Introduction

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PROSTAGLANDINS are naturally-occurring acid lipids. With the exception of those in seminal fluid, they are not stored preformed but are synthesized and released when cells are stimulated. All mammalian tissues investigated are capable of forming prostaglandins. They and the related compounds, thromboxanes and prostacyclin, have a wide range of potent biological activities, some of which are mentioned here and are not only of interest to the pharmacologist but are of importance to the clinician as well. Prostaglandins are not circulating hormones but act close to their site of synthesis before being metabolized.

In 1931, whilst instilling semen into the vagina to bring about artificial insemination, Kurzrok and Lieb observed that the uterus either strongly contracted or relaxed to semen. Semen contains the highest number and concentration of prostaglandins isolated from a single source, so this was one of the first demonstrations of the potent action of prostaglandins on the smooth muscle of the female reproductive tract. Since then, there has been a vast amount of research carried out on prostaglandins including their therapeutic use to induce labour and abortion and their actions have revolutionized obstetric management of the dead fetus and mid-trimester abortion (see Craft, this symposium).

In 1971 Vane demonstrated that aspirin-like drugs prevented the release of prostaglandins. This was subsequently shown to be due to inhibition of the enzyme (cyclo-oxygenase) which stimulates conversion of arachidonic acid to prostaglandins (also to the related compounds thromboxanes and prostacyclin: see below). This finding entirely altered the explanation of the mechanism of action of the aspirin-like drugs. Prostaglandins are not mediators of pain but potentiate the action of the agonists of pain, e.g. histamine, kinins and therefore this action provides an explanation of why aspirin is a weak analgesic. Similarly, since prostaglandins potentiate the mediators of inflammation, inhibition of their synthesis explains at least part of the anti-inflammatory action of aspirin. For instance, prostaglandins are formed in skin during ultraviolet irradiation (sun-burn) and the resulting inflammation is relieved by topical application of

indomethacin (see Plummer, this symposium). Prostaglandin E_2 is pyrogenic and appears in cerebrospinal fluid during fever; the antipyretic effect of aspirin can be explained by the fact that it inhibits the appearance of prostaglandin in the cerebrospinal fluid.

The anti-inflammatory steroids also affect the prostaglandin system but their action is not so easily defined as that of the non-steroid anti-inflammatory drugs. Steroids prevent the release of prostaglandins apparently by at least two mechanisms; firstly, by preventing the availability of substrate (and therefore formation of prostaglandins), and secondly by an action on the cell membrane which prevents the release of prostaglandins formed in the cell. E-type prostaglandins have an anti-ulcerogenic effect so that inhibition of their release by both types of anti-inflammatory drug could explain the side effect of gastric ulceration seen with these drugs.

Knowledge of the synthesis of prostaglandins and related compounds has made important contributions to the understanding of thrombosis. In 1975, Samuelsson, Svensson and Hamberg showed that the endoperoxide precursors of prostaglandins (PGs G_2 and H_2) also form thromboxane A_2 which strongly stimulates aggregation of platelets. This seemed to rationalize the use of aspirin-like drugs to inhibit platelet aggregation and thrombosis. However, in 1976 Dr Vane's group demonstrated that prostaglandins G_2 and H_2 act on blood vessel walls of man and animals to release prostacyclin (prostaglandin I_2) which inhibits platelet aggregation. Therefore, it would seem logical to enhance the formation of a natural inhibitor of platelet aggregation rather than inhibit the formation of it and all the other products of cyclo-oxygenase with aspirin-like drugs.

Prostaglandins have other important implications in disease. E-type prostaglandins are vasodilators and have been infused intra-arterially for treatment of peripheral arterial disease. The prostaglandins also encourage healing of ulcers in the skin and are probably involved in all wound healing. Prostaglandins are released by malignant tumours and seem to play a part in the seeding of metastases.

They also stimulate bone resorption and prevent synthesis of collagen. In asthma the sensitivity of the patient to the bronchoconstrictor action of prostaglandin $F_{2\alpha}$ may be greatly potentiated and there is evidence that synthesis of prostaglandins is increased in sensitized tissues.

Our present knowledge of the prostaglandin system has already given rise to new medical treat-

ment and doubtless there will be further advances in the future. Understanding of the way in which drugs interact with the prostaglandin system has thrown new light on the mechanism of action of the steroid and non-steroid anti-inflammatory drugs and will prove invaluable in the future development of drugs with fewer unwanted side effects.