response to histamine, although this was not statistically significant (Fig. 1A). Two per cent DSCG produced a significant reduction ($P < 0.05$) in the induced bronchoconstriction which lasted for at least 2 h (Figure 1b). When DSCG (50 μg/kg) was given intravenously during a sustained reflex bronchoconstriction, complete reversal of the constriction was seen. The ability of the efferent autonomic nerves to produce a bronchoconstriction was checked throughout the experiment by direct electrical stimulation of the vagus nerves in the neck. DSCG, whether given by aerosol or intravenously did not inhibit the bronchoconstriction produced by direct electrical stimulation.

DSCG is not a bronchodilator or an antagonist of histamine or acetylcholine (Cox, Beach, Blair, Clarke, King, Lee, Loveday, Moss, Orr, Ritchie & Sheard, 1970) and it does not penetrate the central nervous system to any degree (personal communication from Dr B. Clarke, Dept. Metabolic Studies, Fisons Ltd.). We concluded, therefore, that DSCG reduced the bronchoconstriction to histamine aerosol, in our experiments, probably by desensitizing the lung irritant receptors which are thought to be responsible for the initiation of the reflex bronchoconstriction to histamine aerosol (Sellick & Widdicombe, 1971).

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The effects of corticosteroids on the responses of the anococcygeus and gastrocnemius muscles to nerve stimulation in the pithed rat

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Corticosteroids have been used to treat myasthenia gravis (Seybold & Drachman, 1974). The mechanism by which corticosteroids improve neuromuscular functioning in myasthenia is unknown but could be an immunosuppressive action on an auto-immune mechanism, which may cause this disease (Simpson, 1960). Since corticosteroids also have diverse effects on cardiac and smooth muscle (Thorp & Cobbin, 1967; Gibson & Pollock, 1975), this study considered the possibility that corticosteroids might have actions in striated muscle unconnected with an immune defect.

This study sought to determine whether corticosteroids could modify the responses of the rat gastrocnemius muscle to nerve stimulation. For comparison, the responses of a smooth muscle were also investigated. The smooth muscle chosen was the anococcygeus because its responses to agonists *in vitro* were enhanced by treatment of rats with corticosteroids (Gibson & Pollock, 1975). The responsiveness of these two muscles was investigated using the pithed rat preparation, in which a movable electrode was introduced into the spinal canal (Gillespie, MacLaren & Pollock, 1970). This technique permitted electrical stimulation of the spinal motor outflows to the gastrocnemius and anococcygeus in the same rat.

Male Wistar rats were treated with corticosterone (20 mg kg^{-1} day^{-1}, i.p. for 5 days) or prednisolone (20 mg kg^{-1} day^{-1}, i.p. for 4 days) or either saline or ethyl oleate as a control. The effects of reserpine (1 mg/kg, i.p. 20 h before pithing), which releases ACTH and therefore raises blood corticosteroid levels, were also investigated both in intact and in adrenalectomized rats. The rats were anaesthetized with trichloroethylene, respired artificially and pithed by the method of Gillespie, MacLaren & Pollock (1970). The spinal motor outflows were stimulated with supramaximal voltage using a Palmer stimulator. Responses of the muscles were recorded isometrically with Grass strain gauges and a Devices pen recorder. When the responses of the anococcygeus muscle were recorded, the rats received pancuronium bromide (2 mg/kg i.v.) to prevent interference by the contractions of the voluntary muscles.

Corticosterone and prednisolone increased the force of contraction of the single twitch and tetanic responses of the gastrocnemius muscle but the ratio of the tensions developed during these two responses was unchanged from control values. The corticosteroids impaired the ability of the gastrocnemius muscle to maintain a tetanus. Reserpine also increased the tension developed by the gastrocnemius muscle. This effect was absent in adrenalectomised rats. Corticosterone also increased the responses of the anococcygeus muscle to electrical stimulation. This

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occurred especially at low frequencies of stimulation. These results indicate that corticosteroids can enhance the responsiveness of normal striated muscle to electrical stimulation of the motor nerves. The mechanisms underlying this effect are unknown but may involve either presynaptic changes or perhaps, more likely, postsynaptic changes.

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The action of metiamide in anaphylaxis *in vivo* in the guinea-pig

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Bartosch, Feldberg & Nagel (1932) first produced evidence that histamine was released from guinea-pig lungs after anaphylactic shock. Although histamine has been shown to interact with at least two types of receptor (Ash & Schild, 1966), most investigations of the role of histamine in anaphylaxis have studied only H_1-receptors. However, recent work has shown that H_2-receptors may be involved in immune reactions in basophil leucocytes and in the heart (Capurro & Levi, 1973; Chand & Eyre, 1975). In this study the effect of the H_2-receptor antagonist, metiamide (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) in anaphylaxis in the guinea-pig was investigated.

Guinea-pigs were sensitized to egg albumen by its injection (100 mg i.p. and 100 mg s.c.) 3 weeks before challenge. Exposure to an aerosol of 1% egg albumen produced an anaphylactic reaction characterized by dyspnoea and cough. The onset times of anaphylactic symptoms in animals pretreated with metiamide (10 mg/kg and 100 mg/kg s.c.) were 144.3 ± 51.0 s and 78.8 ± 13.3 s respectively and were not significantly different from those of control animals ($P < 0.05$). Mepyramine (1 mg/kg i.p.) extended the time of onset of anaphylactic symptoms (551.9 ± 88.7 s) and the protection was not significantly altered by addition of 10 mg/kg metiamide (541.3 ± 94.0 s, $P < 0.05$).

The aerosol method of studying anaphylaxis is very subjective and only gross effects are seen. Therefore, guinea-pigs anaesthetized with 60 mg/kg pentobarbitone sodium were prepared for the recording of respiratory overflow volume by the method of Konzett & Rössler (1940) as modified by Lessin & Kramer (1969). Heart rate and blood pressure were also monitored by means of a rate meter and pressure transducer. Histamine (0.25 μg–8.0 μg) caused increases in air overflow volume of 8.4–108.4%. The increases were blocked by mepyramine (0.05–5 mg/kg) but unaffected by metiamide (10 μg kg^{-1} min^{-1} i.v.). An increase in heart rate of 8.0 ± 3.1 to 51.1 ± 7.2 bts/min was produced by histamine between doses 2 μg and 16 μg. Mepyramine (5.0 mg/kg) produced a shift to the right of the dose response curve (dose ratio = 2.72) and mepyramine (5 mg/kg) plus metiamide (10 μg kg^{-1} min^{-1}) caused a further shift to the right of the curve. (Dose ratio = 13.34.)

Injection of egg albumen (1 mg i.v.) into sensitized anaesthetized guinea-pig gave maximal increases in air overflow volume accompanied by an increase in heart rate and arterial blood pressure and death followed in 6 to 7 animals within 6 ± 0.83 minutes. Pretreatment with mepyramine (2.5 mg/kg), metiamide (50 μg kg^{-1} min^{-1}) or mepyramine and metiamide in combination increased the number of survivors ($^5/_5$, $^4/_5$, $^5/_5$, respectively). Close inspection of the results suggested that metiamide may have been protecting the guinea-pigs by an action upon the heart. This is consistent with the theory that stimulation of H_2-receptors in the heart plays an important role in anaphylactic death.

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