Although anti-inflammatory glucocorticosteroids fail to inhibit prostaglandin synthetase *in vitro* (Flower, 1974), three such compounds exhibited dose-related inhibition of macrophage prostaglandin production with relative potencies (Table 1) closely paralleling their anti-inflammatory activities.

The pharmacological response of macrophage prostaglandin biosynthesis to both steroids and NSAIDs mimics that of cultured human rheumatoid synovial fragments which contain abundant macrophages and lymphocytes but few polymorphs (Robinson, Smith & Levine, 1973; Kantrowitz, Robinson, McGuire & Levine, 1975); whilst both human lymphocytes (Ferraris & DeRubertis, 1974) and polymorphs (Zurier, 1975) have relatively little prostaglandin biosynthetic capacity. We propose that the macrophage is a relevant *in vitro* model of prostaglandin production in chronic inflammation.

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Effects of indomethacin on prostaglandin levels and leucocyte migration in an inflammatory exudate *in vivo*

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Indomethacin inhibits sub-plantar and intrapleural oedema formation after the injection of carrageenan in the rat and reduces the migration of leucocytes in the pleurisy model (Blackham & Owen, 1975). The drug is a potent inhibitor of prostaglandin synthetase activity *in vitro* and decreases the formation of prostaglandins in developing inflammatory exudates in the whole animal (Ferreira & Vane, 1974). It is possible to construct a unitary hypothesis for all these effects. A primary action of indomethacin on prostaglandin synthetase activity would cause a blockade of prostaglandin formation thus reducing both the increased vascular permeability and cellular infiltration. The latter aspect is involved since prostaglandin E_1 (PGE_1), released from phagocytosing leucocytes has been reported to be chemotactic (Higgs, McCall & Youlten, 1975) and would be expected to sustain the developing inflammation by ensuring a continued entry of more leucocytes into the exudate.

The results of recent work (Ford-Hutchinson, Smith & Walker, 1976) have questioned the chemotactic ability of endogenously produced prostaglandins and we have therefore investigated the possibility that the effects of indomethacin on prostaglandin formation and cellular migration are produced by independent mechanisms. The content of prostaglandins, assayed biologically and expressed as prostaglandin E_2 (PGE_2), and the number of leucocytes were measured in the exudates formed after 9 h in inert plastic sponges implanted subdermally in groups of rats (Ford-Hutchinson, Smith, Elliott, Bolam, Walker, Lobo, Badcock, Colledge & Billimoria, 1975). Each group received either saline (controls), plasma fraction (Walker, Smith, Ford-Hutchinson & Billimoria, 1975), indomethacin or 5, 8, 11, 14-eicosatetraynoic acid (TYA), a specific inhibitor of prostaglandin biosynthesis from fatty acid precursors (Shaw, Jessup & Ramwell, 1972).

The results (Table 1) show that the plasma fraction significantly inhibited the migration of polymorphonuclear and mononuclear leucocytes into the exudate but did not affect the formation of prostaglandins whereas TYA produced the reverse response. Thus the two phenomena are not interdependent. Indomethacin inhibited both the prostaglandin content and the cellular migration, the former was almost completely suppressed at all the doses studied but the latter was inhibited in a dose-response manner. It is concluded that the inhibitory effects of

Table 1 Effect of plasma fraction, indomethacin and TYA on PGE_2 content and total leucocyte counts into the exudate of inert 9 h sponges implanted subdermally in the rat

	PGE_2 ($ng.ml^{-1}$ exudate)	*% Inhibition*	*Total leucocytes ($\times 10^4 ml^{-1}$ exudate)*	*% Inhibition*
Control (15)	13.2 ± 2.4	—	1005 ± 93	—
Plasma fraction (5) 1 ml i.v.	12.9 ± 1.6	2	380 ± 36	62**
Indomethacin (5) 1 mg kg^{-1} p.o.	1.2 ± 0.3	91**	827 ± 142	18*
Indomethacin (5) 3 mg kg^{-1} p.o.	1.0 ± 0.8	95**	484 ± 90	52**
Indomethacin (5) 6 mg kg^{-1} p.o.	1.1 ± 0.3	92**	220 ± 61	78**
TYA (5) 150 mg kg^{-1} i.p.	6.5 ± 2.0	51**	905 ± 138	10
TYA (5) 500 mg kg^{-1} i.p.	2.6 ± 1.1	80**	985 ± 130	2

Results are expressed as means ± s.d. with the number of animals in each group in parentheses. Levels of significance refer to the differences from the results of the control group.
* $P < 0.05$ ** $P < 0.005$

indomethacin on prostaglandin synthetase activity and on leucocyte migration in the sponge model are independent actions of the drug. A component of the experimental anti-inflammatory activity is therefore concerned with an aspect of inflammation not involving a blockade of prostaglandin biosynthesis.

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