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THE ROLE OF THE VAGUS NERVES IN THE RESPIRATORY AND CIRCULATORY REACTIONS TO ANAPHYLAXIS IN RABBITS

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SUMMARY

1. Rabbits, previously sensitized to egg albumen, were anaesthetized and then rendered anaphylactic by a further injection of egg albumen; total lung conductance of flow, lung compliance, breathing rate, tidal volume, end-tidal CO_2 %, systemic arterial and right atrial blood pressures and heart rate were measured. Before induction of anaphylaxis, some rabbits were vagotomized, some had their vagi cooled to block differential conduction, and others were paralysed and artificially ventilated to minimize secondary changes in afferent activity from the lungs and in blood gas tensions.

2. Lung conductance was reduced by anaphylaxis in spontaneously breathing and in artificially ventilated rabbits, and the effect was lessened by vagal cooling and greatly reduced by vagotomy; the hyperventilation of anaphylaxis took the form of an increase in tidal volume rather than in respiratory frequency during vagal cooling, and all changes in ventilation were abolished by vagotomy. These effects are therefore dependent on the integrity of vagal nervous pathways.

3. Lung compliance was reduced by anaphylaxis to a similar degree in all groups of rabbits; all groups showed similar falls in end-tidal CO_2 %. These effects are therefore not dependent on the integrity of vagal conduction.

4. Anaphylaxis reduced systemic arterial blood pressure, the response being smaller when the vagi were cooled or cut.

5. It is concluded that anaphylaxis has direct actions on the pulmonary vascular bed, the distal airways or the alveoli. However, the changes in breathing, blood pressure and large airway calibre are mainly dependent on vagal reflex activity. By analogy with responses to injections of histamine

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and phenyl diguanide (Karczewski & Widdicombe, 1969*b*) it is concluded that anaphylaxis stimulates lung deflation and irritant receptors which mediate much of the reflex responses.

INTRODUCTION

In anaphylactic shock in experimental animals there are conspicuous changes in breathing, the mechanical properties of the lungs, and the circulation (see reviews by Doerr, 1950; Mongar & Schild, 1962). These may be due to a combination of the anaphylactic process in the tissues, the action of active chemicals released into the blood (Doerr, 1951; Rocha e Silva, 1955), and secondary nervously induced reactions (Filipp, 1965). One such last reaction is indicated by the increased efferent fibre discharge seen in the vagus nerves of guinea-pigs during anaphylactic shock (Karczewski, 1962). Furthermore, it has been shown that vagal reflexes play an important part in the respiratory responses to injections of histamine and phenyl diguanide, which stimulate afferent end-organs probably in the lungs and which cause effects that resemble in some respects those of the anaphylactic reaction in rabbits (Karczewski & Widdicombe, 1969*b*). We have therefore studied the effects of vagotomy and of differential block of vagal conduction by cooling on the respiratory and cardiovascular changes in anaphylaxis in rabbits.

METHODS

Twenty-one adult rabbits, of either sex and weighing 1·9–2·8 kg, were sensitized to crystalline egg albumen, by administration of three intraperitoneal doses of 0·2 ml. of a solution, 2 g/100 ml., at 2-day intervals.

After an interval of 3–6 weeks the rabbits were anaesthetized with 30–45 mg/kg of pentobarbitone sodium (Nembutal, Abbott; intravenously) and tracheal, right atrial and femoral arterial catheters were inserted. The apparatus used and the methods of recording and analysing results were as described in a preceding paper (Karczewski & Widdicombe, 1969*a*).

The rabbits were divided into four groups. Seven were given intravenously the challenging dose of antigen (0·2 ml. of a 2% solution of egg albumen) when spontaneously breathing with vagi intact. Four were first paralysed with intravenous gallamine ethiodide (10 mg), artificially ventilated with a minute volume selected to maintain the end-tidal CO_2% as close to the pre-paralysis value as possible, and then given the challenging dose of antigen. Five spontaneously breathing rabbits were injected with antigen while both cervical vagus nerves were cooled to 8–10° C, to block differentially vagal afferent pathways (see Karczewski & Widdicombe, 1969*a*, *b*, and Discussion). Finally, five spontaneously breathing rabbits first had both cervical vagi cut before receiving antigen.

The anaphylactic reactions described below often developed slowly over 2–10 min from the injection time, and the values given are the maximal changes recorded during this time of development. In about half the rabbits control injections of 0·2 ml. saline (0·9 g/100 ml.) were given, before or after the antigen; these never produced significant changes in the variables studied.

Statistical analysis was carried out, first to see if mean size of responses after anaphylaxis was significantly different from control values, that is to indicate the reproducibility of results in the groups of rabbits; and secondly to see if paralysis or interruption of vagal conduction caused a significant change in the size of the responses.

RESULTS

Tables 1, 2 and 3 summarize the results, and Figs. 1 and 2 illustrate representative experiments.

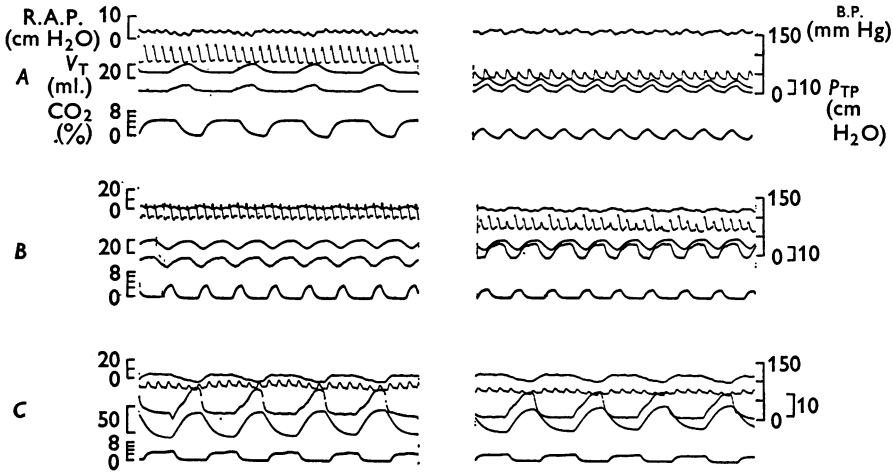

Fig. 1. Effect of vagal cooling and vagotomy on respiratory and cardiovascular changes in anaphylaxis in three spontaneously breathing rabbits. Traces from above down: right atrial pressure (R.A.P.), systemic arterial blood pressure (B.P.), tidal volume (V_T), transpulmonary pressure (P_{TP}), and tidal CO_2%. (In *C* the positions of the tidal volume and transpulmonary pressure traces are reversed; in *B* there was a shift of the level of the transpulmonary pressure trace on the oscilloscope between the two records; the levels of the tidal volume traces in the pairs of records do not imply shifts in functional residual capacity but are due to 'integrator drift'—the records only indicate tidal volume and not volume level of breathing.) Records on the left, before anaphylaxis; on the right, 2–6 min after induction of anaphylaxis. *A*: vagal conduction unimpaired. *B*: vagi cooled to 8–10° C during both records. *C*: vagi cut before both records.

Lung mechanical changes (Table 1). Total lung conductance was nearly halved by anaphylaxis in spontaneously breathing rabbits. The decrease was even greater in paralysed rabbits, which suggests that the response in spontaneously breathing animals may have been lessened by the secondary dilator effects on airway calibre associated with increased minute volume. The decrease in lung conductance on anaphylaxis when the vagi were cooled to 8–10° C was about two thirds of that of spontaneously

breathing rabbits with vagi intact, and the effect was even smaller (one quarter) in vagotomized animals.

Lung compliance was reduced by anaphylaxis, in spontaneously breathing (-28%) and in paralysed (-36%) rabbits. The change in compliance was similar when anaphylaxis was induced during vagal cooling, and the response was only a little smaller in vagotomized rabbits.

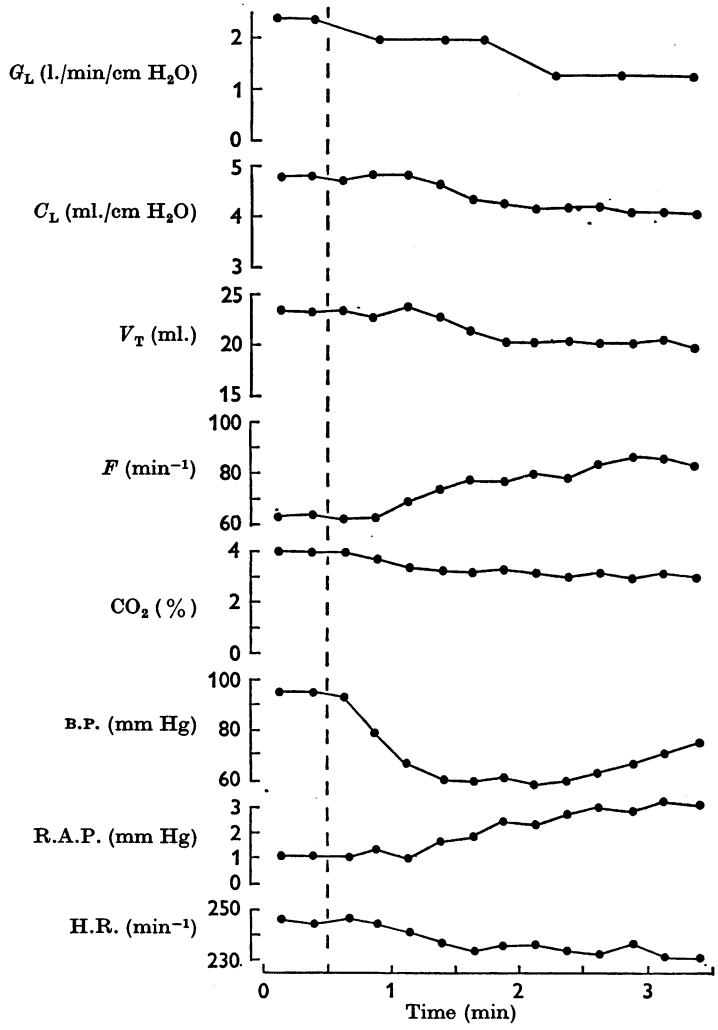

Fig. 2. The time course of changes in (from above down) total lung conductance (G_L), lung compliance (C_L), tidal volume (V_T), breathing frequency (F), end-tidal CO_2%, systemic arterial blood pressure, right atrial pressure and heart rate, in a spontaneously breathing rabbit with vagal conduction unimpaired. Anaphylaxis was induced at the time of the interrupted vertical line.

TABLE 1. Effect of anaphylaxis on lung mechanical properties. Changes are at maximum effect, 2–10 min after challenge with albumen. All rabbits for vagal cooling and vagotomy were spontaneously breathing. Values are means and S.E. with numbers of rabbits in parentheses. Values are given in absolute (abs) and as proportionate changes (%). * $P < 0.05$, ** $P < 0.01$, for the change in the variable due to anaphylaxis for each group of rabbits. † $P < 0.05$, ‡ $P < 0.01$, for the significance of the mean change of each variable due to anaphylaxis after paralysis, vagal cooling or vagotomy respectively compared with spontaneously breathing controls with intact vagi

	Lung conductance (l./min/cm H_2O)			Lung compliance (ml./cm H_2O)		
		Change after albumen			Change after albumen	
Condition	Control (abs)	(abs)	(%)	Control (abs)	(abs)	(%)
Vagi normal, all rabbits	2·17 ± 0·40	−0·87 ± 0·22**	−49 ± 8·4 (11)**	4·8 ± 0·81	−1·5 ± 0·37**	−31 ± 5·5 (11)**
Vagi normal not paralysed	2·83 ± 0·46	−1·02 ± 0·33*	−41 ± 11·0 (7)**	5·7 ± 1·09	−1·7 ± 0·74	−28 ± 8·0 (7)*
Vagi normal paralysed	1·02 ± 0·30	−0·60 ± 0·11*	−63 ± 9·5 (4)**	3·2 ± 0·69	−1·1 ± 0·29*	−36 ± 7·0 (4)*
Vagi cooled (8° C) not paralysed	3·80 ± 0·84	−1·08 ± 0·36*	−27 ± 7·7 (5)*	5·1 ± 0·90	−1·8 ± 0·52*	−31 ± 6·6 (5)**
Vagi cut, not paralysed	3·12 ± 0·84	−0·30 ± 0·12	−10 ± 2·5 (5)*†	6·1 ± 1·09	−1·4 ± 0·40*	−23 ± 5·4 (5)*

Respiratory changes (Table 2). In spontaneously breathing rabbits with vagal conduction intact, anaphylaxis was associated with a large increase in breathing frequency and a small (not significant) decrease in tidal volume, minute volume being considerably increased. When the vagi were cooled to 8–10° C, anaphylaxis did not increase breathing frequency but there was a large (42 %) increase in tidal volume, in spite of the fact that vagal cooling itself caused deeper and slower breathing (Karczewski & Widdicombe, 1969*a*). Anaphylaxis after vagotomy caused no significant change in breathing frequency, and a small decrease in tidal volume; the latter may be associated with the simultaneous decrease in lung compliance. With vagal conduction unimpaired anaphylaxis caused no change in functional residual capacity or a transient small increase (up to one third of tidal volume).

End-tidal CO_2 % was decreased by anaphylaxis. The effect was smaller but still statistically significant for anaphylaxis during paralysis with constant ventilation and during vagal cooling and after vagotomy. It could not, therefore, be correlated with changes in minute volume, tidal volume or frequency of breathing.

Cardiovascular changes (Table 3). Blood pressure was nearly halved by anaphylaxis, both in spontaneously breathing and in paralysed rabbits. This hypotension was much smaller in rabbits whose vagi were cooled or cut.

Heart rate was reduced by anaphylaxis, both in spontaneously breathing and paralysed rabbits, but the response was small and not statistically significant. During vagal cooling and after vagotomy, anaphylaxis caused small and statistically insignificant changes in heart rate.

Right atrial pressure was increased by anaphylaxis in spontaneously breathing rabbits, and similar increases were seen on anaphylaxis during vagal cooling and after vagotomy. The numbers of rabbits were small and the results not statistically significant. Right atrial pressure changes were not determined for paralysed rabbits.

DISCUSSION

In the intact animal rendered anaphylactic a change in any of the variables studied could be due to one or more of (1) a direct anaphylactic reaction in the appropriate tissue, (2) a secondary reaction due to chemical changes induced elsewhere by the anaphylaxis, (3) a secondary effect of respiratory or haemodynamic alterations or (4) a secondary reflex response initiated by one of the preceding. We have tried to analyse the responses observed by using paralysed rabbits, in which secondary changes in pulmonary ventilation are minimized; rabbits with vagi cooled to 8–10° C, in

TABLE 2. Respiratory effects of anaphylaxis. Changes are at maximum effect, 2–10 min after challenge with albumen. All rabbits for vagal cooling and vagotomy were spontaneously breathing. Values are means and S.E., with numbers of rabbits in parentheses. Values are given in absolute units (abs) and as proportionate changes. * $P < 0.05$, ** $P < 0.01$, for the change in the variable due to anaphylaxis for each group of rabbits. † $P < 0.05$, ‡ $P < 0.01$, for the significance of the mean change of each variable due to anaphylaxis after paralysis, vagal cooling or vagotomy respectively compared with spontaneously breathing controls with intact vagi

	Frequency of breathing (per min)		Tidal volume (ml.)			CO_2 (%)	
				Change after albumen			
Condition	Control (abs)	Change after albumen (abs)	Control (abs)	(abs)	%	Control (abs)	Change after albumen (abs)
Vagi normal, all rabbits	—	—	—	—	—	4·2±0·19	−1·3±0·19 (11)**
Vagi normal, not paralysed	50±5·1	+32±10·2 (7)*	21±2·3	−3±1·8	−16±9·5 (7)	4·3±0·24	−1·5±0·20 (7)**
Vagi normal, paralysed	—	—	—	—	—	4·1±0·37	−1·1±0·20 (4)*
Vagi cooled (to 8° C) not paralysed	68±6·4	−8±5·1 (5)‡	19±2·1	+8±1·2**‡	+42±8·4 (5)**‡	3·2±0·26	−0·8±0·27 (5)*†
Vagotomy, not paralysed	33±8·1	+4±1·7 (5)†	45±10·6	−4±0·6**	−10±2·3 (5)*	3·4±0·65	−0·8±0·19 (5)*†

TABLE 3. Cardiovascular changes in anaphylaxis. Changes are at maximum effect, 2–10 min after challenge with albumen. All rabbits for vagal cooling and vagotomy were spontaneously breathing. Values are means and S.E., with numbers of rabbits in parentheses. Values are given in absolute units. * $P < 0.05$, ** $P < 0.01$, for the change in the variable due to anaphylaxis for each group of rabbits. † $P < 0.05$, ‡ $P < 0.01$, for the significance of the mean change of each variable due to anaphylaxis after paralysis, vagal cooling or vagotomy respectively compared with spontaneously breathing controls with intact vagi

	Blood pressure (mm Hg)		Right atrial pressure (cm H_2O)		Heart rate (per min)	
Condition	Control	Change after albumen	Control	Change after albumen	Control	Change after albumen
Vagi normal, all rabbits	102±8·7	−42±12·6 (11)**	—	—	282±12	−11±6·1 (11)
Vagi normal, not paralysed	107±12·3	−48±17·0 (7)*	1·0±1·01	+3·3±1·89 (4)	291±14	−11±8·5 (7)
Vagi normal, paralysed	92±10·4	−30±18·9 (4)	—	—	267±33	−12±9·4 (4)
Vagi cooled (to 8° C), not paralysed	104±2·9	−13±6·6 (5)	1·2±0·31	+0·2±1·12 (4)	285±29	+2±7·6 (5)
Vagotomy, not paralysed	98±10·1	−8±7·8 (4)	1·0±0·95	+6·0±1·60 (2)	249±15	−7±9·6 (5)

which efferent bronchomotor fibres are at least partially conducting, whereas afferent pathways are differentially blocked; and vagotomized rabbits, in which the great majority of bronchomotor efferent and pulmonary afferent fibres must be interrupted. In Fig. 3 responses to anaphy-

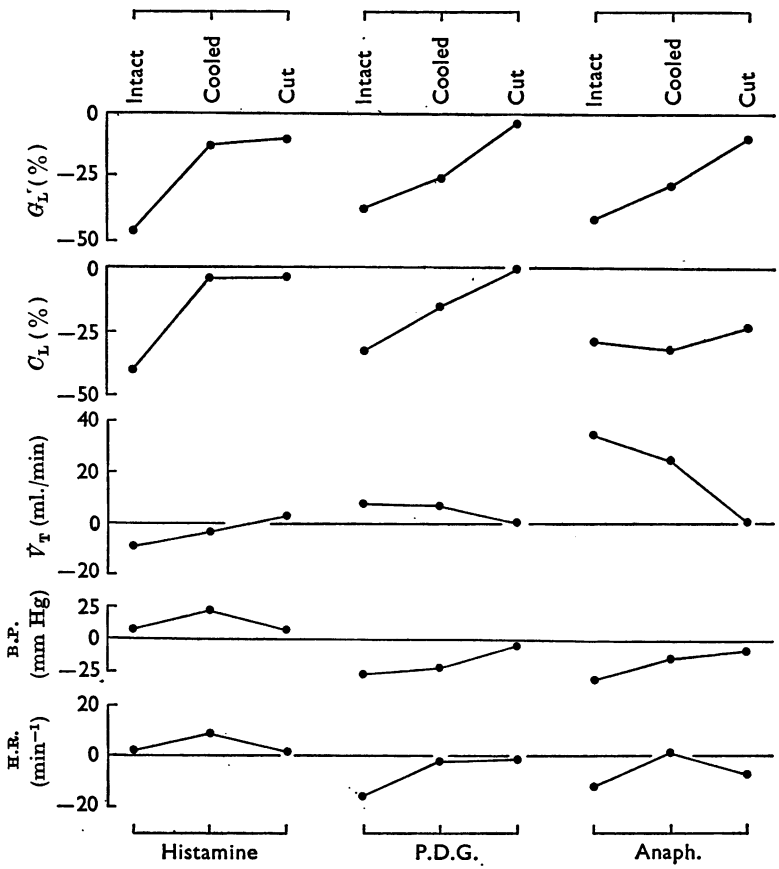

Fig. 3. Comparison of the effects in spontaneously breathing rabbits of intravenous injections of histamine acid phosphate, 100 μg/kg (left-hand records); phenyl diguanide, 100 μg (P.D.G., middle records) and anaphylaxis (Anaph., right-hand records) on, from above down: lung conductance (G_L, % change), lung compliance (C_L, % change), minute volume ($\dot{V}_T$), systemic arterial blood pressure (B.P.) and heart rate (H.R.). Values are means from this paper and from Karczewski & Widdicombe (1969*b*). Each triad of values gives the maximal changes before interruption of vagal conduction, during vagal cooling to 8–10° C, and after bilateral vagotomy. For histamine and phenyl diguanide each triad is for the same rabbits in each group; for anaphylaxis different groups of rabbits were used for each triad of values. Values for end-tidal CO_2 % and right atrial pressure are excluded because closely similar patterns were shown for the three conditions and stimuli (see Tables).

laxis are compared with those to intravenous injections of histamine, which acts via vagal afferent fibres (probably from irritant receptors in the lungs) blocked by cooling to 8–10° C; and with those to phenyl diguanide, which stimulates lung deflation receptors with vagal fibres which still conduct when cooled to 8–10° C (Paintal, 1955; Dawes, Mott & Widdicombe, 1951; Karczewski & Widdicombe, 1969*b*). The results for histamine and phenyl diguanide are taken from Karczewski & Widdicombe (1969*b*).

In common with both histamine and phenyl diguanide, anaphylaxis lowered end-tidal CO_2% and increased right atrial pressure, whether the vagi were intact or cut, and whether the rabbit was breathing spontaneously or paralysed and artificially ventilated. Anaphylaxis in the rabbit is known to cause a strong pulmonary vasoconstriction, especially of the veins (Doerr, 1950; Lecomte, 1956; Wcisło, Gina & Pawlik, 1963), and this could increase right atrial pressure and cause pulmonary oedema and a fall in end-tidal CO_2% (Karczewski & Widdicombe, 1969*b*).

The decrease in lung compliance in anaphylaxis was also dependent neither on a vagal reflex nor on changes in the pattern of breathing. However, the similar decrease in lung compliance after phenyl diguanide was mainly secondary to the rapid shallow breathing, since it was largely abolished by paralysis or by vagotomy. The decrease in lung compliance after histamine was present but considerably reduced by paralysis or vagotomy. Thus both histamine and anaphylaxis seem to have some direct action on the smooth muscle of the distal airways. Contraction of such muscle can decrease compliance without appreciable decrease in lung conductance (Olsen, Colebatch, Mebel, Nadel & Staub, 1965; Colebatch, Olsen & Nadel, 1966; De Kock, Nadel, Zwi, Colebatch & Olsen, 1966) or anatomical dead space (Severinghaus & Stupfel, 1955), since the greater elastic pull of the lungs keeps open the larger airways, where the main component of resistance to air flow resides (Mead, 1961; Green, 1966; Widdicombe, 1966).

There were clear similarities between the responses to anaphylaxis and to injections of phenyl diguanide. In both instances there were falls in systemic arterial blood pressure which were abolished or very greatly diminished by vagotomy. Both phenyl diguanide and anaphylaxis caused decreases in heart rate, which were abolished by vagal cooling, but the changes were small and for anaphylaxis were not statistically significant. With normal vagi both stimuli caused hyperpnoea, but during vagal cooling anaphylaxis caused an increase in tidal volume whereas phenyl diguanide increased breathing frequency. However, both these effects were prevented by vagotomy. The respiratory responses to phenyl diguanide were prompt and transient, whereas those to anaphylaxis were gradual and

maintained, so that compensatory processes may have developed in the anaphylactic reactions and may have contributed to the difference.

The results are therefore consistent with the systemic arterial and respiratory effects of anaphylaxis being mainly a vagal reflex and mediated by the same end-organs as those stimulated by phenyl diguanide, with vagal afferent fibres not blocked by cooling to 8–10° C (Fig. 3). These are probably lung deflation receptors (Paintal, 1955; Widdicombe, 1964) which are also sensitive to injections of 5-hydroxytryptamine (released in anaphylaxis in the rabbit), other vasoactive drugs, and pulmonary vascular congestion and embolism (Paintal, 1963) and may be stimulated in pulmonary oedema and pneumonia (Frankenstein & Sergeeva, 1966). We cannot say whether, in our experiments, deflation receptors were stimulated by release of chemicals or mechanically by changes in the pulmonary vascular bed or distal airways.

On the other hand the anaphylactic responses differed from those due to intravenous injections of histamine in some respects. Vagal cooling to 8–10° C prevented the respiratory effects of histamine; and histamine caused a primary rise in systemic arterial blood pressure and a small but variable increase in heart rate. The decrease in conductance due to histamine was decreased equally by vagal cooling and vagotomy, and was thought to be due mainly to stimulation of lung irritant receptors. Similarly, the decrease in conductance due to phenyl diguanide in paralysed rabbits was decreased equally by vagal cooling and by vagotomy. With anaphylaxis vagotomy reduced the conductance response more than did vagal cooling, but the rabbits were not paralysed. Thus histamine-sensitive end-organs, probably irritant receptors in the lungs (De Kock *et al.* 1966; Karczewski & Widdicombe, 1969*b*), could also be involved in the anaphylactic responses in our experimental conditions, but cannot explain the respiratory and cardiovascular responses.

A role for the vagus nerves in anaphylactic reactions has been claimed and contested but, at least with regard to bronchial reactions, few measurements have been made in the intact animal using direct methods of assessing bronchial calibre; most methods, such as that of Konzett & Rössler (1940), have mainly determined lung compliance, which may be affected by pulmonary vascular congestion (Widdicombe, 1963), or have been in deeply anaesthetized animals (Collier, Holgate, Schachter & Shorley, 1960) whose vagal reflexes might be blocked. Our results clearly indicate a positive role of the vagus nerves in some anaphylactic reactions. Also in favour of vagal reflex involvement are the observations: that the pulmonary effects of anaphylaxis are lessened by atropine (Auer & Lewis, 1910; Schild, 1936; Alberty, 1959), vagotomy (Auer & Lewis, 1910), and general anaesthesia (see Doerr, 1950; Filipp, 1965); and that anaphy-

laxis increases nervous discharge in both afferent and efferent fibres of the vagus nerves (Karczewski, 1962, 1964). The direct reactions studied in isolated airway tissues in organ-baths seem to play only a small part in the intact animal in the experimental conditions we have used.

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