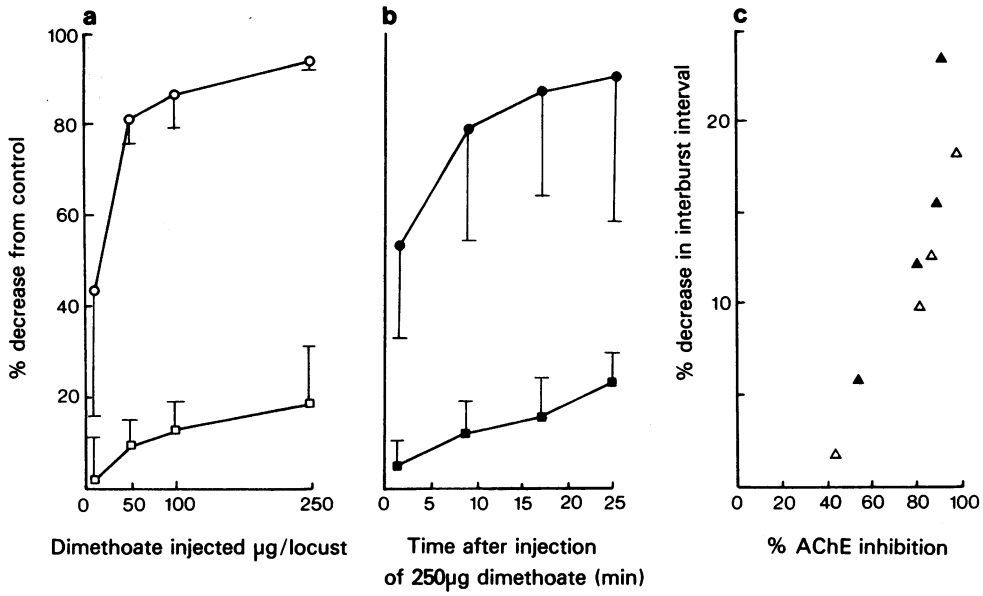

Figure 1 a. AChE, (○) and interburst interval (□) means and s.d. (n = 4) after different doses of dimethoate.
b. AChE (●) and interburst interval (■) means and s.d. (n = 4) at stated times after injection of 250 µg dimethoate.
c. Decrease in interburst interval as a function of AChE after using different doses of dimethoate (△) and 250 µg dimethoate (▲) for different times. Computed from the data of a and b.

The effects of α- and β-adrenoceptor agonists on inflammatory exudation in rabbit and guinea-pig skin

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We have investigated the effects of locally-injected adrenoceptor agonists on plasma exudation in the reversed passive Arthus (RPA) reaction, and on exudation responses produced by histamine, in the skin of the rabbit and guinea-pig.

Plasma exudation and blood flow changes were measured in skin sites as the accumulation of [^{131}I]-albumin and clearance of locally-injected ^{133}Xe, as previously described (Williams, 1976).

Neither noradrenaline (via α-adrenoceptors) nor isoprenaline (via β-adrenoceptors) produced an increase in vascular permeability when injected into rabbit or guinea-pig skin. In both species noradrenaline (10–50 ng/0.1 ml) produced a reduction in blood flow and isoprenaline (50–500 ng/0.1 ml) produced an increase in blood flow. However, in the guinea-pig the isoprenaline effect was not significant in several experiments.

In both species, noradrenaline reduced plasma exudation induced by histamine; e.g. in the rabbit, histamine (2.5 µg/0.1 ml) = 113.6 ± 4.1 µl, noradrenaline (50 ng/0.1 ml) = −1.0 ± 0.8 µl, histamine + noradrenaline = 25.0 ± 2.0 µl, $n = 6$ sites. This effect of noradrenaline, which was abolished by locally-injected phenoxybenzamine, was presumably due to a reduction in blood supply to the tissue.

In the rabbit, isoprenaline produced a marked increase in histamine-induced plasma exudation; e.g. histamine (2.5 µg/0.1 ml) = 11.4 ± 2.7 µl, isoprenaline (0.5 µg/0.1 ml) = 1.7 ± 1.1 µl, histamine + isoprenaline = 56.3 ± 7.4 µl, $n = 6$ sites.

This marked potentiation effect by isoprenaline was also observed in the RPA reaction suggesting that the effect of vasodilatation on plasma exudation outweighed any possible β-adrenoceptor inhibition of endogenous mediator release. The potentiation phenomenon was abolished by locally-injected propranolol, but, using a range of β-adrenoceptor agonists and antagonists, we were not able to distinguish β_1 and β_2 effects.

Unlike in the rabbit, the exudation in RPA reactions of the guinea-pig was inhibited by locally-injected isoprenaline (in spite of an induced increase in blood flow in some experiments). This was not due merely to an inhibition of mediator release, since exudation induced by histamine was also reduced in some experiments, e.g. histamine (1.0 µg/0.1 ml) = 38.4 ± 2.0 µl, isoprenaline (0.5 µg/0.1 ml) = 1.0 ± 0.5 µl, histamine + isoprenaline = 13.1 ± 3.3 µl, $n = 6$ sites. This suggests a β-adrenoceptor inhibitory effect on vessel wall permeability in this species. A similar phenomenon has been observed previously in the hamster using the β-adrenoceptor agonist, terbutaline (Svensjö, Persson & Arfors, 1976), and more recently using the same compound in the guinea-pig (O'Donnell & Persson, 1978).

Inflammatory exudation can be modulated at three levels by adrenoceptor agonists: (a) by affecting mediator release, (b) by affecting vessel wall permeability responses and (c) by increasing or decreasing blood supply. In this study (a) was not clearly distinguished but examples of both (b) and (c) were demonstrated.

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The effects of different particulate stimuli on the extracellular release of prostaglandins and lysosomal enzymes from mouse peritoneal macrophages *in vitro*

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The presence of macrophages is a characteristic feature of chronic inflammatory lesions. The ability of isolated macrophages to secrete lysosomal enzymes selectively on challenge with particulate inflammatory stimuli may contribute to their role in chronic inflammation and connective tissue damage (Page, Davies & Allison, 1974; Davies & Allison, 1976). In addition, macrophages from inflammatory exudates (Bray & Gordon, 1976) and normal or thioglycollate-stimulated macrophages exposed to zymosan (Davies, Bonney, Dahlgren, Pelus, Kuehl & Humes, 1977) will secrete prostaglandins *in vitro*.

Asbestos, zymosan and immune complexes have all been shown to stimulate the selective release of lysosomal enzymes from macrophages (Davies, Allison, Ackerman, Butterfield & Williams, 1974; Ringrose, Parr & McLaren, 1975; Cardella, Davies & Allison, 1974). However, the concomitant release of lysosomal enzymes and prostaglandins by these agents is not so well documented.

A comparison has been made of the effects of zymosan, asbestos and immune complexes (BSA-rabbit anti-BSA) on lysosomal enzyme (β-glucuronidase) release and prostaglandin production by normal mouse peritoneal macrophages exposed to these agents *in vitro*. Major differences have been observed in the patterns of release induced by the three materials, indicating that lysosomal enzyme release and prostaglandin secretion by phagocytosing macrophages are not directly related.

The effects of some antirheumatic drugs on the release of lysosomal enzymes by zymosan and asbestos have been studied. Gold (sodium aurothiomalate), flurbiprofen and indomethacin increased the intracellular levels of lysosomal enzymes without affecting significantly the absolute amount of enzyme released into the culture medium, irrespective of the stimulant used. In contrast, prednisolone inhibited zymosan-induced but not asbestos-induced lysosomal enzyme release, suggesting a difference in the modes of action of these agents.