like drugs inhibit the initial stages of the reaction, probably the attack on the substrate. There may be certain exceptions, however, as in the case of phenylbutazone and benzydamine, where there is some evidence that these drugs interfere with the breakdown of the cyclic endoperoxide rather than its formation (Flower et al., 1973).


**Contribution of Prostaglandins to the Inflammatory Signs and Symptoms**

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Inhibition of prostaglandin biosynthesis is a general property of aspirin-like drugs, demonstrated at concentrations found in body fluids during therapy (see Flower, 1974; Ferreira & Vane, 1974). All cells so far studied have the capacity to generate prostaglandins. Distortion or trauma of the cell membrane is a common thread between the different prostaglandin-producing stimuli (Piper & Vane, 1971), which may be mechanical, chemical or pathological. Prostaglandins are generated in many forms of damage in both animals and man, including carrageenin inflammation (Willis, 1969; Di Rosa et al., 1971), thermal injury to the skin (Jonsson, 1971; Jonsson & Harnberg, 1972; Arturson et al., 1973) anaphylaxis (Piper & Vane, 1969), monoarticular arthritis (Blackham et al., 1973), experimental uveitis (Eakins et al., 1973), allergic and contact eczema (Greaves et al., 1971), u.v.-induced inflammation (Greaves & Søndergaard, 1970) and rheumatoid arthritis (Higgs et al., 1974).

We shall now discuss whether prostaglandin release contributes to the genesis of fever, inflammation and pain, for if it does, then its abolition can account for the anti-pyretic, anti-inflammatory and analgesic actions of aspirin-like drugs.

**Fever**

Fever is often associated with inflammation. Prostaglandin E₂ is the most powerful pyretic agent known when injected either into cerebral ventricles or directly into the anterior hypothalamus (Milton & Wendlandt, 1971; Feldberg & Saxena, 1971). The hyperthermic effect is dose-dependent, almost immediate and lasts for about 3h.

As in peripheral inflammatory responses, there is a generation of prostaglandin E-like substance in the central nervous system during fever (Feldberg & Gupta, 1973), and the concentrations in the cerebrospinal fluid rise after intravenous injection of pyrogen by 2.5–4.0-fold, sometimes to as much as 35 ng/ml.

Aspirin-like drugs do not abolish either the formation of endogenous pyrogen by leucocytes (Clark & Moyser, 1972) or the pyretic action of prostaglandins injected into the third ventricle of cats. However, they inhibit both the generation of prostaglandins in the central nervous system and the fever caused by pyrogens or 5-hydroxytryptamine given into the cerebral ventricles. The 5–10-fold increase in prostaglandin release into
the cerebrospinal fluid observed at the height of endotoxin-induced fever in dogs was suppressed by the administration of indomethacin (Milton, 1973).

**Pain**

In man intravenous prostaglandins cause pain along the veins into which they are infused, and also cause headaches (Bergström et al., 1959; Collier et al., 1972). This contrasts with bradykinin, for in normal subjects, intravenous bradykinin, which produces systemic and intra-cranial vasodilatation, does not cause pain (Sicuteri et al., 1967).

Prostaglandins administered in high concentrations intradermally (Ferreira, 1972) or intramuscularly (Karim, 1971) cause a long-lasting overt pain. In concentrations likely to be found at inflamed sites, prostaglandins do not cause overt pain; they do, however, cause hyperalgesia (i.e. a state in which pain can be elicited by normally painless mechanical or chemical stimulation). Other putative mediators of inflammation did not cause hyperalgesia when given intradermally (Ferreira, 1972). The hyperalgesia elicited by small amounts of prostaglandin E₁ given intradermally (Solomon et al., 1968; Juhlin & Michaelsson, 1969), or infused subdermally (Ferreira, 1972) was very long-lasting. The subdermal-infusion experiments, which were designed to mimic the continuous release of mediators at the site of an injury, showed that the hyperalgesic effects of prostaglandins were cumulative, since they depend not only on the concentration of the prostaglandins, but also on the duration of the infusion. This cumulative sensitizing activity at the pain receptors was later observed in dog spleen (Ferreira et al., 1973), dog knee joint (Ferreira et al., 1974) and rat paw (Willis & Cornelsen, 1973). We used the reflex rise in blood pressure, induced by bradykinin injections into the spleen or into the knee joints of lightly anaesthetized dogs, as an indication of sensory stimulation (Ferreira et al., 1973). Doses of bradykinin known to release prostaglandin from the spleen caused a reflex rise in blood pressure, in proportion to the dose used. The hypertensive effect was decreased by indomethacin, which also abolished prostaglandin release. When prostaglandin E₁ was given with bradykinin in the indomethacin-treated dogs, the reflex increase in blood pressure was restored, sometimes to greater than control values.

Bradykinin injected into the cavity of the knee joints elicits a hypertensive reflex similar to that obtained with intrasplenic injections (Ferreira et al., 1974). Local treatment of the joints with indomethacin or aspirin inhibit the response, and addition of prostaglandins restores it after treatment. Moreover, in the presence of exogenous prostaglandin, E₂ aspirin or indomethacin are ineffective in blocking bradykinin-induced reflex hypertension. This observation rules out the possibility suggested by Lim et al. (1964) and Lim (1968) that aspirin-like drugs antagonize the action of bradykinin directly.

**Erythema**

Prostaglandins cause erythema in man and animals; prostaglandin E₁ is effective at doses as low as 1 ng; but for prostaglandin F₁, approx. 1 μg is needed (Solomon et al., 1968; Juhlin & Michaelsson, 1969; Crunkhorn & Willis, 1971). These vascular effects of prostaglandins are not shared by other putative mediators of inflammation, for like hyperalgesia they are long-lasting (sometimes up to 10 h).

**Oedema**

Prostaglandins, like bradykinin, histamine and 5-hydroxytryptamine, cause increased vascular permeability by inducing vascular leakage at the post-capillary and collecting venules (Kaley & Weiner, 1971). Although most active substances exhibit a general relation between ability to increase vascular permeability and erythema formation, these effects result from actions on different components of the vessel. Whereas erythema involves pooling of blood in arterioles and venules, oedema is the result of events occurring mainly in the venules (Majno et al., 1972).

We and others have shown that the oedema caused by bradykinin and various inflammatory stimuli is also potentiated by prostaglandins (Moncada et al., 1973; Thomas &
The potentiator BPP₉₉ had no effect on normal paw volume, but significantly increased the oedema when given at 0.0, 0.5, 1.4 or 6h after carrageenin (Ferreira et al., 1974). This enhancement was also seen in animals treated with indomethacin. Soya-bean trypsin inhibitor, which prevents bradykinin formation, abolished the potentiation.

These results indicate that bradykinin is being formed during all of the first 6h of carrageenin oedema and reinforce our previous conclusion that the late phase of carrageenin oedema results mainly from the potentiating action of prostaglandins on the effects of other mediators, especially bradykinin.

In conclusion, the anti-inflammatory, analgesic and anti-pyretic action of aspirin can be satisfactorily explained by inhibition of the prostaglandin biosynthesis brought about by the traumatizing stimulus. The fact that aspirin only removes a potentiating factor explains why this group of drugs cannot completely abolish the inflammatory response.


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**Metabolic Interconversion of the Prostaglandins**

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The naturally occurring E- and F-type prostaglandins exhibit a wide variety of biological actions, the majority of which are of short duration owing to rapid metabolism of the prostaglandin. The several enzyme systems involved have been studied in some detail for two main reasons. First, their activity may influence the physiological or pathological function of an endogenous prostaglandin, and secondly certain non-substrates of these enzymes, which still retain high biological activity, will have a prolonged duration of action and may therefore be useful in clinical medicine.

**15-Hydroxyprostaglandin dehydrogenase and Δ-13 prostaglandin reductase**

15-Hydroxyprostaglandin dehydrogenase is an important enzyme which converts a number of 15(S) prostaglandins into their 15-oxo counterparts (Scheme 1) (Ånggård & Samuelsson, 1966). The 15-oxo prostaglandins, which are considerably less active than their precursors (Ånggård, 1966; Kloeze, 1969; Pike et al., 1967), can be further metabolized to 13,14-dihydro derivatives by a Δ-13-reductase enzyme (Ånggård & Samuelsson, 1964). Both these enzymes are widely distributed, high activities being found in lung, spleen and kidney (Ånggård et al., 1971).

13,14-Dihydro PGE₂*, and α-dinor and α-tetranor PGE₂ are poor substrates for the 15-hydroxyprostaglandin dehydrogenase (Nakano et al., 1969). Since a large number of prostaglandin metabolites have the α-dinor or α-tetranor-13,14-dihydro-15-oxo structure it is most likely that oxidation in vivo at C-15 precedes both reduction of the 13,14 double bond and β-oxidation of the α side chain.

The dehydrogenase present in lung may function to prevent prostaglandins released into systemic venous blood from reaching organs via their arterial blood supply. It has been shown that PGE₂ and PGF₂α lose most of their biological activity during a