}, and that in dogs even higher, and was accompanied by significant hypotension. Prostacyclin

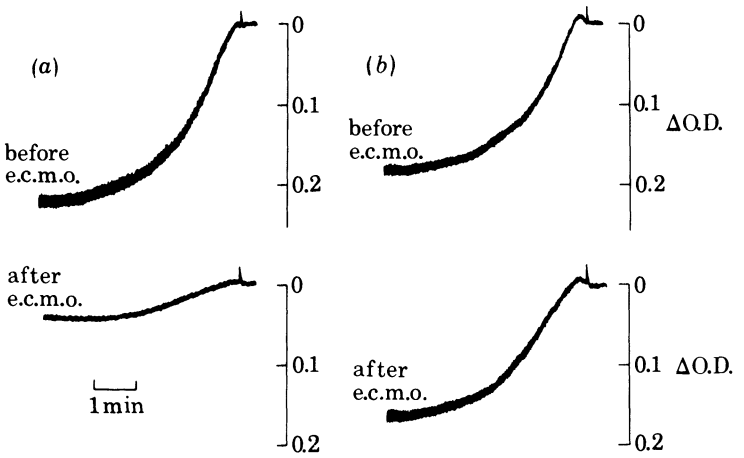

FIGURE 5. Reduction in platelet aggregation in response to ADP-induced extracorporeal membrane oxygenation. ADP concentration, 5 μM. (*a*) Control animals; (*b*) animals receiving PGI_2. Platelet responsiveness was preserved in the animals receiving PGI_2.

is labile, with a half-life in blood of only a few minutes. During veno-venous bypass (Coppe *et al.* 1979), its regional administration was possible by infusion into the venous outflow line, confining the effect of the drug to the extracorporeal circuit. Thus, during bypass the ability of platelets to aggregate could be totally inhibited in the extracorporeal circuit, while simultaneous blood samples drawn from the pulmonary artery displayed a nearly normal platelet aggregation response. Unfortunately, the more rapid flow rates required for total cardiopulmonary bypass made it impossible to limit the effect of prostacyclin to the extracorporeal circuit, which magnified the problem of prostaglandin-induced hypotension.

Several centres have reported clinical trials of prostacyclin infusion in cardiopulmonary bypass in man. The reports (Walker *et al.* 1980; Radegran *et al.* 1980; Bunting *et al.* 1981; Pokar *et al.* 1981) describe a total of nearly 100 patients receiving prostacyclin infusions during extracorporeal circulation for open-heart operations. Since man is more sensitive to PGI_2 than are most experimental animals, lower doses of the agent have been possible, 20–50 ng kg^{-1} min^{-1} being customary. Partial prevention of platelet consumption has been achieved in all of these studies, with significantly higher platelet concentrations circulating immediately after bypass. There is evidence of reduced platelet activation, including lower levels of plasma β-thromboglobulin and platelet factor 4 than in controls, less accumulation of circulating debris on arterial filters, and prevention of the usual increase in screen filtration pressure attributed to circulating platelet aggregates. A reduced frequency of post-bypass psychiatric changes has been claimed, presumably by prevention of microembolization to the brain.

Total prevention of platelet loss has not been achieved at these rates of prostacyclin infusion, nor has there been a consistant improvement in post-bypass platelet function. Improved results

PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

might be obtained with higher doses of prostacyclin, but this is impractical because of the serious hypotensive effects of vasodilation induced by the drug, which has limited the tolerable dose. Decreased urine output in patients receiving prostacyclin was reported and is not unexpected, considering the reduction in perfusion pressure induced by the drug. Reduction in the dose of heparin required has been reported by several authors, as judged by the activated clotting time or other coagulation tests. Heparin sparing has been explained by the absence of platelet secretion of the heparin antagonist, platelet factor 4, in the presence of prostacyclin (Bunting *et al.* 1979). No deaths have been blamed on the administration of prostacyclin during cardiopulmonary bypass, although one patient in the series reported by Radegran *et al.* (1980) died of an intra-operative myocardial infarction while receiving prostacyclin. Several authors make mention of the significant effects of prostacyclin on blood pressure and the need for aggressive fluid administration or administration of vasopressors.

Hypotensive side effects may be a serious barrier to the wider use of prostacyclin during cardiopulmonary bypass. Although the thrombocytopenia and alteration in platelet function that complicate cardiopulmonary bypass are a significant source of haemorrhagic complications, practising cardiac surgeons have learned to compensate for defective haemostasis in open-heart patients by meticulous attention to surgical technique and an aggressive attitude toward re-exploration of the chest, should haemorrhagic drainage be excessive in the early post-operative period. No study of prostacyclin infusion during cardiopulmonary bypass in man has yet shown preservation of normal platelet function or unequivocal evidence of reduction in intra-operative or post-operative blood loss. It seems likely that to achieve these goals it will be necessary to accomplish a total paralysis of platelet function during contact of the blood with the extracorporeal circuit. The heparin-sparing effect of prostacyclin is of interest but is not of obvious clinical benefit to the patient.

The development of open-heart surgery is one of medicine's great achievements of the past three decades. Complicated operations on the heart and great vessels are routinely performed with minimal mortality, to which haemorrhage makes only a small contribution. The introduction of serious hypotensive cardiac, renal or cerebral side effects of a new drug, even if infrequent, would be intolerable in current practice. Development of more selective agents with the ability to stimulate platelet adenylate cyclase but without the vasodilating effects of prostacyclin would seem to be essential before this approach to cardiopulmonary bypass can be adopted more widely.

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PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

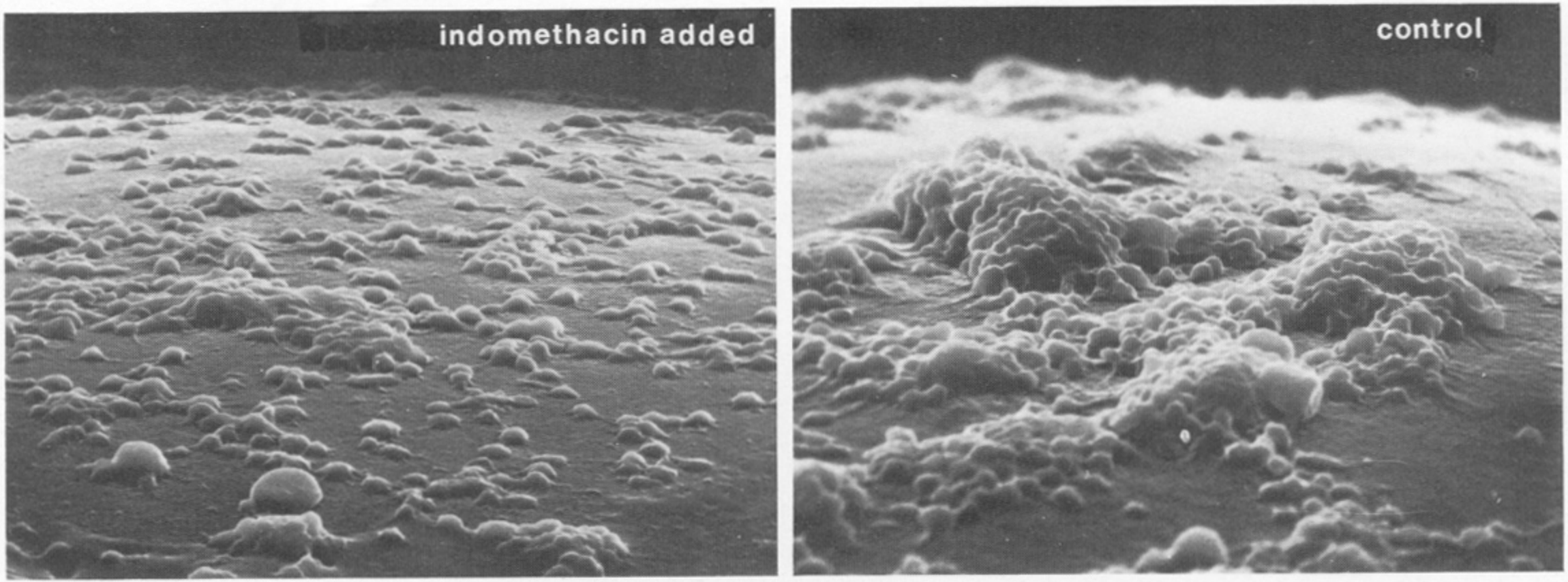

FIGURE 2. Suppression of platelet aggregation by 10^{-4} M indomethacin. Platelet adhesion to the bead surface is not inhibited. From Salzman *et al.* (1977).

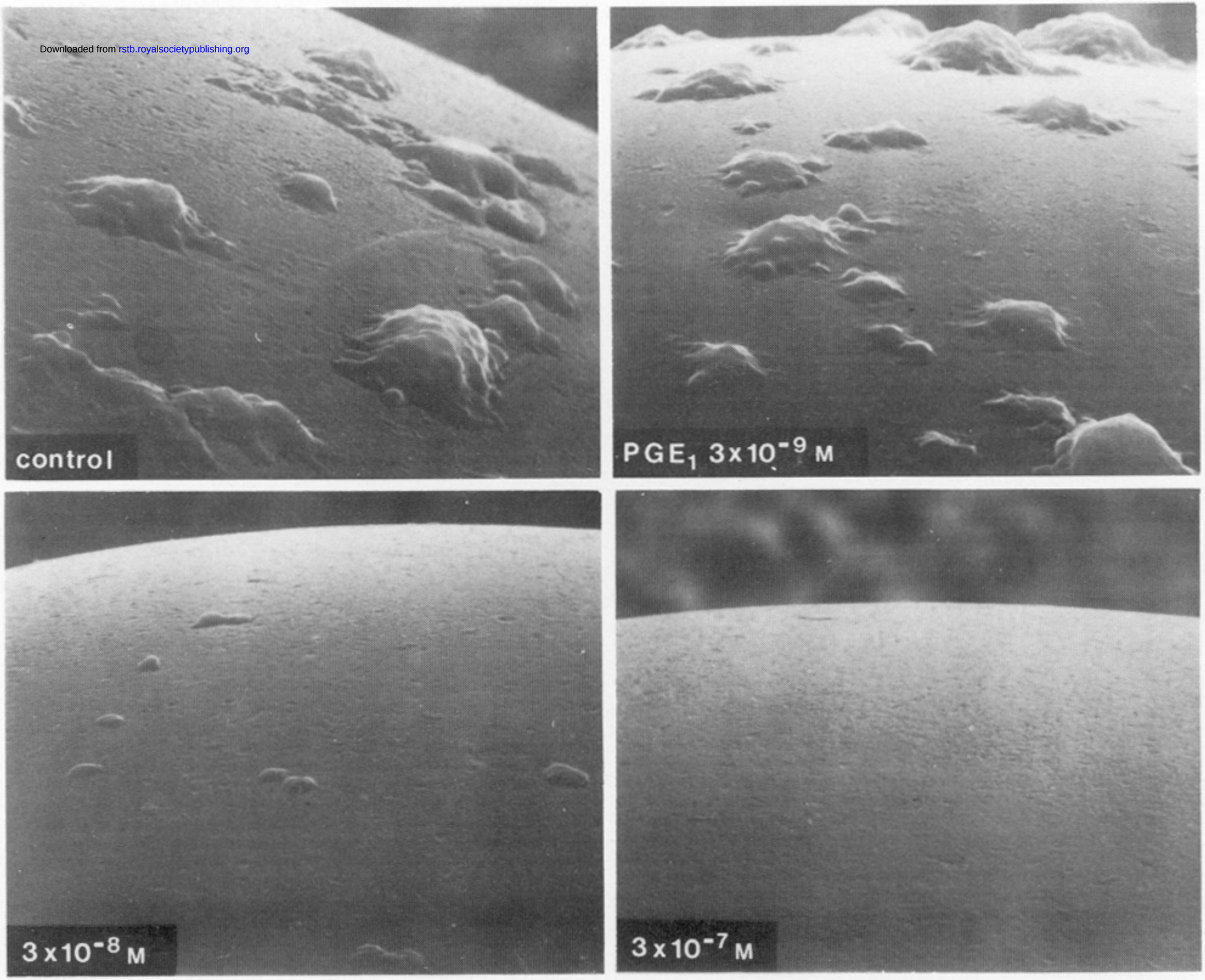

FIGURE 3. Effect of prostaglandin E_1(3×10^{-9} M to 3×10^{-7} M) on platelet interaction with polystyrene beads.