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The inhibition by dexamethasone and disodium cromoglycate of anaphylactic bronchoconstriction in the rat

M. K. CHURCH*, H. O. J. COLLIER† AND G. W. L. JAMES*

Department of Pharmacological Research, Division of Medical and Scientific Affairs, Parke, Davis and Company, Staines Road, Hounslow, Middlesex

Summary

1. A method for the measurement of anaphylactic bronchoconstriction in the rat is described.

2. Dexamethasone inhibited this response in a dose-related manner.

3. Disodium cromoglycate antagonized the response. A bell-shaped dose-response curve was obtained with peak activity at 1 mg/kg i.v.

4. Meclofenamate was not active when given alone or in combination with dexamethasone.

5. Methysergide significantly inhibited the response. Mepyramine, atropine, propranolol and adrenalectomy did not significantly modify the response.

6. The relationships of anaphylactic bronchoconstriction in the rat to anaphylactic bronchoconstriction in the guinea-pig and to human asthma are discussed.

Introduction

In 1950 Carryer, Koelsche, Prickman, Maytum, Lake & Williams reported that injections of cortisone relieved the symptoms of bronchial asthma in pollen-sensitive patients. Since then, glucocorticoids have often been successfully used in the treatment of chronic asthma and status asthmaticus. Their selection for anti-asthmatic use is, however, based on their anti-inflammatory and anti-rheumatic activity, as no satisfactory laboratory test has been found for assessing the ability of these drugs to lessen anaphylactic bronchoconstriction.

Since intense bronchoconstriction is a cardinal feature of anaphylaxis in the guinea-pig (Auer & Lewis, 1910; Biedl & Kraus, 1910), this animal has usually been chosen for the experimental simulation of asthma. In its reaction to drugs this model resembles human bronchial asthma in that bronchoconstriction is reduced by catecholamines and potentiated by agents blocking β-adrenoceptors for adrenaline (McNeill, 1964; Collier & James, 1967), but it differs from bronchial asthma in three respects. First, the antihistamines and the antiphlogistic acids are more effective against anaphylactic bronchoconstriction in the guinea-pig than against asthma in man. (Herxheimer, 1953; Stresemann, 1963a). Second, steroids beneficial in human asthma, have not been conclusively demonstrated to reduce

*Present address: Pharmacology Laboratory, Research and Development Department, Roussel Laboratories Limited, Kingfisher Drive, Covingham, Swindon, Wilts.
†Present address: Miles Laboratories Limited, Stoke Poges, Slough, Bucks.

anaphylactic bronchoconstriction in the guinea-pig (Harris & Harris, 1950; Humphrey, 1951; Gross & Haefeli, 1952; Herxheimer & Rosa, 1952; Feinberg, Malkiel & McIntyre, 1953; Goadby & Smith, 1964; Fregnan & Suchowsky, 1968; Hicks, 1969). Third, disodium cromoglycate is ineffective against anaphylactic bronchoconstriction in the guinea-pig (Cox, 1967).

In the rat, neither a quantitative assessment of anaphylactic bronchoconstriction nor its modification by drugs has been reported. In this species, cutaneous anaphylaxis, mortality or anaphylactic hypotension (Fregnan & Suchowsky, 1968) have been used as an indication of the level of anaphylaxis. We describe a method for the measurement of anaphylactic bronchoconstriction in the rat and of the inhibitory effects of dexamethasone, disodium cromoglycate and other drugs against this response.

Methods

Materials

Atropine sulphate, dexamethasone sodium phosphate, diethyl ether, disodium cromoglycate (Intal), meclofenamate sodium (Sodium *N*-(2, 6 dichloro-*m*-tolyl) anthranilate), mepyramine maleate, methysergide bimaleate and (±)-propranolol hydrochloride were used.

Nippostrongylus brasiliensis

The nematode parasite *Nippostrongylus brasiliensis* was maintained, the larvae collected for sensitization and the adult worms harvested for antigen as described by Ogilvie (1967). To prepare antigen, adult worms were crushed in a hand homogenizer and the supernatant obtained after centrifugation was diluted to contain 500 worm equivalents/ml. All animals used were sensitized unless designated non-sensitized.

Anaphylactic bronchoconstriction and its inhibition by drugs

Wistar rats weighing 200–350 g were sensitized by infection with approximately 5,000 larvae of *N. brasiliensis* injected subcutaneously. Five weeks later, animals were lightly anaesthetized with ether and the brain and spinal cord destroyed by pithing. The trachea was cannulated and the rat ventilated with a Starling miniature respiratory pump of stroke volume 5–7 ml at 90 strokes/minute. The sidearm of the tracheal cannula was connected to a non-return water valve set at a pressure of 7·5 cm water. For intravenous administration of substances the jugular vein was cannulated. Tracheal flow was measured with a pneumotachograph and recorded on a multichannel electronic recorder. To attain greater sensitivity of recording, only inspiratory or expiratory flow was recorded.

Animals were challenged intravenously with 500 worm equivalents/kg of *N. brasiliensis*. The resultant decrease in tracheal flow was used as an assessment of bronchoconstriction and was recorded for 10 min after challenge. At the end of the experiment, the maximum possible bronchoconstriction was obtained by clamping the trachea. This trace was measured at 30 s intervals from 0–10 min with a D-Mac pencil-follower (Christianson, Dinneen, James & Perkins, 1967) and responses expressed as a mean percentage of the maximum possible bronchoconstriction over this time period. To test the significance of drug effect the responses

were subjected to an analysis of variance. In any one experiment the common residual variance was used to test pairs of individual treatments (Davies, 1954; Collier & James, 1967).

Results

Response to antigen

In an experiment with 24 rats, 12 animals were sensitized with *N. brasiliensis* 5 weeks beforehand and 12 were not sensitized. In the sensitized group, intravenous challenge with 500 worm equivalents/kg antigen reduced the tracheal flow by a mean of 64%. A mean reduction of 3% was observed in the non-sensitized group (Fig. 1). This figure shows that the reduction in tracheal flow of the two groups became different almost immediately and reached a peak at 2·5 minutes. The difference between the mean responses to antigen was highly significant ($P<0{\cdot}001$).

Effects of drugs on anaphylactic bronchoconstriction

In an experiment in which 39 animals were used, dexamethasone 5 mg/kg was given intraperitoneally at 1, 4, 24 or 48 h before challenge to groups of 9–11 rats. The resulting time-response curve for the inhibition of anaphylactic bronchoconstriction is illustrated in Figure 2. The maximum inhibition (58%) was obtained when dexamethasone was given 24 h before challenge. This was significantly ($P<0{\cdot}025$) different from control.

In an experiment with 94 animals, one dose of dexamethasone was given intraperitoneally 24 h before challenge to each of 6 groups of 12–13 rats, using 4-fold increments within a dose range of 0·0156 to 16 mg/kg. One further group of 19 animals was not treated. Dexamethasone inhibited the anaphylactic bronchoconstriction. There was a highly significant ($P<0{\cdot}001$) regression of response on log dose. The regression line did not deviate significantly from linearity. Inhibitory effects over the dose range 0·0625 to 16 mg/kg were significant

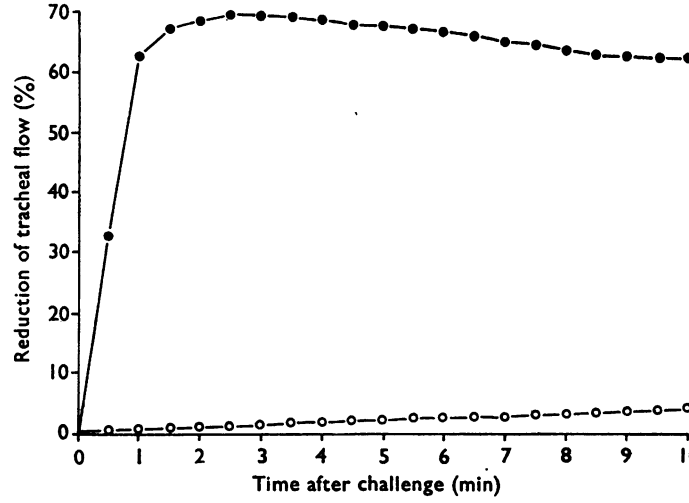

FIG. 1. The effect of sensitization on anaphylactic bronchoconstriction in the rat. Each curve is the mean tracheal flow obtained in groups of 12 rats. O——O, Non-sensitized controls; ●——●, rats sensitized with 5,000 *N. brasiliensis* larvae 5 weeks before challenge.

($P<0.05$) (Fig. 3). In a further experiment, dexamethasone administered by the oral route produced a similar dose-related inhibition of response, but was five times less active than when given intraperitoneally.

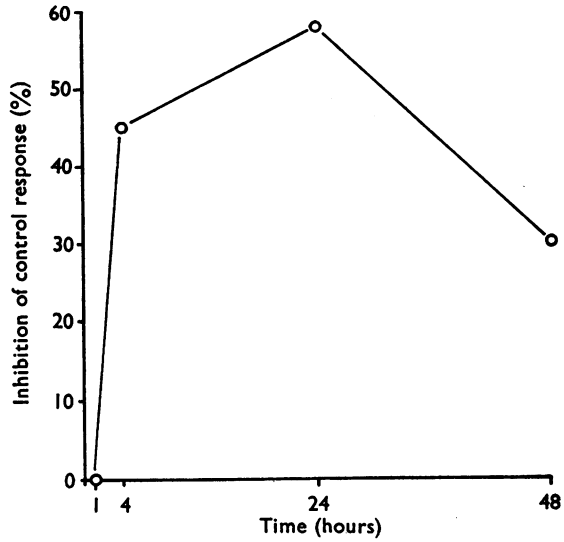

FIG. 2. The time-response relationship of dexamethasone against anaphylactic bronchoconstriction in the rat. Each point is the mean response obtained in 9–11 pithed rats sensitized 5 weeks previously with *N. brasiliensis*. The ordinate is the percentage inhibition of the bronchoconstriction obtained in control animals. The abscissa is the time in hours between injection of dexamethasone (5 mg/kg i.p.) and challenge with antigen (500 worm equivalents/kg i.v.).

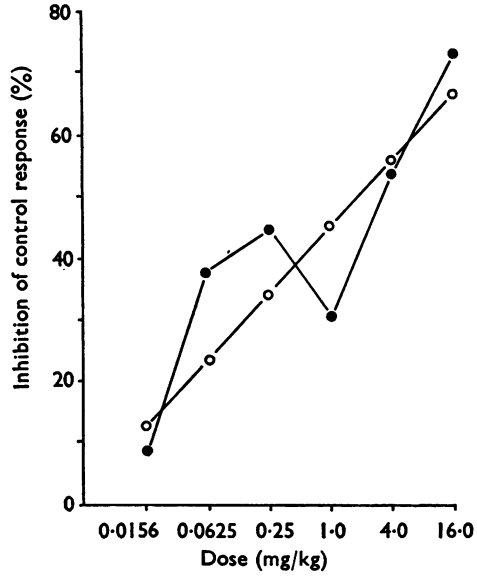

FIG. 3. The dose–response relationship of dexamethasone against anaphylactic bronchoconstriction in the rat. Rats, sensitized 5 weeks previously with *N. brasiliensis*, were given dexamethasone intraperitoneally 24 h before challenge. Control animals received 0·9% NaCl (w/v) (saline). Animals were pithed and challenged with 500 worm equivalents/kg of antigen. The abscissa is the dose of dexamethasone and the ordinate the percentage inhibition of the control bronchoconstriction response. ●——●, Experimental results; ○——○, 'best fit' line calculated from the regression coefficient.

In an experiment with 72 rats, disodium cromoglycate at 0·1, 0·33, 1·0, 3·3 or 10 mg/kg was given intravenously to groups of 12 animals 5 min before challenge. A further group of 12 animals was untreated. A bell-shaped dose-response curve was obtained (Fig. 4). The most active dose, 1 mg/kg, was the only dose that significantly ($P<0·05$) inhibited the response on challenge.

In an experiment with 47 animals, one dose of meclofenamate was given intravenously to each of three groups of 12 rats at 0·25, 1·0 or 4·0 mg/kg. One further group of 11 rats was not treated. Over this dose range, meclofenamate did not significantly inhibit anaphylactic bronchoconstriction.

In two experiments in which 184 animals were used, 8 groups of 10–12 rats were treated as follows: one group received no treatment, one group received meclofenamate 1 mg/kg i.v., 5 min before challenge. Three groups received dexamethasone at 0·0625, 0·5 or 4·0 mg/kg intraperitoneally 24 h before challenge, and the remaining three groups received similar doses of dexamethasone combined with 1 mg/kg meclofenamate given intravenously 5 min before challenge. In this experiment, meclofenamate alone did not significantly inhibit anaphylactic bronchoconstriction. Dexamethasone alone at doses of 0·5 and 4 mg/kg significantly ($P<0·05$) inhibited anaphylactic bronchoconstriction. Meclofenamate in the presence of dexamethasone did not significantly increase the anti-anaphylactic effect of dexamethasone (Fig. 5).

In an experiment with 24 rats, atropine 1 mg/kg was given intraperitoneally 30 min before challenge to one group of 12 animals, the remainder were untreated. Atropine did not significantly alter the anaphylactic response of lung to challenge.

In four experiments with 89 animals, methysergide 0·1 mg/kg was given intravenously 5 min before challenge to 43 animals, the remainder were untreated. Methysergide significantly ($P<0·001$) inhibited anaphylactic bronchoconstriction in every experiment.

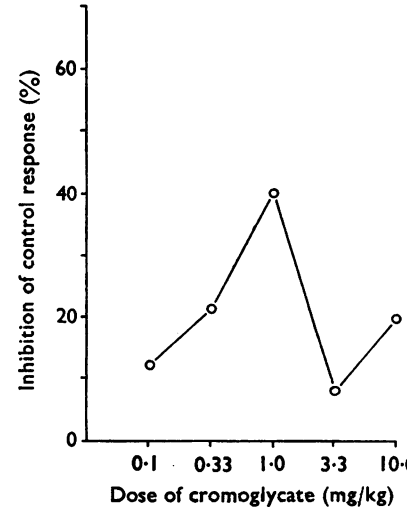

FIG. 4. The dose–response relationship of disodium cromoglycate against anaphylactic bronchoconstriction in the rat. Rats, sensitized 5 weeks previously with *N. brasiliensis*, were given disodium cromoglycate intravenously 5 min before challenge with 500 worm equivalents/kg of antigen. Control animals received saline. The abscissa is the dose of cromoglycate and the ordinate the percentage inhibition of the control bronchoconstriction response.

In an experiment in which 24 animals were used, propranolol, 10 mg/kg intraperitoneally, was given 30 min and 5 mg/kg intravenously was given 5 min before challenge to one group of 12 animals. The remaining animals were not treated. Propranolol did not significantly increase the intensity of the anaphylactic response of lung.

In an experiment with 24 rats, bilateral adrenalectomy was performed 30 min before challenge on one group of 12 animals. The remaining animals were intact. Adrenalectomy did not significantly increase anaphylactic bronchoconstriction.

Discussion

The human asthmatic when in contact with the allergen to which he is sensitive, exhibits symptoms of severe respiratory distress. Similarly, the sensitized guinea-pig responds, on challenge with a severe bronchoconstriction (Auer & Lewis, 1910; Biedl & Kraus, 1910). In the rat, anaphylaxis is characterized by hypotension and death following engorgement of the heart and small intestine, although slight respiratory distress has been reported (Sanyal & West, 1958; Ogilvie, 1967). The experiments described here show that a severe bronchoconstriction can be elicited in the sensitized rat in response to challenge with antigen.

The antibodies responsible for human asthma are thought to be reaginic, recently characterized as IgE, non-precipitating antibodies (Johansson, 1967; Ishizaka & Ishizaka, 1968). Anaphylactic bronchoconstriction in the guinea-pig is mediated by IgG precipitating antibodies (Benacerraf, 1968). The antibodies responsible for systemic anaphylaxis in the rat, as in man, are reaginic and of the IgE family (Ogilvie, 1967; Stechschulte, Orange & Austen, 1970; Jones & Edwards, 1971). Anaphylactic bronchoconstriction in the rat, therefore, provides a model which is probably immunologically similar to human bronchial asthma.

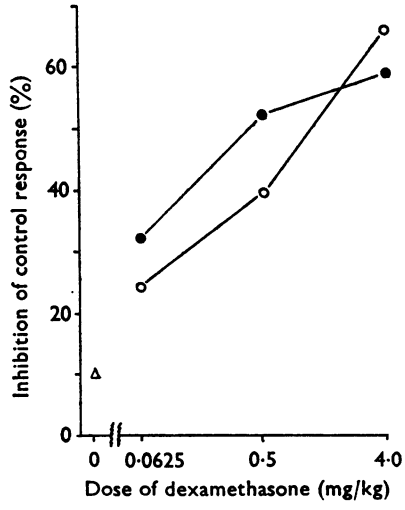

FIG. 5. The effect of meclofenamate on the dose–response relationship of dexamethasone against anaphylactic bronchoconstriction in the rat. Each point is the mean of response obtained in groups of 11–12 pithed rats sensitized 5 weeks previously with *N. brasiliensis*. Dexamethasone was given intraperitoneally 24 h and meclofenamate, 1 mg/kg, was given intravenously 5 min before challenge with 500 worm equivalents/kg of antigen. ○——○, Dexamethasone alone; ●——●, dexamethasone and meclofenamate; △, meclofenamate alone.

The humoral factors involved in the mediation of human asthma and guinea-pig and rat anaphylactic bronchoconstriction appear to differ between the various species. The failure of atropine to reduce anaphylactic bronchoconstriction in our preparation of the rat indicates that neither acetylcholine nor vagal responses play a significant role in anaphylactic bronchospasm. These results have been paralleled in the deeply anaesthetized guinea-pig (Collier & James, 1967). In man, although atropine is effective in bronchitis, it is less effective in the treatment of bronchial asthma.

In the rat, histamine is released during anaphylactic shock (Mota, 1963). However, mepyramine did not significantly lessen anaphylactic bronchoconstriction in this species. This accords with the findings that histamine, injected intravenously, does not cause bronchoconstriction in the rat *in vivo* (Bhoola, Collier, Schachter & Shorley, 1962) nor does it constrict rat isolated bronchial muscle *in vitro* (Brocklehurst, 1958a), although Foggie (1937) reported weak constriction of isolated, perfused rat lung with large doses of histamine. This is in contrast to the guinea-pig where histamine is released during anaphylaxis and where anaphylactic bronchoconstriction may be partially suppressed by antihistamine (Staub & Bovet, 1937; Armitage, Herxheimer & Rosa, 1952; Brocklehurst, 1958a; Collier & James, 1967).

In man, histamine causes bronchoconstriction when given by injection (Samter, 1933; Curry, 1946), or by inhalation (Herxheimer, 1949). It is also released from chopped human lung *in vitro* (Schild, Hawkins, Mongar & Herxheimer, 1951; Parish, 1967; Sheard, Killingback & Blair, 1967). Antihistamines, although of use in nocturnal asthma in children (Herxheimer, 1949), are relatively ineffective when given alone in the treatment of chronic asthma.

That methysergide reduced anaphylactic bronchoconstriction in the rat by nearly 70% suggests that, in this species, 5-hydroxytryptamine is the major mediator of this form of bronchoconstriction. In the guinea-pig and man, however, 5-hydroxytryptamine does not significantly participate in this reaction (Herxheimer, 1955; Brocklehurst, 1958b; Collier & James, 1967).

Meclofenamate, like acetylsalicylate and other antipyretic drugs, antagonizes bronchoconstriction in the guinea-pig induced by bradykinin, SRS-A and ATP, but not that induced by acetylcholine, histamine or 5-hydroxytryptamine (Collier, James & Schneider, 1966). Non-steroidal anti-inflammatory drugs inhibit the release of prostaglandin $F_{2\alpha}$ from guinea-pig lung (Piper & Vane, 1971; Vane, 1971) but not its bronchoconstrictor activity on injection (Berry & Collier, 1964; James, 1969). Meclofenamate also significantly inhibits anaphylactic bronchoconstriction in the guinea-pig, thus implicating at least some of the above mediators in this reaction. Non-steroidal anti-inflammatory drugs also block the contraction of human isolated bronchial muscle induced by prostaglandin $F_{2\alpha}$ (Collier & Sweatman, 1968) and the production of prostaglandins in human tissues *in vitro* (Smith & Willis, 1971) and *in vivo* (Collier & Flower, 1971). Although bradykinin and SRS-A are bronchoconstrictors in man (Herxheimer & Stresemann, 1961a, 1963; Stresemann, 1963b) their antagonism by antipyretic drugs has been unsuccessful in most patients (Herxheimer & Stresemann, 1961b; Stresemann, 1963a). Similarly, the efficacy of these drugs against bronchial asthma, though real in some cases, is generally disappointing (Cook, 1947; Herxheimer & Stresemann, 1961b; Pearson, 1963; Clarke, 1969). What action they have may be due to blockade of synthesis or

action of prostaglandin $F_{2\alpha}$ (Collier, 1971). The failure of fenamate to modify anaphylactic bronchoconstriction in the rat accords with the clinical picture (McNichol, 1966; H. Herxheimer, personal communication) and suggests that bradykinin, SRS-A and prostaglandin $F_{2\alpha}$ do not play a major role in the mediation of this reaction.

The finding that the β-adrenoceptor blocking drug, propranolol, and adrenalectomy did not significantly potentiate anaphylactic bronchoconstriction in the rat was at variance with results obtained in the guinea-pig (Collier & James, 1967) and in man (McNeill, 1964). This suggests that the role of the sympathetic nervous system is not as great in our model of rat anaphylaxis as it is in guinea-pig anaphylaxis.

The inhibition of allergic bronchoconstriction in the rat by steroids accords with the clinical picture in man but not with the results obtained in the guinea-pig (Hicks, 1969). The linear dose-response relationship indicates an anti-anaphylactic effect of dexamethasone. The doses used correspond with doses used in man. The lowest dose that significantly protected the rat (0·0625 mg/kg) is equivalent to a single dose of 4 mg in a human subject. The time of peak effectiveness of dexamethasone, 24 h, also accords with that of steroids in acute asthma. In the guinea-pig, dexamethasone (5 mg/kg i.p.) given daily for 4 days before challenge failed to inhibit anaphylactic bronchoconstriction (Church & James, unpublished results). The failure of guinea-pigs to respond to steroids indicate that either: (1) the immunological pathway leading to the release of humoral mediators differs from that of man and the rat; or (2) the steroid sensitive links of the chain in man and the rat are not steroid sensitive in the guinea-pig.

Disodium cromoglycate caused a bell-shaped dose-related inhibition of anaphylactic bronchoconstriction in the rat. The failure to produce linear dose-related activity and the immediate efficacy of this compound indicate that its mode of action is not steroid-like.

In the guinea-pig, anaphylactic bronchoconstriction is antagonized by fenamate (Collier & James, 1967) but not by steroid. In the rat the picture is reversed, dexamethasone but not fenamate being active. In man the possibility that these two drugs potentiate each other or have additive effects has been mooted (Jick, Pinals, Ullian, Slone & Muench, 1965). Results cited here show that in the rat, meclofenamate does not significantly alter the inhibition of anaphylactic bronchoconstriction by dexamethasone. Similarly, in the guinea-pig, dexamethasone did not modify the inhibitory effect of meclofenamate (Church & James, unpublished). In man, where both dexamethasone and fenamate may reduce the asthmatic response (Pearson, Baylis & Smellie, 1961; Jackson, Raymer & Etter, 1968) some potentiation may be possible.

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REFERENCES

ARMITAGE, P., HERXHEIMER, H. & ROSA, L. (1952). The protective actions of antihistamines in the anaphylactic microshock of the guinea-pig. *Br. J. Pharmac. Chemother.*, **7**, 625–636.

AUER, J. & LEWIS, P. A. (1910). The physiology of the intermediate reaction of anaphylaxis in the guinea-pig. *J. exp. Med.*, **12**, 151–175.

BENACERRAF, B. (1968). Properties of immunoglobulins which mediate the release of vasoactive amines in experimental animals. In: *Immunopharmacology*, Volume 11 of the Third International Pharmacological Meeting, 1966, ed. Schild, H. O., pp. 3–13. London: Pergamon.

BERRY, P. A. & COLLIER, H. O. J. (1964). Bronchoconstrictor action and antagonism of a slow reacting substance from anaphylaxis of isolated guinea-pig lung. *Br. J. Pharmac. Chemother.*, **23**, 201–216.

BHOOLA, K. D., COLLIER, H. O. J., SCHACHTER, M. & SHORLEY, P. G. (1962). Action of some peptides on bronchial smooth muscle. *Br. J. Pharmac. Chemother.*, **19**, 190–197.

BIEDL, A. & KRAUS, R. (1910). Experimentelle studien uber anaphylaxie. *Wien klin. Wschr.*, **23**, 385–388.

BROCKLEHURST, W. E. (1958a). Histamine and other mediators in hypersensitivity reactions. In: *Proc. Third Int. Congress of Allergology, Paris*, ed. Halpern, B. N. & Haltzer, A., pp. 361–376.

BROCKLEHURST, W. E. (1958b). The action of 5-hydroxytryptamine on smooth muscle. In: *5-Hydroxytryptamine*, ed. Lewis, G. P., pp. 172–176. London: Pergamon.

CARRYER, H. M., KOELSCHE, G. A., PRICKMAN, L. E., MAYTUM, C. K., LAKE, C. F. & WILLIAMS, H. L. (1950). Effect of cortisone in bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. *J. Allergy*, **21**, 282–287.

CHRISTIANSON, A. H., DINNEEN, L. C., JAMES, G. W. L. & PERKINS, A. C. (1967). A method for measurement and statistical analysis of large numbers of experimental tracings. *J. Pharm. Pharmac.*, **19**, 837–840.

CLARKE, C. A. (1969). Asthma from aspirin. *Br. med. J.*, **1**, 256.

COLLIER, H. O. J. (1971). Prostaglandins and aspirin. *Nature, Lond.*, **232**, 17–19.

COLLIER, H. O. J. & JAMES, G. W. L. (1967). Humoral factors affecting pulmonary inflation during acute anaphylaxis in the guinea-pig *in vivo*. *Br. J. Pharmac. Chemother.*, **30**, 283–301.

COLLIER, H. O. J., JAMES, G. W. L. & SCHNEIDER, C. (1966). Antagonism by aspirin of bronchoconstriction and nociception induced by adenosine -5′ triphosphate. *Nature, Lond.*, **212**, 411–412.

COLLIER, H. O. J. & SWEATMAN, W. J. F. (1968). Antagonism by fenamates of prostaglandin $F_{2\alpha}$ and slow reacting substance on human bronchial muscle. *Nature, Lond.*, **219**, 864–865.

COLLIER, J. G. & FLOWER, R. J. (1971). Effect of aspirin on human seminal prostaglandins. *Lancet*, **2**, 852–853.

COOK, R. A. (1947). *Allergy in Theory and Practice*, p. 161. Philadelphia: Saunders.

COX, J. S. G. (1967). Disodium cromoglycate (FPL 670) (Intal): a specific inhibitor of reaginic antigen-antibody mechanisms. *Nature, Lond.*, **216**, 1328–1329.

CURRY, J. J. (1946). The action of histamine on the respiratory tract in normal and asthmatic subjects. *J. clin. Invest.*, **25**, 785–791.

DAVIES, O. L. (1954). *Statistical Methods in Research and Production*, 2nd edit., pp. 71–117. London: Oliver and Boyd.

FEINBERG, S. M., MALKIEL, S. & MCINTYRE, F. C. (1953). The effect of stress factors on asthma induced in guinea-pigs by aerosolized antigens. *J. Allergy*, **24**, 302–308.

FOGGIE, P. (1937). The action of adrenaline, acetylcholine and histamine on the lungs of the rat. *Q.J. exp. Physiol.*, **26**, 225–233.

FREGNAN, G. B. & SUCHOWSKY, G. K. (1968). New corticoid 3-(2′chloroethoxy)-6-formyl-9α fluoro $\Delta^{3,5}$ pregnadien derivatives in experimental allergy. *Eur. J. Pharmac.*, **3**, 251–256.

GOADBY, P. & SMITH, W. G. (1964). Observations on the anaphylactic activity of hydrocortisone and related steroids. *J. Pharm. Pharmac.*, **16**, 108–114.

GROSS, VON F. & HAEFELI, H. (1952). Die Wirkung von Desoxycorticosteron, Cortison und Antihistaminkörpern auf den anaphylaktischen Shock des nebennierenlosen Meerschweinchens. *Int. Arch. Allergy*, **3**, 44–53.

HARRIS, S. & HARRIS, T. N. (1950). Effect of cortisone on some reactions of hypersensitivity in laboratory animals. *Proc. Soc. exp. Biol. Med., 1950*, **74**, 186–189.

HERXHEIMER, H. (1949). Antihistamines in bronchial asthma. *Br. J. Med.*, **2**, 901–905.

HERXHEIMER, H. (1953). The protective action of antihistaminic and sympathomimetic aerosols in anaphylactic microshock of the guinea-pig. *Br. J. Pharmac. Chemother.*, **8**, 461–465.

HERXHEIMER, H. (1955). The 5-hydroxytryptamine shock in the guinea-pig. *J. Physiol., Lond.*, **128**, 435–445.

HERXHEIMER, H. & ROSA, L. (1952). The action of cortisone in the anaphylactic shock of the guinea-pig. *J. Physiol., Lond.*, **118**, 7*P*.

HERXHEIMER, H. & STRESEMANN, E. (1961a). The effect of bradykinin aerosol in guinea-pig and man. *J. Physiol., Lond.*, **158**, 38*P*.

HERXHEIMER, H. & STRESEMAN, E. (1961b). Anti-asthmatic effect of phenazone and amidopyrine. *Nature, Lond.*, **192**, 1089–1090.

HERXHEIMER, H. & STRESEMANN, E. (1963). The effect of slow reacting substance (SRS-A) in guinea-pigs and in asthmatic patients. *J. Physiol., Lond.*, **165**, 78–79*P*.

HICKS, R. (1969). Corticosteroid modification of guinea-pig anaphylaxis. *J. Pharm. Pharmac.*, **21**, 202–203.

HUMPHREY, J. H. (1951). The effect of cortisone upon some experimental hypersensitivity reactions. *Brit. J. exp. Path.*, **32**, 274–283.

ISHIZAKA, K. & ISHIZAKA, T. (1968). Human reaginic antibodies and immunoglobulin E. *J. Allergy*, **42**, 330–363.

JACKSON, R. H., RAYMER, W. J. & ETTER, R. L. (1968). An evaluation of Ponstel® (mefenamic acid) in chronic bronchial asthma and pulmonary emphysema. *J. Kansas. med. Soc.*, **69**, 474–478.

JAMES, G. W. L. (1969). The use of the *in vivo* trachea preparation of the guinea-pig to assess drug action on lung. *J. Pharm. Pharmac.*, **21**, 379–386.

JICK, H., PINALS, R. S., ULLIAN, R., SLONE, D. & MUENCH, H. (1965). Dexamethasone and dexamethasone-aspirin in the treatment of chronic rheumatoid arthritis. *Lancet*, **2**, 1203–1205.

JOHANSSON, S. G. O. (1967). Raised levels of a new immunoglobulin class (IgND) in asthma. *Lancet*, **2**, 951–953.

JONES, V. E. & EDWARDS, A. J. (1971). Preparation of an antiserum specific for rat reagin. *Immunology*, **21**, 383–385.

MCNEILL, R. S. (1964). Effect of a β-adrenergic blocking agent, propranolol, on asthmatics. *Lancet*, **2**, 1101–1102.

MCNICHOL, M. W. (1966). In: *Fenamates in Medicine, A Symposium.* Suppl. *Annals of Physical Medicine*, ed. Hume Kendall, P., pp. 70–71. London: Baillière, Tindall & Cassell.

MOTA, I. (1963). Passive cutaneous anaphylaxis induced with mast cell sensitizing antibody. The role of histamine and 5-hydroxytryptamine. *Life Sciences*, **12**, 917–927.

OGILVIE, B. M. (1967). Reagin like antibodies in rats infected with the nematode parasite *Nippostronglylus brasiliensis*. *Immunology*, **12**, 113–131.

PARISH, W. E. (1967). Release of histamine and slow reacting substance with mast cell changes after challenge of human lung sensitised passively with reagin *in vitro*. *Nature, Lond.*, **215**, 738–739.

PEARSON, R. S. B. (1963). In: *Salicylates; An International Symposium*, ed. Dixon, A. St. J., Martin, B. K., Smith, M. J. H. & Wood, R. H. N., p. 170. London: Churchill.

PEARSON, R. S. B., BAYLIS, J. H. & SMELLIE, H. C. (1961). Treatment of chronic asthma with prednisolone and the newer steroids. *Br. med. J.*, **1**, 315–319.

PIPER, P. J. & VANE, J. R. (1971). The release of prostaglandins from lung and other tissue. In: *Prostaglandins*, ed. Ramwell, P. W. & Shae, J. E., *Ann. N.Y. Acad. Sci.*, **180**, 363–385.

SAMTER, M. (1933). Asthma bronchiale und Histaminempfindlichkeit. *Z. ges. exp. Med.*, **89**, 24–35.

SANYAL, R. K. & WEST, G. B. (1958). Anaphylactic shock in the albino rat. *J. Physiol., Lond.*, **142**, 571–584.

SCHILD, H. O., HAWKINS, D. F., MONGAR, J. L. & HERXHEIMER, H. (1951). Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen. *Lancet*, **2**, 376–381.

SHEARD, P., KILLINGBACK, P. G. & BLAIR, A. M. J. N. (1967). Antigen induced release of histamine and SRS-A from human lung passively sensitized with reaginic serum. *Nature, Lond.*, **216**, 283–284.

SMITH, J. B. & WILLIS, A. L. (1971). Aspirin selectively inhibits prostaglandin production in human platelets. *Nature, New Biology*, **231**, 235–237.

STAUB, A-M. & BOVET, D. (1937). Action de la thymoxyéthyldiéthylamine (929F) et des éthers phénoliques sur le choc anaphylactique du cobaye. *C. r. Séanc. Soc. Biol.*, **125**, 818–823.

STECHSCHULTE, D. J., ORANGE, R. P. & AUSTEN, K. F. (1970). Immunochemical and biologic properties of rat IgE. *J. Immunol.*, **105**, 1082–1086.

STRESEMANN, E. (1963a). Die Wirkung von antipyretischen und analgetischen Substanzen auf das menschliche Bronchialasthma und das experimentelle Meerschweinchenasthma. *Acta Allergologica*, **18**, 211–234.

STRESEMANN, E. (1963b). The effect of bradykinin aerosol on the lung function in humans and guinea pigs and the influence exerted by various substances on the experimental bradykinin-induced bronchospasm. *Acta Allergologica*, **18**, 235–255.

VANE, J. R. (1971). Inhibition of prostaglandin synthesis as a mechanism of action of aspirin-like drugs. *Nature, New Biology*, **231**, 232–235.

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