Prostaglandin synthetase inhibitors and leucocytic emigration

Non-steroidal anti-inflammatory agents (NSAA's) such as indomethacin, phenylbutazone, aspirin and mefenamic acid are reported to act in the late phase of carrageenan foot oedema inflammation by suppressing mononuclear cell emigration (Di Rosa, Papadimitriou & Willoughby, 1971b). It has been shown, however, that in the late phase of carrageenan pleurisy, aspirin suppresses polymorphonuclear (PMN) and mononuclear cell emigration (Vinegar, Truax & Selph, 1973). The late phase of both carrageenan pleurisy and foot oedema is thought to be mediated by prostaglandins (PG's) (Di Rosa, Giroud & Willoughby, 1971a; Velo, Dunn & others, 1973), but their connection with cell populations is still uncertain. We have examined the inhibitory effects of six potent PG synthetase inhibitors (ketoprofen, flurbiprofen, sudoxicam, naproxen, fenoprofen and indomethacin) given orally, on rat carrageenan foot oedema (Winter, Risley & Nuss, 1962); rat carrageenan pleurisy (Vinegar & others, 1973) and rat turpentine pleurisy (Spector, 1956). The *in vitro* rank order of potency of the drugs in inhibiting lung PG synthetase is in the order given in parentheses above (unpublished observations).

Carrageenan and turpentine pleurisy were induced in female Ash Wistar rats, 180–200 g, by the intrapleural injection of 0·25 ml of 1% carrageenan in saline and 0·1 ml turpentine oil respectively. Five hours after carrageenan injection and 3 h after turpentine injection, the intrapleural exudate was collected and measured and total and differential leucocyte counts made. Drugs were administered orally 30 min before intrapleural injection. Carrageenan foot oedema was induced in female Ash/CSE rats, 150–180 g, by the subplantar injection of 0·1 ml 1% carrageenan in saline. The feet were measured 4 h after injection and drugs given orally 1 h before injection. Generally there were 5 rats in each group for the pleurisy experiments and 10 rats per group for the foot oedema experiments.

The ID30's of the drugs for the inhibition of intrapleural and subplantar oedema formation after carrageenan injection is shown in Table 1. The effects of these agents on percentage (%) total PMN and mononuclear cell migration is compared with their % exudate inhibition in the rat carrageenan pleurisy model (Fig. 1). Turpentine induced a large pleural exudate at 3 h in the absence of a marked cell infiltration. None of the drugs (given at 30 mg kg^{-1}, except fenoprofen which was given at 100 mg kg^{-1}) reduced the exudate volume significantly from control values.

It appears that in carrageenan pleurisy, inhibition of exudate formation by NSAA's is intimately associated with inhibition of PMN migration into the pleural cavity, but bears no correlation with the inhibition of mononuclear cells which also occurs at 5 h.

The potent NSAA's are thought to exert their anti-inflammatory activity on car-

Table 1. *Comparison of the inhibition of carrageenan pleural exudate and foot oedema by six potent PG synthetase inhibitors, measured at 5 and 4 h respectively.*

Drug	Inhibition of carrageenan pleural exudate Oral ID 30 mg kg^{-1}	Inhibition of carrageenan foot oedema Oral ID 30 mg kg^{-1}
Ketoprofen	1·90	1·65
Flurbiprofen	~0·50	0·76
Sudoxicam	2·20	~1·30
Naproxen	2·60	~1·00
Fenoprofen	20·00	9·00
Indomethacin	1·20	2·10

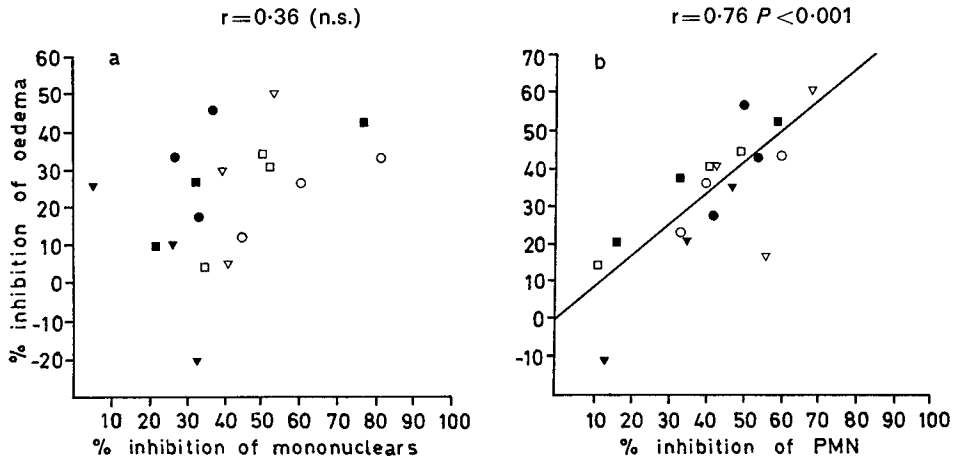

FIG. 1. Correlations between percentage exudate inhibition and percentage mononuclear cell inhibition (a) and between percentage exudate inhibition and percentage PMN inhibition (b) in carrageenan pleurisy. Drugs: ketoprofen ■, indomethacin ●, sudoxicam ○, fenoprofen ▼, flurbiprofen ▽ and naproxen □.

rageenan foot oedema by inhibiting PG synthetase (Flower, Gryglewski & others, 1972). The source of the PG's could be the PMN's, which appear at the same time in both carrageenan foot oedema and pleurisy (Vinegar & others, 1973) and have been shown to release E-type PG's when phagocytosing dead bacterial cells (Higgs & Youlten, 1972) or carrageenan (McCall & Youlten, 1974). The presence of large numbers of PMN's in carrageenan pleurisy may be due initially to the production of chemotactic fragments derived from complement following its activation by carrageenan (Di Rosa & others, 1971a). PMN's then sustain the reaction by phagocytosing carrageenan and releasing inflammatory substances such as lysosomal enzymes (Weissmann & Dingle, 1961) and PGE_1 which has both chemotactic (Kaley & Weiner, 1971) and permeability-inducing properties (Crunkhorn & Willis, 1971). Our results suggest that, in carrageenan pleurisy, potent PG synthetase inhibitors will inhibit cell infiltration possibly via a reduction in chemotactic PG's and that the drugs reduce exudate indirectly, by decreasing the number of PMN's reaching the inflamed site [Ford-Hutchinson, Smith & others (1975) have observed a reduction in migration of PMN's in sponge-induced inflammation in rats after treatment with aspirin-like drugs]. This disagrees with the conclusions of Di Rosa, and his colleagues (1971) who maintain that the PG phase of carrageenan oedema correlates with mononuclear cell infiltration. The inability of the anti-inflammatory drugs tested to reduce turpentine induced permeability suggests that non-specific effects of these drugs on blood vessels, endothelia or histamine and 5-HT should be discounted.

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Evidence that renal vasodilation by dopamine in dogs does not involve release of prostaglandin

Renal vasodilation induced by the intra-arterial administration of dopamine has been attributed to activation of dopamine-specific receptors (Goldberg, 1972). Bell & Lang (1973) reported that electrical stimulation of areas in the midbrain of dogs produced renal vasodilation which was blocked by the dopamine receptor antagonist haloperidol, and suggested that the renal vasculature was innervated by nerves which released dopamine as a neurotransmitter.

Certain prostaglandins (PG), namely those of the A, B and E types, produce increases in renal blood flow (Higgins, Vatner & Braunwald, 1973; Lee, 1972; Marchand, Greenburg & others, 1973). Furthermore, PGE-like substances have been shown to be released from kidney in response to exogenously administered vasoactive substances such as angiotensin (McGiff, Crowshaw & others, 1970), bradykinin (Rogers, 1972) and noradrenaline (McGiff, Crowshaw & others, 1972). Release of PG in response to vasoconstrictor stimuli has been proposed as an intrinsic renal autoregulatory system (Sweet, Kadowitz & others, 1972; Aiken & Vane, 1973). If PG mediated the renal vasodilator effect of dopamine, then inhibition of PG synthesis might be expected to reduce or prevent increases in renal blood flow produced by dopamine. This hypothesis was examined by employing the non-steroidal anti-inflammatory drug indomethacin which has been demonstrated to block PG release (Davis & Norton, 1972; Aiken & Vane, 1973).

Mongrel dogs were anaesthetized with intravenously administered sodium pentobarbitone, 35 mg kg^{-1}. Left renal arterial blood flow was measured with an electromagnetic flowmeter (Biotronex); intra-arterial drug infusions were accomplished via an L-shaped 23-gauge needle inserted directly into the renal artery proximal to the site of application of the flow probe. Left renal blood flow and systemic arterial blood pressure (femoral artery) were recorded.