To determine whether chronic barbitone administration or withdrawal affects sensitivity to acetylcholine-like drugs, the effects were studied of physostigmine (3 μg) or pilocarpine (50 μg) administered intraventricularly, on rectal temperature. All animals were pretreated (30 min) with atropine methylnitrate (2 mg/kg intraperitoneally). Body temperature was chosen because: (1) it is decreased by injection of acetylcholine, carbachol or oxotremorine into the hypothalamus or cerebral ventricles, an effect prevented by atropine (Lomax & Jenden, 1966; Lomax & Kirkpatrick, 1969); (2) barbiturates depress the hypothalamic temperature regulating centre and the barbitone dependent rat is partially tolerant to this effect. Thus the mean body temperature of barbitone dependent animals (37·3$\pm$1·1 (20) °C) was only slightly below that of a control group (37·6$\pm$0·7 (24) °C); (3) the tolerance mechanisms involved at this site may be the same as those in other parts of the brain.

The fall in body temperature produced by either drug was similar in control and withdrawn animals, but a slower return to normal was observed in the withdrawn group. In contrast, a prolonged hyperthermia followed pilocarpine in barbitone-dependent rats; with physostigmine a biphasic response was observed, an initial rise in temperature followed by a fall, with a return to normal after 2 h.

Thus, in the rat, chronic barbitone administration and withdrawal can affect, both qualitatively and quantitatively, the change in body temperature caused by pilocarpine and physostigmine.

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The relationship between the anti-inflammatory and irritant properties of inflammatory exudate

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A possible mechanism for the systemic anti-inflammatory effects of counter-irritants is that at a site of inflammation a factor or factors are produced which then enter the blood stream and exert the action at a distant site (Laden, Blackwell & Fosdick, 1958). This hypothesis gained support from Robinson & Robson (1966), who showed that inflammatory exudate, obtained from polyester sponges implanted subcutaneously in rats, exerted anti-inflammatory effects, possibly due to the presence of the humoral mediators postulated by Laden, Blackwell & Fosdick (1958). However, results obtained by Atkinson, Boura & Hicks (1969) indicated that the anti-inflammatory activity of sponge exudate was itself mediated through a counter-irritant mechanism.

Contrary to the findings of Robinson & Robson (1966), sponge exudate was found to be markedly irritant. Furthermore, such material was shown to exert systemic but no local anti-inflammatory activity. The object of the present work was a confirmation of the possible relationship between the two activities of sponge exudate.

Anti-inflammatory activity was assessed using the carrageenin rat paw oedema test (Winter, Risley & Nuss, 1962); the substances under test being administered intraperitoneally (10 ml/kg dose vol.). Irritant activity was estimated by measuring the increase in paw volume following subplantar injection (0·1 ml/paw dose vol.) of the substances under test. The anti-inflammatory and irritant properties of sponge exudate were compared with those of a known irritant, carrageenin.

Examination of the dose-response curves revealed a good correlation between each type of activity for both carrageenin and sponge exudate over the range of concentrations investigated (0·0125–0·2%, carrageenin; 1·25–20%, sponge exudate). The correlation coefficients were 0·88 and 0·98 respectively. These results indicated that the two activities of sponge exudate were directly related.

Billingham (1968) showed that the anti-inflammatory potency of sponge exudate varied according to its time of collection. The irritant potency of exudate harvested 1, 2, 3, 4, 6 and 8 days following sponge implantation was evaluated and compared to the corresponding anti-inflammatory potency (10% concentration used for each determination). The two curves obtained did not significantly differ from parallelism, thus indicating a correlation.

It might be expected that there should be some correlation between the anti-inflammatory and irritant activities of counter-irritants with respect to time, and thus evaluation of these parameters was undertaken. It was found that maximum anti-inflammatory activity was almost always associated with maximum irritation in the case of both carrageenin (0·05%) and sponge exudate (10%). However, the anti-inflammatory activity tended to deviate as the irritation waned.

These results further support a counter-irritant mode of anti-inflammatory action for rat inflammatory exudate.

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The inhibition of allergic reactions by sympathomimetic amines and methylxanthines

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Sympathomimetic amines have been shown to be potent inhibitors of the antigen-induced histamine release from passively sensitized human lung (Assem & Schild, 1969). This inhibition was obtained with very low concentrations (5×10^{-12} to 5×10^{-9}M isoprenaline), and it was suggested that it might be due to the effect of the sympathomimetic compounds on β-adrenoceptors. The degree of inhibition of allergic reactions was influenced by several factors, for example, inhibition is greater with submaximal than with maximal antigen concentrations.