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Screens for anti-inflammatory drugs

It has recently been shown by Willis (1969), Di Rosa, Giroud & Willoughby (1971), Di Rosa, Papadimitriou & Willoughby (1971) that the oedema induced in rats feet by injection of carrageenan is mediated by histamine and 5-hydroxytryptamine (5-HT) during the first hour, after which the increased vascular permeability is maintained by kinin release up to $2\frac{1}{2}$ h. From $2\frac{1}{2}$–6 h the mediator appears to be a prostaglandin, release of which is closely associated with migration of leucocytes into the inflamed site. All the mediators appear to be dependent upon an intact complement system for their activation and release (Giroud & Willoughby, 1970). Examination of the non-steroidal anti-inflammatory drugs on this model has shown that they suppress mainly the last phase of the response, namely the "prostaglandin phase." Their ability to suppress this phase correlates directly with their ability to suppress mononuclear leucocyte migration into the inflamed tissues. Thus the oedema and its suppression during the period $2\frac{1}{2}$–6 h after injection of carrageenan serves as an index of leucocyte migration. It has been suggested that this explains why the model of acute inflammation can successfully be employed in the search for new non-steroidal anti-inflammatory agents (Di Rosa, Papadimitriou & Willoughby, 1971).

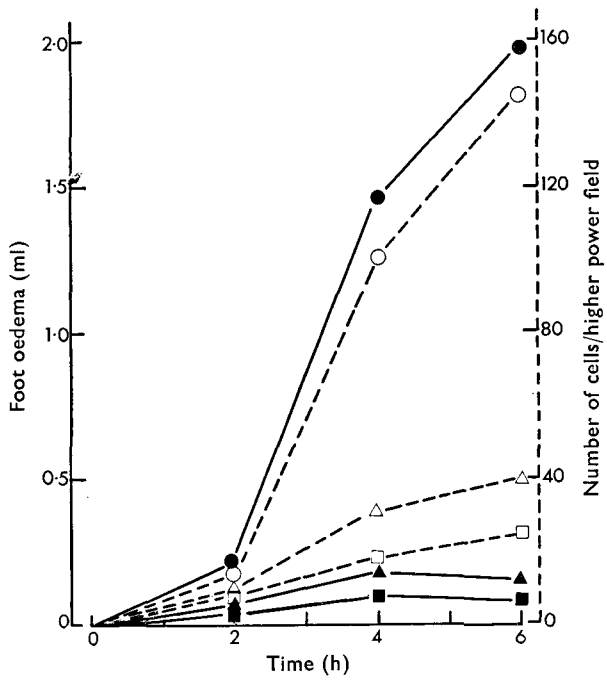

FIG. 1. Foot oedema (solid symbols) and cell emigration (open symbols) in histamine, 5-HT and kininogen-depleted rats after subcutaneous injection (0·1 ml) into the foot of either 1% carrageenan (circles), 6% dextran (triangles) or 1% formalin (squares).

In the present study rats were depleted of their tissue stores of histamine and 5-HT with compound 48/80 (Di Rosa, Giroud & Willoughby, 1971) and of kininogen with cellulose sulphate (Di Rosa, Papadimitriou & Willoughby, 1971). These depleted animals then received injections of various irritants into the sub-plantar aspect of the hind paw and the foot swelling was measured at 2, 4 and 6 h after the injection as previously described (Di Rosa, Giroud & Willoughby, 1971). In similarly treated rats cell counts were made of the total numbers of leucocytes migrating into the inflamed site.

Fig. 1 shows that 0·1 ml of 1% carrageenan provoked a good oedema despite the depletion of the earlier mediators (histamine, 5-HT and kininogen), the oedema is closely paralleled by the migration of leucocytes into the inflamed site.

In contrast, the oedema provoked by 0·1 ml of 6% dextran or 0·1 ml of 1% formalin failed to elicit either a good increase of vascular permeability or leucocyte migration. This could be interpreted as providing further support for the concept of the inter-relation of leucocyte migration and activation of prostaglandins during this phase of the inflammatory response.

It has previously been shown by Winter, Risley & Nuss (1962) that suppression of 4 h carrageenan oedema in the rat paw correlates well with potential therapeutic activity of anti-inflammatory agents. It is suggested that the failure of formalin and dextran to provoke a leucocyte response indicates a failure of these injurious stimuli to serve as useful models in the search for new anti-inflammatory agents. On the other hand used with care such models can provide an indication of potential antihistamine, anti-5HT or antikinin activity.

In looking for new *in vivo* screens for non-steroidal anti-inflammatory agents it is proposed that a necessary prerequisite of the injurious stimulus should be its ability to provoke a migration of leucocytes preferably of the mononuclear type which in turn will lead to activation of the so-called prostaglandin mediated phase.

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