LETTERS TO THE EDITOR

Prostaglandins and anti-inflammatory drugs in the dog knee joint

The role of the prostaglandins (PG) in inflammatory and allergic processes is currently under investigation, and evidence indicates both stimulatory and inhibitory properties depending upon experimental conditions. PGE_1, E_2 and $F_2\alpha$ have been characterized as mediators of inflammation and allergy by virtue of their ability to increase vascular permeability after intradermal injection (Arora, Lahiri & Sanyal, 1970; Crunkhorn & Willis, 1971) or after complement activation (Giroud & Willoughby, 1970). Further experimental evidence indicates release of PGE_2 and $F_2\alpha$ from sensitized lung tissue in anaphylactic shock (Piper & Vane, 1969); the presence of PGE's in rat inflammatory exudates (Willis, 1970), and their effectiveness as a leucocytic chemotactic factor (Kaley & Weiner, 1971; Di Rosa & Willoughby, 1971). Additionally, blockade of the production of PGE_2 and $F_2\alpha$ by the anti-inflammatory agents aspirin and indomethacin strongly suggests an inflammagenic role for these prostaglandins (Vane, 1971; Collier, 1971). In contrast, PGE_2 reduced ankle swelling in rats afflicted with adjuvant arthritis (Aspinall & Cammarata, 1969); PGE_1 inhibited lysosomal enzyme discharge from polymorphs (Zurier & Weissmann, 1971); and various PG's inhibited the immunoglobulin-mediated release of slow reacting substances of anaphylaxis in the rat (Koopman, Orange & Austen, 1970).

We have attempted to expand these observations by studying the effects of several PG's and various non-steroidal anti-inflammatory agents in a suitable tissue space, the dog knee joint.

Unanaesthetized, fasted mongrel dogs, 10 to 15 kg, were injected into the knee (stifle) joint with solutions of PG in a manner previously described (Rosenthale, Kassarich & Schneider, 1966). Responses were evaluated by a modification of a dolorimeter described by Van Arman, Carlson & others (1970). Prostaglandins were solubilized in a 0·06M phosphate buffer, pH 7·4, and kept frozen until used, when appropriate dilutions were made with saline. Anti-inflammatory drugs were prepared as fine suspensions in water and administered orally using a stomach tube.

PGE_1 and E_2 induced within 15 min a long-lasting inflammatory effect when injected into the dog knee joint (Fig. 1A). PGE_1 was approximately ten times as potent as PGE_2 in this respect. The onset of incapacitation was more rapid than that obtained with an injection of urate crystals. A different picture was presented by $PGF_2\alpha$, which induced an initial small short-lived effect, followed by a gradual delayed increase in incapacitation over 4 h. These studies support a pro-inflammatory effect for PGE_1, PGE_2 and $PGF_2\alpha$ in the dog stifle joint.

Aspirin, phenylbutazone and indomethacin at doses known to have anti-inflammatory activity against urate crystal-induced joint inflammation in dogs (Rosenthale & others, 1966; Van Arman & others, 1970), were ineffective in preventing the incapacitation induced by PGE_1 or E_2 (Fig. 1B). Activation of the Hageman factor, kinins, polymorph cell migration, the release of lysosomal enzymes and other such agents have been implicated in the synovitis resulting from the injection of sodium urate crystals intrasynovially. Our data do not preclude a role for PG's in urate-

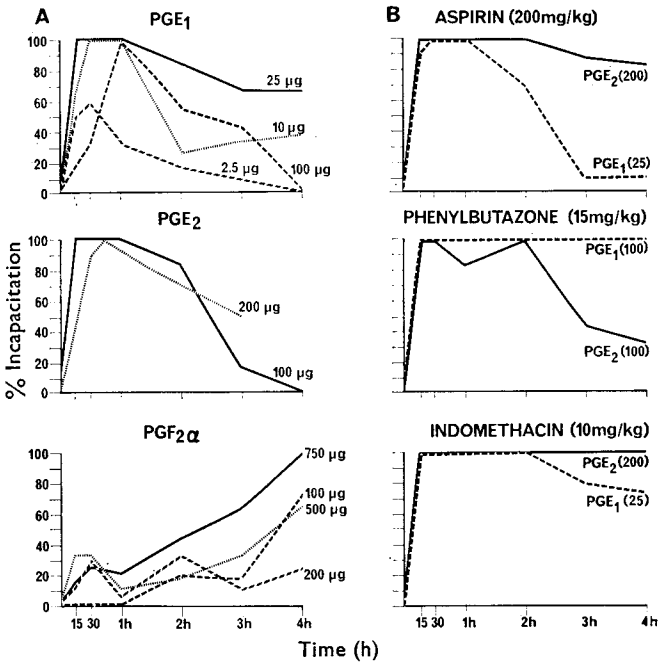

FIG. 1. A. Effect of PG's on dog knee joint. PG given at zero time at the total doses indicated. Three to 4 dogs per dose.
B. Effect of anti-inflammatory drugs on inflammation induced by PG. Drugs administered orally at doses shown, 60 min before PG, 3 to 4 dogs per dose.

induced synovitis, since inhibition of PG synthesis as suggested by Vane (1971) and Ferreira, Moncada & Vane (1971), may be the mode of action of non-steroidal anti-inflammatory agents.

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