approximately 10 times more potent than metyrapone on a molar basis.

In two experiments on the isolated uterus of the non-pregnant rat (primed with 200 μg oestradiol benzoate i.m. 18 h previously) metyrapone antagonized contractile responses to acetylcholine and to PGE_2 but responses to $PGF_{2\alpha}$ suggested slight stimulation.

These results suggest that metyrapone has a non-specific direct smooth muscle inhibiting action. They also support the earlier suggestion (Parnham & Sneddon, 1975) that metyrapone has a differential effect on the synthesis of PGF and PGE in the pregnant rat uterus *in vitro*, similar to that recently observed with gold salts and phenylbutazone on sheep seminal vesicles (Stone, Mather & Gibson, 1975).

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Effects of anti-inflammatory drugs on macrophage prostaglandin biosynthesis

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Chronic inflammation in diseases such as rheumatoid arthritis is typified by a persistent mononuclear cell infiltrate in which macrophages are prominent. Macrophages, derived from inflammatory exudates, generate substantial concentrations of prostaglandin activity when cultured *in vitro* (Bray, Gordon & Morley, 1974). We have, therefore, examined the effect of established anti-inflammatory drugs on macrophage prostaglandin biosynthesis *in vitro*.

Macrophage-rich peritoneal exudate cell populations (60–80% macrophages) were collected from guinea-pigs, 2–3 days after intraperitoneal injection of 20 ml 2% starch solution. Cells (1×10^6/ml) were cultured in Eagles MEM containing antibiotics, and 10% heat-decomplemented foetal calf serum, in 5% CO_2 in air at 37°C for 24 hours. Prostaglandin E-like activity in the supernatant was measured by radioimmunoassay utilizing sheep anti-PGE_2/BSA antiserum whose cross-reactivity was PGE_2 (100%), PGE_1 (55%), $PGF_{2\alpha}$ (1.5%), 15 keto-PGE_2 (1.2%), PGA_2 (0.6%) and PGB_2 (0.2%).

Macrophage PG production was 12.0 ± 2.76 ng PGE_2 equivalent/10^6 cells per 24 h (range 2.2–43.2). In agreement with previous studies (Vane, 1971; Flower, 1974), non-steroidal anti-inflammatory drugs (NSAIDs) caused dose-related inhibition of prostaglandin biosynthesis with rank order of potency (Table 1) approximating anti-inflammatory activity.

Table 1 Inhibition of macrophage prostaglandin synthesis

Drug	*ID_{50} (ng/ml)*	*Relative Potency**
Arylalkanoic Acids:		
Indomethacin	1.15(8)†	100
Ketoprofen	13.6 (2)	2.06
Naproxen	225 (2)	0.12
Pyrazolidinediones:		
Phenylbutazone	1450 (2)	0.15
Feprazone	400 (2)	0.55
Salicylates:		
Acetyl Salicylic Acid	280 (2)	0.35
Sodium Salicylate	5300 (2)	0.018
Glucocorticosteroids:		
Hydrocortisone	108 (2)	1.01
Prednisolone	26.7 (2)	4.09
Dexamethasone	4.35(2)	25.13

* Relative potency was obtained by comparison of the ID_{50} with the ID_{50} for indomethacin (expressed as 100) determined in the same experiment.
† Number of experiments in parenthesis.

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