plasma; 2 cat lungs – cat plasma; 2 cat lungs – cat whole blood; 1 guinea-pig lung – Krebs Ringer solution and 2 guinea-pig lungs – horse plasma. The lungs were perfused (37°C) in a recirculating system with constant volume inflow (approximately 150 ml/min for cat and rabbit lungs, 20–30 ml/min for guinea-pig lungs). They were ventilated with 5% CO_2 in air at a constant tidal volume. Ten ml/min of the venous effluent was pumped to superfuse a rat stomach strip, a rat colon and a chick rectum for the continuous bioassay of PGs (Vane, 1969). The superfusate was then returned to the lung perfusion circuit. The tissues were sensitive to calibrating doses of 1 ng/ml PGE_2 and $PGF_{2\alpha}$.

Pulmonary oedema was induced by elevating the outflow pressure of the lungs to 10–30 mmHg for 10–70 minutes. In all lungs this manoeuvre caused gross alveolar oedema as evidenced by cessation of ventilatory movement, translucent appearance of lungs and foam in the trachea.

In none of the 14 experiments did raised outflow pressure or oedema development cause any release of PGs which could be detected on the tissues. Theoretically, PG-release of less than 0.5–1 ng/ml might have escaped detection. However, in four experiments, serial radioimmunological determinations of $PGF_{2\alpha}$ were performed on extracts of the perfusate. These experiments verified the findings with bioassay that no PGs were released during raised outflow pressure or subsequent oedema.

In conclusion, the present experiments suggest that neither vascular distension nor oedema is a stimulus for increased synthesis of prostaglandins in isolated, perfused lungs.

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Effects of synthetic prostaglandin analogues on platelet aggregation and secretion

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Stable synthetic analogues of prostaglandin E_2 (PGE_2) and prostaglandin H_2 (PGH_2) induce platelet aggregation (Corey, Nicolau, Machida, Malmsten & Samuelsson, 1975; Gordon & MacIntyre, 1976), but the platelet responses to these agents have not been fully characterized. We have now compared the effects of 11-deoxy-15(RS)-15-methyl PGE_2 (Wy 17,186), 16,16 dimethyl PGE_2, and a 9,11-azo-prostanoid analogue of PGH_2 (azo-PGH_2) on platelet aggregation and secretion, and have investigated the effects of selected inhibitors on these responses.

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Platelet aggregation was measured photometrically in 0.1 ml samples of human citrated platelet-rich plasma (PRP) pre-labelled with [^{14}C]-5-hydroxy-tryptamine (5-HT) and [^{3}H]-adenine. The reaction was terminated by the addition of 4 volumes ice-cold 0.4% w/v EDTA in iso-osmotic saline, followed by rapid centrifugation (15,000 *g*:30 s), and sub-samples of the platelet-free supernatant were taken for liquid scintillation counting and for fluorimetric measurement of β-N-acetyl glucosaminidase release. For inhibitor studies, drugs or an equal volume of solvent were pre-incubated in PRP at 37°C before measurement of aggregation and release.

Each compound induced a dose-dependent aggregation response, which was reversible ('primary aggregation') at low concentrations (Azo-$PGH_2 \leqslant$ 0.05 μM; 16,16 dimethyl $PGE_2 \leqslant 3$ μM; Wy 17,186 $\leqslant$ 6 μM) and irreversible ('secondary aggregation') at higher concentrations. Intermediate concentrations produced biphasic responses. No release of β-N-acetyl glucosaminidase was observed even with high concentrations of agonist, but irreversible aggregation responses were accompanied by dose-dependent release (up to 50%) of [^{14}C]-5-HT, with less than 10% release of [^{3}H]-adenine. No [^{14}C]-5-HT was released

during primary aggregation. Aggregation and 5-HT release were inhibited by agents (PGE_1 0.1 μM; PGD_2 0.1 μM; adenosine 1 μM) which increase intracellular cyclic AMP, and by dibutyryl cyclic AMP (0.5 mM). Secondary aggregation and the associated release of 5-HT were blocked by indomethacin (0.1 mM), but this inhibitory effect could be readily overcome by increasing the concentration of agonist. 2-n-amylthio-AMP (10–100 μM) blocked secondary but not primary aggregation responses. 2-n-amylthio-AMP is apparently a specific ADP antagonist: it inhibits primary aggregation induced by ADP but not by adrenaline, vasopressin or 5-HT, and its inhibitory effect (unlike that of PGD_2, PGE_1 or adenosine) is not blocked by 9-(tetrahydro-2 furyl) adenine (SQ 22536), an inhibitor of platelet adenylate cyclase (Harris, Phillips & Goldenberg, 1975).

The actions of the prostaglandin analogues Wy 17,186, 16,16 dimethyl PGE_2 and azo-PGH_2 are similar, and are more complex than previously recognized. They directly induce a primary aggregation response and stimulate secondary aggregation and release by an indomethacin sensitive process, possibly triggered by platelet-platelet contact in the primary phase. In addition, they induce secondary aggregation and release by an indomethacin insensitive process. The secondary aggregation responses appear to be mediated by released ADP. In these respects, the complicated behaviour of these compounds resembles that of the native endoperoxides (Salzman, unpublished observations).

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Levels of prostaglandin F and E in cerebrospinal fluid of cats during pyrogen-induced fever

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Prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) and prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) occur in cat brain (Horton & Main, 1967) however, Feldberg, Gupta, Milton & Wendlandt (1973) using bioassay failed to detect either prostaglandin in cat cerebral spinal fluid (CSF). Since $PGF_{2\alpha}$ is pyrogenic in cats (Ewen, Milton & Smith, 1976) we have measured the levels of PGF in the CSF of afebrile and febrile animals by the more sensitive techniques of radioimmunoassay.

Pyrogen (the O-somatic antigen of *Shigella dysenteriae*) dissolved in sterile, pyrogen-free 0.9% saline was injected intravenously (20 μg/kg) in a volume not exceeding 0.4 ml. Control animals were injected with a similar volume of sterile 0.9% saline. Two samples of CSF (approximately 0.5 ml) were collected from the cisterna magna before injection and four samples were collected afterwards. The interval between successive CSF samples was 75 minutes. Rectal temperature was recorded continuously.

Samples of CSF were extracted with ethyl acetate and assayed for PGE (after alkaline conversion to prostaglandin B) and PGF by a double antibody technique (Dighe, Emslie, Henderson, Simon & Rutherford, 1975) without prior separation.

Two distinct types of febrile responses to pyrogen injection were observed. In some animals which had not previously received pyrogen the fever developed after a long latency (90 min), whereas in animals which had received pyrogen before, the fever developed after a short latency (30 min). The level of PGF and PGE measured in CSF taken during the two types of fever and during control experiments are shown in the Table.

In the short latency fevers significant increases of both PGEs and PGFs which paralleled the increases in deep body temperature were seen, and these results are compatible with both prostaglandins having a role