reverse effect (Dawson & Tomlinson, 1974).

Walker (1973) has shown that some non-steriodal anti-inflammatory compounds increase SRS-A release, although these compounds are known to be inhibitors of PG synthetase (cyclo-oxygenase) under many conditions (Vane, 1971). The relationship between PG and SRS-A release has been further analysed using these compounds in preparations derived from passively sensitized human lung and actively sensitized guinea-pig lung (Sheard, Killingback & Blair, 1968; Brocklehurst, 1960).

Indomethacin (1 μg/ml), TYA (10 μg/ml) and aspirin (25 μg/ml) inhibited a microsomal preparation of PG synthetase from guinea-pig lung by 50%, whilst phenylbutazone (10 μg/ml) was virtually ineffective. It was not possible to produce a consistent preparation of this enzyme from human lung. At the same concentrations, the three anti-inflammatory compounds potentiated the release of SRS-A by at least 50% from both human and guinea-pig lungs, but had little effect on histamine release. TYA had no effect on SRS-A or histamine release.

$PGF_{2\alpha}$ and thromboxane B_2 (TXB_2) increased the release of SRS-A from challenged guinea-pig lung whilst PGE_2 reduced it (Table 1). The levels of the parent PGs released on challenge are low, but that of TXB_2 reaches 1 μg/ml (Dawson, Boot, Cockerill, Mallen & Osborne, 1976). It appears that the most important member of the PG family in the modulation of SRS-A release is TXB_2. The data further lead to the speculation that compounds such as indomethacin may preferentially inhibit the formation of parent PGs, leaving the thromboxane pathway from arachidonic acid relatively untouched. PGE_2 and $PGF_{2\alpha}$ are known to modify the adenyl and guanyl cyclase systems in lung tissue, which have been shown to regulate mediator release. Experiments to examine the effects of TXB_2 on the cyclic nucleotides and to analyse PG and Tx release in the presence of non-steroidal anti-inflammatory drugs are in progress.

Table 1 Effect of prostaglandin-like substances on SRS-A release from immunologically challenged guinea-pig lung. ($n=9$)

concentration (μg/ml)	% change in SRS-A release (mean ± s.e. mean) in the presence of PGE_2	$PGF_{2\alpha}$	TxB_2
0.1	0		0
1.0	−20 ± 15	+21 ± 12	+49 ± 22
10.0	−29 ± 6	+40 ± 10	+63 ± 34

+ = increased release; − = reduced release

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Hydrostatic pulmonary oedema is not a stimulus for prostaglandin synthesis in isolated, perfused lungs

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Isolated lungs can be induced to synthetize and release prostaglandins (PGs) by a variety of mechanical and chemical stimuli (Piper & Vane, 1971). It has been suggested that the stimulus for PG synthesis may be distortion of cell membranes (Piper & Vane, 1971). Said & Yoshida (1974) have reported release of PGs during formation of oedema in isolated cat lungs. In their experiments oedema was induced by prolongation of perfusion time. This is, however, a non-specific method of induction. Thus PG synthesis might occur secondary to cellular injury, which also might be responsible for the pulmonary oedema.

In the present experiments we caused lung oedema by elevating the hydrostatic pressure in the pulmonary circulation in order to study the effect of vascular distention and increased extravascular lung water on pulmonary PG-synthesis.

Isolated lungs were prepared as described by Hauge, Lunde & Waaler (1966). The following combinations of species and perfusates were used: 5 rabbit lungs – horse plasma; 2 cat lungs – horse

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