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RECEPTORS IN THE TRACHEA AND BRONCHI OF THE CAT

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The afferent nerve fibres arising from the lungs have been described by Adrian (1933) who distinguished deflation fibres and slowly adapting fibres excited by inflation of the lungs. Knowlton & Larrabee (1946) described a further group of rapidly adapting stretch fibres which they suggested were responsible for the Hering-Breuer deflation reflex and for Head's paradoxical reflex; these last two reflexes excite inspiratory activity, the former being produced by forced deflation of the lungs, the latter by large inflations. The aim of the present experiments was to test the truth of this suggestion and to discover the exact anatomical origin of the rapidly adapting fibres. During its course this work developed into a systematic examination of afferent nerve endings in the tracheobronchial system. There seems to have been no previous work on this subject, although Keller & Loeser (1926) suggested that the vagal activity caused by forced deflation of the lungs might come from the trachea; but they did not establish this localization, and their multi-fibre records are difficult to interpret. To determine the reflex action of the tracheobronchial receptors, reflexes which could be elicited from the airways have been studied, and the results of this work have been published separately (Widdicombe, 1954).

A brief account of some of this work has already been given (Widdicombe, 1952*a*, *b*).

METHODS

Cats have been used, anaesthetized with chloralose (60 mg/kg) after induction with ethyl chloride and ethyl ether. Intraperitoneal pentobarbitone sodium (32 mg/kg) was sometimes used. Tracheal cannulae were inserted unless otherwise stated.

Systemic blood pressure was measured with a mercury manometer. The e.c.g. was sometimes recorded, using a resistance-capacity amplifier of conventional design, with display on a cathode-ray oscilloscope. Changes in volume of the cats' lungs were measured, using the body plethysmograph described by Dawes, Mott & Widdicombe (1951). The changes could be observed on a cathode-ray oscilloscope using a float spirometer designed for this purpose (Widdicombe, 1954). Intratracheal and intrapleural pressures were measured by electrical condenser manometers and displayed on another oscilloscope. For the measurement of the adaptation indices of pulmonary

stretch receptors the lungs were inflated by a motor-driven syringe; this could deliver up to 100 ml. of air, the injection taking place in either approximately 1 sec or ½ sec. The time of inflation was recorded by an electrical signal from the syringe. Deflations and larger inflations were made either by connecting the tracheal cannula to a pressure bottle, or by mouth.

Nervous action potentials were recorded from small strands dissected from the appropriate nerve trunk, usually the left vagus. Each electrode consisted of a small Perspex tube filled with 0·9% (w/v) sodium chloride solution which moistened a tuft of sable hair at the tip; a chlorided silver wire was sealed into the other end of the tube and connected the saline to an input lead of a pre-amplifier. The nerve strands were placed upon the sable hairs, and were prevented from drying by the saline. The action potentials were amplified and displayed on a cathode-ray oscilloscope. The amplifier was resistance-capacity coupled, with an equivalent noise resistance of 6000 Ω, and a maximum discrimination ratio of 1 : 50,000. A high-pass filter (cut-off 75 c/s) and a low-pass filter (cut-off 5000 c/s) were included in the circuit.

The vagal trunk was cooled by placing it on a hollow silver thermode (1 cm square) which was mounted in the corner of the dissecting platform; cold alcohol was circulated through the thermode, and the temperature of the latter measured by means of a thermocouple. Fuller details of this technique have been given elsewhere (Dawes *et al.* 1951).

For the localization of mechanoreceptors in the tracheobronchial tree this part of the respiratory system was isolated *in situ*. Under artificial ventilation, the chest was opened in the mid-line, the azygos vein tied and cut, and a cannula inserted in the right main bronchus at its origin; the proximal stump of the right main bronchus was tied off. The right lung was now artificially ventilated through the cannula, and this maintained the cat in good condition. The left upper lobe was tied off, so that the trachea, left main bronchi and left lower lobe formed a closed channel (Fig. 1). Nerve fibres from receptors in these zones were dissected from the left vagus nerve. To localize the receptors an endobronchial catheter was constructed; this was of polythene tubing with a double lumen, the smaller tube being used to inflate a small rubber balloon at the catheter tip, and the larger lumen to distend the lung beyond the balloon (Fig. 1). The catheter was similar in design to an endotracheal anaesthetic catheter. With the catheter in place in the left main bronchi it was possible to distend either the left lower lobe or the trachea and main bronchi proximal to the balloon, without affecting the other area. Passage of the catheter into the air passages was itself sufficient to localize any tracheobronchial receptors, since they were stimulated by touch by the catheter tip; the depth of insertion of the catheter could be recorded and compared with post-mortem measurements.

To study receptors in the tracheobronchial tree (excluding the lungs) the left lower lobe was tied off as well (Fig. 2). In such a cat the left cervical vagus nerve contained active afferent nerve fibres only from the trachea and main bronchi, the mediastinum and the heart and great vessels. The dissection of fibres from the air passages was greatly facilitated by the elimination of the great number of pulmonary stretch receptors.

Several procedures to stimulate cough receptors were used. Sulphur dioxide was generated by adding dilute hydrochloric acid to crystals of sodium thiosulphate, and air was blown through the mixture into the trachea (Widdicombe, 1954). Ammonia was administered by blowing air through a solution of the gas into the trachea. Powdered talc and starch were blown into the air passages through an endotracheal catheter.

Anaesthetic gases were administered from an Oxford vaporizer, calibrated for use with a Palmer pump. Procaine solution was sprayed into the tracheobronchial tree from a clinical 'atomizer'.

RESULTS

Pulmonary inflation receptors

The two groups of pulmonary stretch receptors were identified by Knowlton & Larrabee (1946) by their rates of adaptation to maintained inflation of the lungs. Any receptor was assigned to one or other class on the basis of its

'adaptation index'; this index showed the decline in frequency of discharge from the time of maximum frequency to the 2nd sec of inflation. It was expressed as a percentage and was calculated from the formula

$$\text{Adaptation index} = \frac{\text{Peak frequency} - \text{average frequency during 2nd sec of inflation}}{\text{Peak frequency}} \times 100.$$

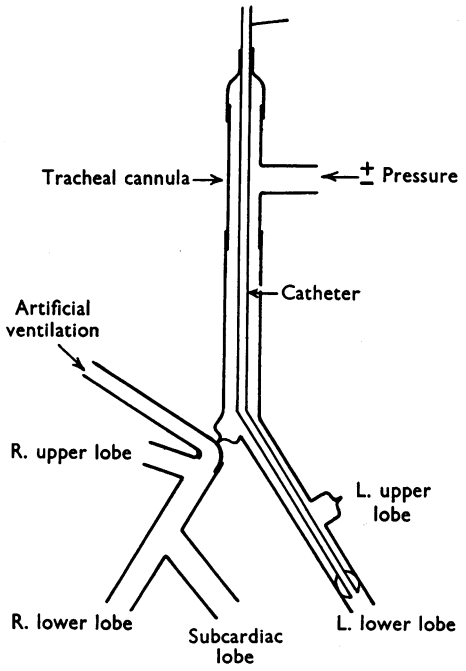

Fig. 1

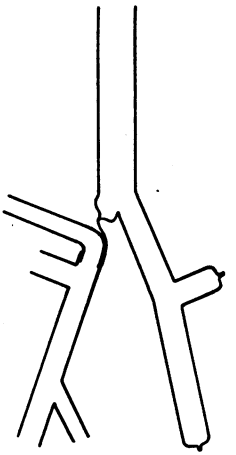

Fig. 2

Fig. 1. Diagram of the cat's trachea and main bronchi showing the preparation for localization of mechanoreceptors. A cannula is tied into the right main bronchus, and the left upper lobe is tied off. An endobronchial catheter is shown *in situ* with a balloon at its tip inflated in the bronchus to the left lower lobe. This lobe can be inflated through the catheter, and the trachea and bronchi proximal to the balloon inflated and deflated through the tracheal cannula.

Fig. 2. As Fig. 1, but the left lower lobe has been tied off as well. The trachea and left main bronchi are isolated *in situ*.

The index will be used in this paper in order to compare results; some errors are introduced by its use, and these will be considered in the Discussion. One practical point is that Knowlton & Larrabee did not indicate whether the 2nd sec of inflation was measured from the beginning or the end of inflation, or from the point of peak frequency. In the results given below the point of peak frequency has been taken; this usually coincided with the end of inflation as measured from the volume changes of the lungs.

One hundred single vagal fibres which were excited by inflation of the lungs were dissected. Each nerve strand placed on the electrodes was tested by large inflations (up to 200 ml.) to discover any high threshold receptors, and the adaptation index of each ending was calculated from the responses to two to fifteen inflations with different volumes, using the motor-driven syringe. The activity of four typical receptors is illustrated in Fig. 3. *A* is from a slowly adapting pulmonary stretch ending of the type described by Adrian (1933). *B*, *C* and *D* are from rapidly adapting receptors; *C* shows a prominent cardiac rhythm, while *D* discharges only during the phase of inflation. It was with these last three types of receptor that this work is especially concerned.

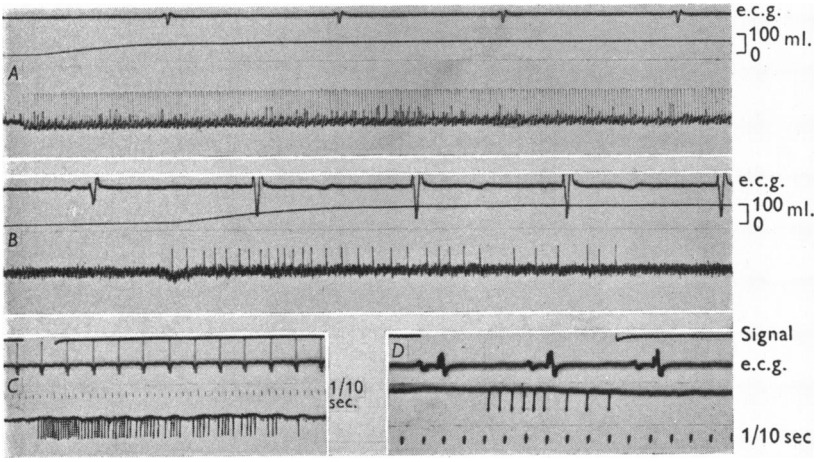

Fig. 3. Action potentials from four respiratory mechanoreceptors excited by inflations of the lungs. *A*, a slowly adapting pulmonary stretch receptor; *B*, a rapidly adapting pulmonary stretch receptor; *C*, a rapidly adapting ending with a superimposed cardiac rhythm; *D*, a receptor which discharged only during the inflation. In *A* and *B* the lung volume changes are shown (middle trace); in *C* and *D* an inflation of 100 ml. was made during the gap in the signal trace. The e.c.g. is also shown. The time marks in *D* also apply to *A* and *B*.

A histogram showing the number of receptors with each adaptation index is shown in Fig. 4. Knowlton & Larrabee constructed a histogram for ninety receptors showing three groups of endings; a slowly adapting group with an index under 55% (53% of receptors), a rapidly adapting one with an index over 80% (39%) and an intermediate one (8%); receptors in the last group could be assigned to one or other of the two main classes from 'the characteristic pattern of discharge'. While the results given here show the presence of rapidly adapting receptors, no division into two or three groups was found, and it was not always possible to assign 'intermediate' endings to slowly or rapidly adapting classes. Furthermore, Knowlton & Larrabee found that 16%

of their receptors had an index of 100% compared with 7% in these experiments; these endings stopped firing within 1 sec of the end of inflation. One possible explanation is that they were not using sufficiently suprathreshold stimuli, and that larger inflations would have prolonged the discharge and lowered the adaptation index. To test this, very large inflations (up to 250 ml.) were made for a number of rapidly adapting receptors, and the majority of them discharged into or beyond the 2nd sec after inflation. A few still had an adaptation index of 100% with these excessive inflations, but the importance of using well suprathreshold stimuli was emphasized. Because of the lack of a clear definition between rapidly and slowly adapting receptors in this analysis, an arbitrary division has been drawn at the 70% adaptation index point. Those endings (22%) adapting more rapidly than this almost invariably gave a response similar to that described by Knowlton & Larrabee.

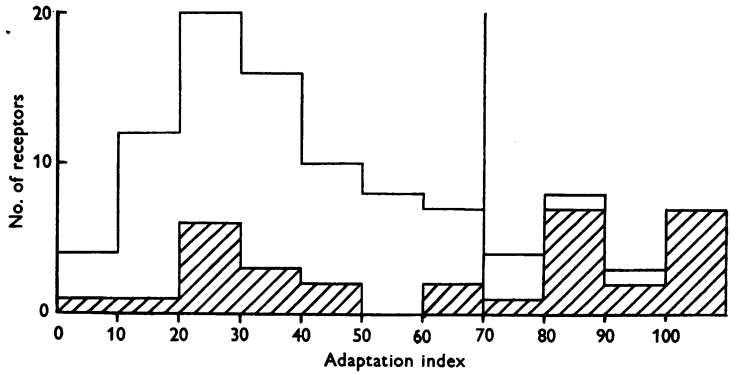

Fig. 4. Histogram showing the numbers of inflation receptors at each adaptation index. The indices are in groups of ten, except 100%, which is shown separately. The shaded histogram represents the endings which also responded to deflation. Receptors to the right of the vertical line were 'rapidly adapting'.

For each receptor the left vagus nerve was cooled to determine the temperature at which conduction in the afferent nerve fibre was blocked. In Fig. 5 these temperatures are compared with the corresponding adaptation indices. For receptors with indices under 70% the fibres were blocked between 8 and 19° C; these figures agree with those of Torrance & Whitteridge (1948) for pulmonary stretch receptors. The rapidly adapting receptors had a rather lower range (6–16° C). Knowlton & Larrabee measured the conduction velocities of fourteen stretch fibres, and found that those from rapidly adapting receptors were lower than those from slowly adapting endings. These two observations suggest that rapidly adapting receptors have afferent nerve fibres somewhat smaller than those from slowly adapting endings. In Fig. 5 the results from one cat have been omitted. In this animal six single nerve fibres were isolated with adaptation indices between 15 and 44%, and these fibres

were blocked by temperatures from 3 to 8° C; since in every other cat the figures were scattered throughout the entire temperature range of 8–19° C, it was thought possible that the thermode calibration was at fault on this occasion.

Each nerve strand was tested by deflating the lungs. The numbers of receptors excited are shown by the shaded histogram in Fig. 4; the rapidly adapting endings almost all responded, and the 100% group invariably did so. In Fig. 6 the inflation thresholds are compared with the corresponding adaptation indices. As the index increases there is a steady widening of the range of

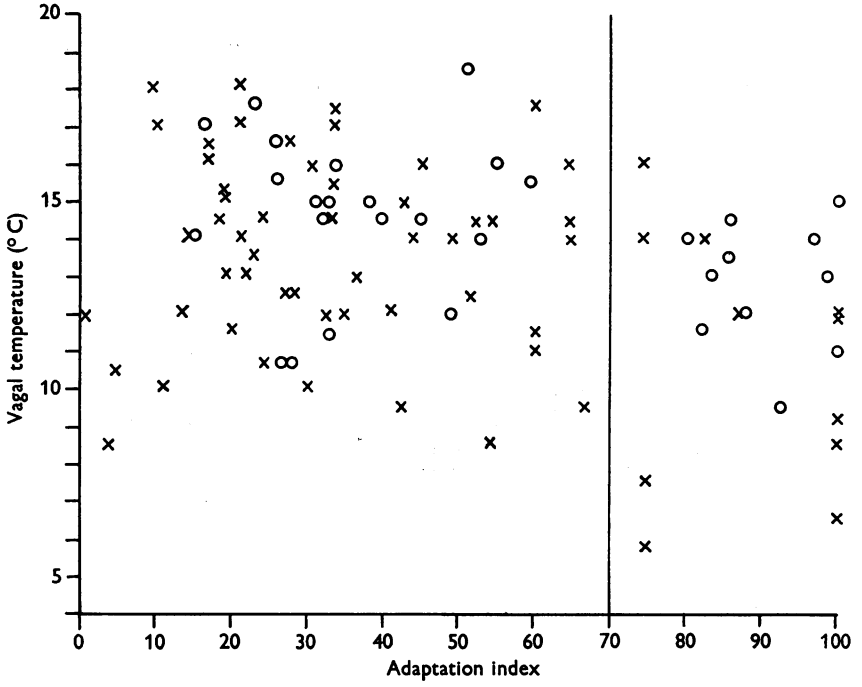

Fig. 5. The relationship between adaptation index and the vagal temperature needed to block conduction in the afferent nerve fibres. ×, closed chests; ○, open chests.

thresholds, and for any adaptation index the receptors have thresholds spread between zero and the maximum for that index. The large number of endings concentrated in the low-threshold, low-index group are the pulmonary stretch receptors analysed by Adrian (1933).

A survey of the 100 receptors examined suggested that one group had distinctive properties. These were the receptors which had an adaptation index of 100% and fired off only during the passage of air into the lungs. Fig. 3*D* illustrates the response of one of these endings. However strong the stimulus, these receptors did not discharge by more than a single action potential after inflation was complete. The endings gave a characteristic response to four

mechanical stimuli; inflation of the lungs, deflation, and opening the trachea to atmospheric pressure after both inflation and deflation all caused a short discharge of impulses limited to the time that the lungs were moving. The receptors did not respond to pulling the trachea. Six of the seven receptors with an adaptation index of 100% (Fig. 4) behaved in this way. This type of ending is further illustrated in Fig. 7. Inflations up to 100 ml. could not induce this receptor to discharge after the period of inflation, although it fired off briefly on release of the inflation (not shown) and on deflation and release of the deflation. Occasionally other receptors were stimulated both by a volume change and by restoration of the resting volume (as mentioned by Knowlton & Larrabee) but only the six receptors referred to above had a discharge

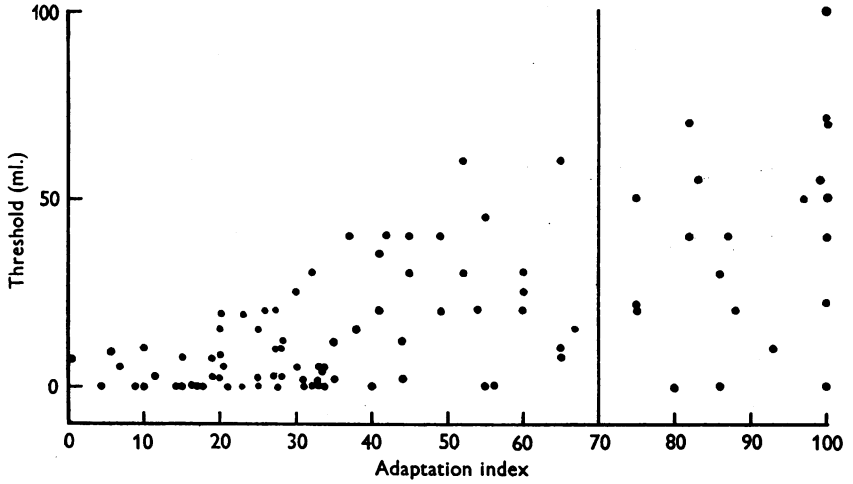

Fig. 6. The relationship between adaptation index and inflation threshold.

limited to the period of volume change. Evidence will be presented later for believing that they belong to a separate physiological group.

Apart from this small group of receptors which had not previously been described, these experiments have not confirmed the conclusion of Knowlton & Larrabee that the adaptation index was alone sufficient to differentiate pulmonary stretch receptors into two physiological groups. A study of the localization of the sensory endings proved more fruitful in distinguishing between different types.

The localization of 'rapidly adapting pulmonary stretch receptors'

It seemed possible that the rapidly adapting stretch receptors were not pulmonary volume receptors but lay in the walls of the trachea and bronchi. Since the response to *deflation* was usually at a slowly adapting rate, it was likely that the rapid adaptation to *inflation* was a mechanical artifact. When

air was blown into the lungs and the trachea then closed, the intratracheal pressure declined rapidly, although the volume change was maintained (Fig. 8); this was presumably due to continued stretch of the lung. This overshoot in pressure may be accompanied by a distension and then partial collapse of the tracheobronchial tree; with the chest closed, simultaneous measurements of intratracheal and intrapleural pressures show that there is an overshoot of the *pressure difference* between the two spaces, although the intrapleural pressure rises and then falls. Any mechanoreceptors in the air passages might be expected to show a declining response after expansion of the lungs seemed complete.

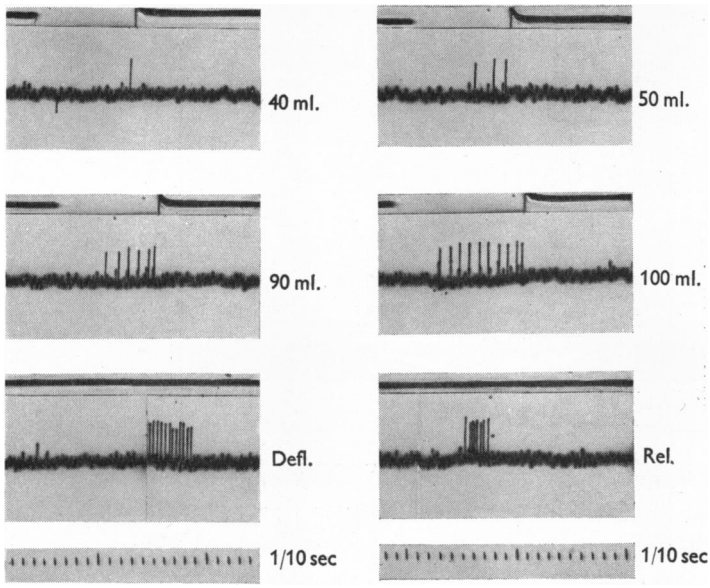

Fig. 7. Cat, 2·7 kg. Chloralose, 60 mg/kg. A rapidly adapting receptor which discharged only during the passage of air into the chest. Increasing the inflation volumes (shown) did not prolong firing after the inflation. The ending was also stimulated by deflation (Defl.) and by release of the deflation (Rel.).

In order to see if the 'rapidly adapting pulmonary stretch receptors' lay in the trachea and bronchi, the cats' right lungs were maintained on artificial ventilation, while the left lower lobe, the left main bronchi and the trachea were left in continuity; an endobronchial catheter was constructed (Fig. 1). The experiments gave unequivocal results. With a fibre that had a 'rapidly adapting' response, the catheter was passed down into the left bronchi and on reaching a point opposite the hilum the receptor discharged rapidly and continuously in response to touch by the catheter tip. On pushing the catheter further down, the balloon passed beyond the receptor; after distending the

balloon and thus occluding the bronchus, inflation of the left lower lobe beyond the balloon was without effect upon the ending. In all, thirteen receptors which gave rapidly adapting responses to pulmonary inflation were examined in this way, and in each instance a point in the trachea or bronchi was reached which when touched by the catheter led to a discharge of nerve impulses. In eight instances it was possible to distend the balloon beyond the ending, and

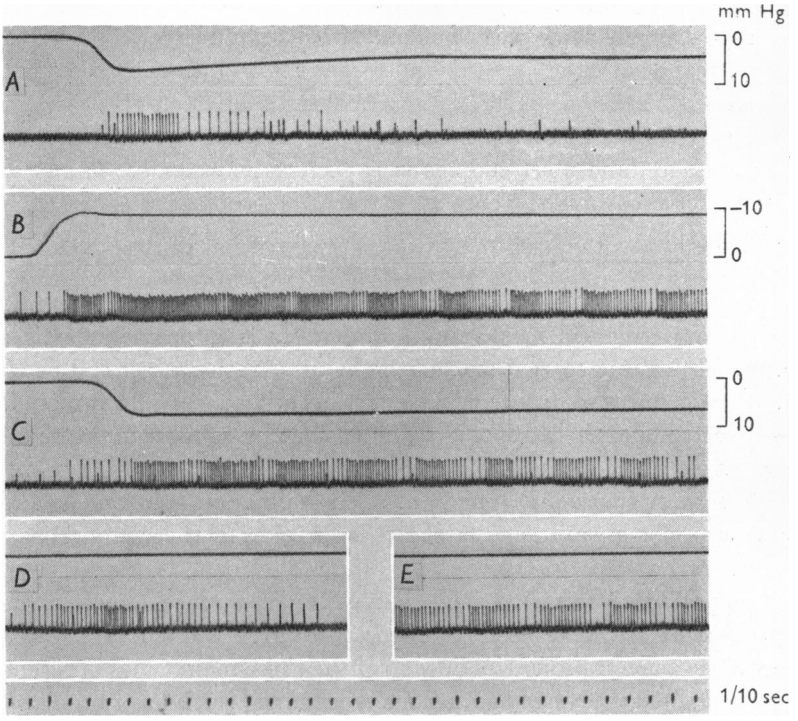

Fig. 8. Cat, 2·7 kg. Chloralose, 60 mg/kg. Localization of a 'rapidly adapting' receptor. Upper trace: intratracheal pressure (positive downwards). Lower trace: action potentials. *A*, inflation of the left lower lobe through the trachea caused a 'rapidly adapting' response; *B*, deflation of the left lower lobe through the trachea; *C*, inflation of the trachea and main bronchi alone, an endobronchial catheter in place, caused a slowly adapting discharge; *D*, excitation of the receptor with the endobronchial catheter; *E*, pushing the bronchi towards the heart produced a cardiac rhythm.

inflation of the distal pulmonary tissue never stimulated the receptor; distension of the trachea and bronchi, however, always produced a response. For each of these eight receptors the response to inflation of the trachea and bronchi was at a slowly adapting rate, although for only three were accurate measurements made. These three endings had adaptation indices of 99, 82 and 85 % before passing the catheter, and of 62, 32 and 51 % respectively when only the trachea and bronchi were distended. An example is shown in Fig. 8. This

receptor adapted rapidly to inflation (*A*); on deflation (*B*) its discharge was rather slowly adapting with a prominent cardiac modulation. Distension of the trachea and bronchi alone (*C*) caused a slowly adapting discharge, and it could be excited by touch with the catheter tip (*D*). The nature of the cardiac modulation is seen in *E*, when the bronchi were pushed gently over towards the heart; the mechanical effect of the ventricular beat caused the cardiac pulses.

As a control experiment fifteen slowly adapting pulmonary stretch receptors were treated in the same way; not only was it impossible to excite them by touch with the catheter, but they all responded to inflation of the left lower lobe and not to distension of the tracheobronchial tree. It was possible to stimulate a number of the tracheobronchial receptors by touch from outside the air passages, and most endings were seen to lie well clear of any alveolar tissue; this was always the case with tracheal receptors. This ruled out any possibility that the endings were lying in alveolar tissue just outside the bronchial wall.

Having shown that the 'rapidly adapting pulmonary stretch receptors' were bronchial and tracheal mechanoreceptors, a more extensive investigation of their properties was carried out. With the preparation described in Methods (Fig. 2), vagal fibres coming from receptors in the trachea and left main bronchi were dissected, and their response to distension and collapse of the air passages noted. Every effort was made to exclude mediastinal receptors (Adrian, 1933); since these were frequently found and their distinction from tracheobronchial endings was not always easy, a short description of their properties will be given.

Action potentials from 166 single nerve fibres from mechanoreceptors *in the trachea and bronchi* have been recorded; three groups of endings were clearly defined. The general properties of each of the three main types of receptor will first be described, and then the various procedures which have been applied to them will be considered under separate headings.

Group I: slowly adapting tracheobronchial stretch receptors

Nearly half the receptors (82, 49%) gave a regular discharge on inflation and deflation of the air passages, at a rather slowly adapting rate. Fig. 9 shows a typical example. This receptor was discharging when the intratracheal pressure was atmospheric; raising the pressure (*A*) caused an increase in discharge rate, the response being similar to that seen with pulmonary stretch receptors; collapse of the air passages (*B*) was a weaker stimulus. In *C*, the bronchial wall was deformed by touching it from outside, and in *D*, polythene tubing was passed into the bronchus and increased the discharge. This receptor lay near the origin of the bronchus to the left upper lobe. *D* illustrates a further point; with the slowly adapting receptors a mechanical stimulus from within the air passages was never as effective as distension of the airways, unless the poly-

thene tubing was of large enough diameter to distend the bronchus. Receptors in the trachea were only weakly stimulated by touch with a polythene catheter (since the tubing scarcely deformed the tracheal walls) while endings deep in the bronchi were more strongly excited.

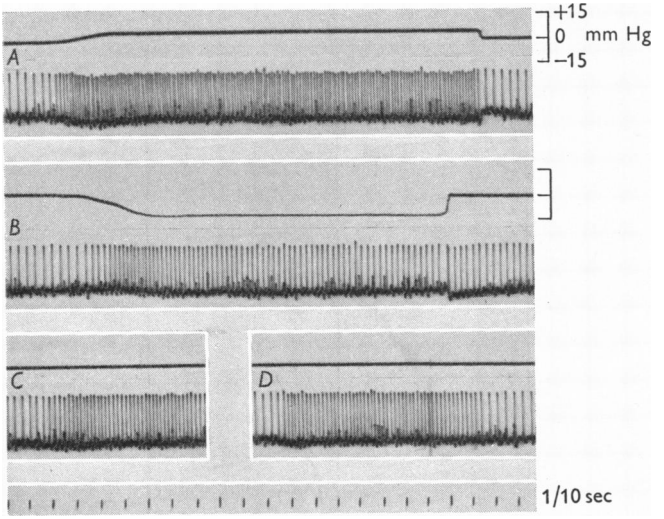

Fig. 9. Cat, 3·7 kg. Chloralose, 60 mg/kg. A slowly adapting bronchial receptor. *A*, distension of the air passages caused an increase in discharge rate; *B*, deflation caused a similar but smaller effect; *C*, stimulation of the receptor by touching the outside of the bronchial wall; *D*, stimulation of the receptor with an endobronchial catheter.

A general picture of the responses of this group of receptors is shown diagrammatically in Fig. 10. Of the sixty-one endings included only two (group *C*) did not respond to deflation. This clearly differentiated them from pulmonary stretch receptors, of which only 19% were excited by deflation (Fig. 4). Three receptors were stimulated by deflation but not by inflation. Apart from the rapidly adapting endings to be described in the next section, from over 400 vagal fibres from respiratory mechanoreceptors only seven responded to deflation of the lungs and air passages but not to inflation; three of these endings were not localized, and the other four were found to lie in the main bronchi.

As suggested in Fig. 10 the 'slowly adapting' receptors had, in fact, a wide range of adaptation indices. Groups *A–D* had indices from 0 to 50% for both inflation and deflation of the trachea and bronchi; groups *E* and *G* had indices from 50 to 100%. Receptors in group *F* were more rapidly adapting on inflation than on deflation. Since these receptors are of the type illustrated in Fig. 8, their adaptation indices would be considerably higher if the lobes of the lung were inflated through the trachea and bronchi. Intratracheal pressure/response curves were drawn for a number of slowly adapting receptors, and four

of these are plotted in Fig. 11. The non-linear shape of the curves is very different from the approximately linear stretch/response curves of pulmonary stretch receptors (Adrian, 1933; Knowlton & Larrabee, 1946; Whitteridge & Bülbring, 1944). It seemed possible that the response of the slowly adapting receptors might bear a more linear relationship to *tracheobronchial volume* than

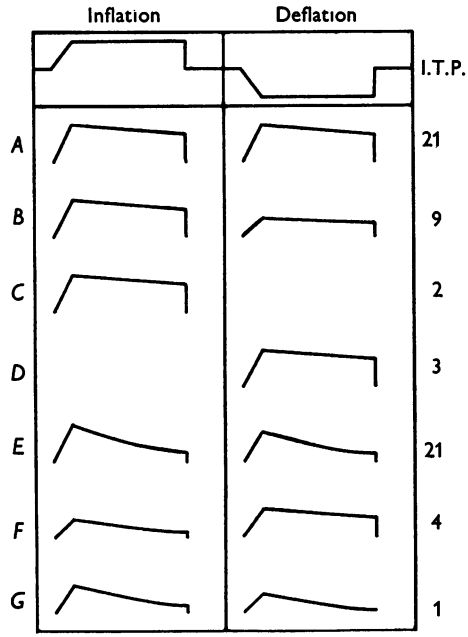

Fig. 10. Diagram of the patterns of response of slowly adapting bronchial receptors. I.T.P., intratracheal pressure. Each curve is a diagrammatic frequency of response/time curve for a 2 sec inflation (left) and deflation (right). The intratracheal pressure curves give the timing of the stimuli, and the numerals indicate the number of receptors which gave each type of response. For fuller description see text.

to intratracheal pressure. In seven cats intratracheal pressure/tracheal volume curves were plotted for the trachea and main bronchi by filling the air passages with saline or olive oil and measuring the volume change when pressures were applied. One such graph is shown in Fig. 12; at high positive and low negative pressures any given change in pressure had less effect on the tracheal volume than when the intratracheal pressure was nearer to atmospheric. The conversion of the graphs in Fig. 11 to tracheal volume/response curves (Fig. 13) made them much more linear.

Group II: rapidly adapting tracheal endings

These endings were immediately distinguished by the timing of their response and by the mechanical stimuli which excited them. They gave a short discharge during a rise or fall of intratracheal pressure, with only one or two action

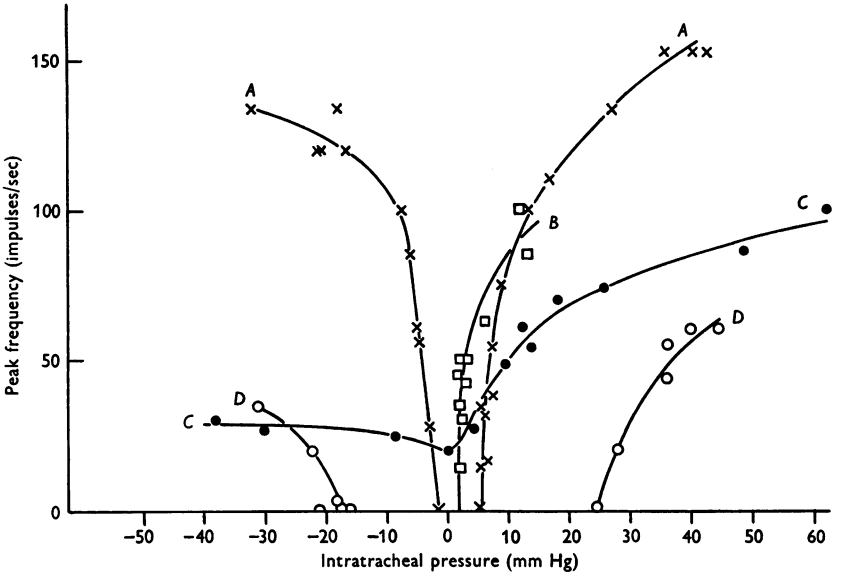

Fig. 11. Cat, 2·3 kg. Chloralose, 60 mg/kg. Stimulus/response curves for four slowly adapting bronchial receptors. Ordinate: peak frequency of response. Abscissa: intratracheal pressure. *A*, a typical receptor; *B*, one which did not respond to deflation; *C*, an ending which was firing spontaneously with intratracheal pressure atmospheric; *D*, a high-threshold receptor.

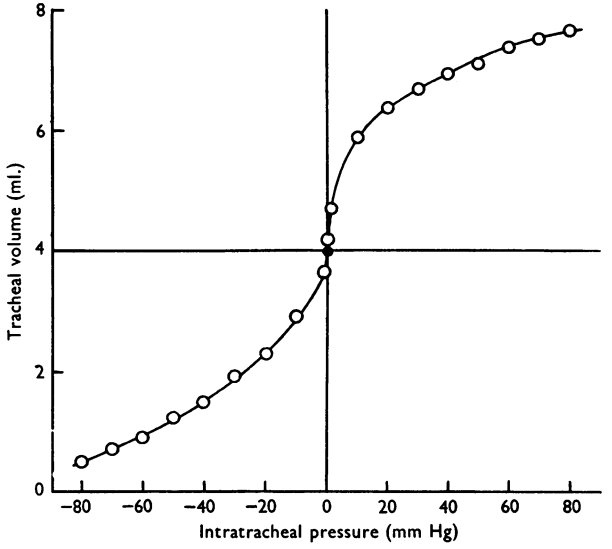

Fig. 12. Cat, 2·3 kg (as Fig. 11). The relationship between intratracheal pressure and the volume of the trachea and left main bronchi.

potentials afterwards; when the pressure was released they fired off again with a short burst of impulses lasting a fraction of a second. They were, therefore, very rapidly adapting to volume changes of the air passages. Forty-six (28%) receptors belonged to this group, and the responses of one is shown in Fig. 14. With this receptor the effects of inflation and release of the distension (*A*) were smaller than those due to deflation and release of the collapse (*B*). The endings were readily excited by touch from within the tracheal lumen (*C*), but a long-lasting regular discharge could never be produced. Rapid jerky movement of

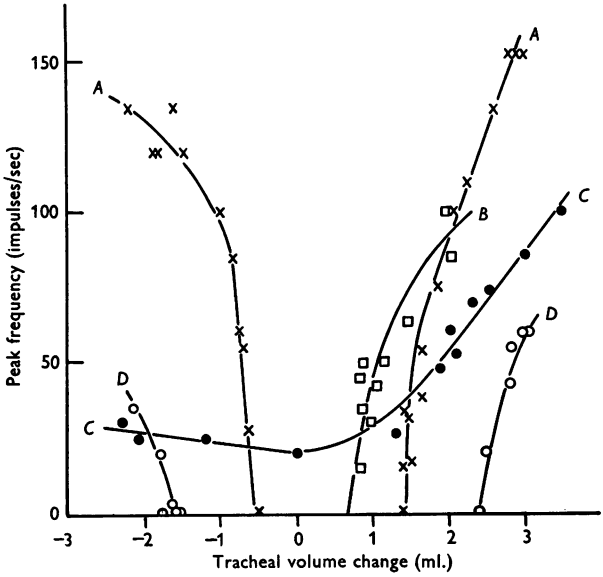

Fig. 13. Cat, 2·3 kg (as Figs. 11 and 12). The same receptors as in Fig. 11 showing the relationship between tracheal volume and peak frequency of discharge.

the catheter caused an irregular discharge while smooth insertion of the tubing led to a short response (similar to that after tracheal inflation) as the catheter tip passed the site of the receptor. Those receptors with a high threshold were considerably easier to excite by an endotracheal catheter than by volume changes, and the degree of deformation of the tracheal wall was less when a catheter stimulated the receptor than when a just threshold pressure change was used. This is strikingly different from the behaviour of the slowly adapting endings. Many of the rapidly adapting endings could not be stimulated by touching the tracheal wall from the outside, unless the wall were pinched or grossly deformed.

The fact that these receptors discharged only during inflation, deflation and release of the pressures might be because they were stimulated by tracheal airflow rather than by changes in tracheal diameter. To test this possibility

the effect of continuous passage of air through the trachea was observed for eight receptors. Six of these were only excited if the pressure changes were above the thresholds, when they gave rapidly adapting responses. The other two gave relatively long discharges at an irregular rate. The cats in which these two endings were found, had considerable tracheobronchial secretion, and to produce the discharge air had to be drawn through at varying pressures; it was thought likely that the continuous irregular discharge of the receptors was due to movement of mucus in the trachea.

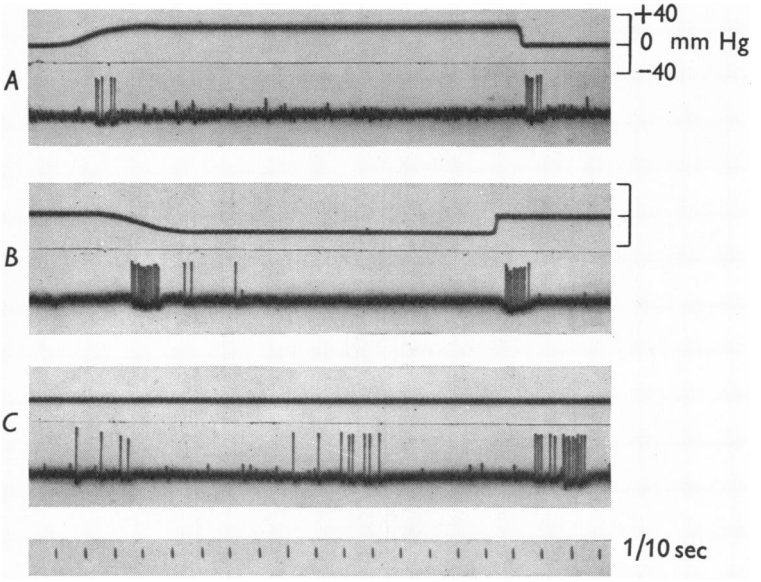

Fig. 14. Cat, 3·2 kg. Chloralose, 60 mg/kg. A rapidly adapting tracheal receptor. *A*, inflation of the trachea; *B*, deflation; *C*, stimulation of the receptor by touch with an endotracheal catheter.

A consideration of the patterns of discharge (Fig. 15) provides another reason for believing that airflow was not the stimulus. Only seven receptors were excited by all four pressure changes (group *A*), so that only these could be responding to airflow in both directions. If a receptor were stimulated by airflow in one direction only it should respond to inflation and release of deflation, or to deflation and release of inflation; no receptor was excited by either pair of stimuli alone. The largest group (*E*) was excited by deflation and release of the deflation, and these two stimuli were effective for thirty-three of the forty endings. Inflation stimulated twenty-three receptors, and release of inflation eleven; thus collapse and its release brought into play far more rapidly adapting tracheal endings than distension and its release.

Group III: intermediate receptors

A number of receptors were discovered whose properties fitted neither with the rapidly adapting nor with the slowly adapting receptors. The majority of these were mediastinal endings, which could usually be identified by the regular high-frequency discharge caused by mediastinal displacement. However, thirty-eight (23%) endings remained which could not be classified with any of these three types. At first sight their activity seemed intermediate

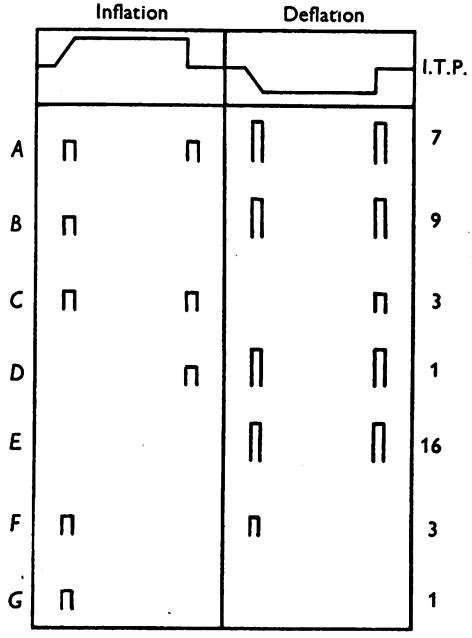

Fig. 15. Diagram of the patterns of response of rapidly adapting tracheal receptors, arranged as in Fig. 10. For description see text.

between the rapidly and slowly adapting endings, and raised the possibility that the definitions of these classes had been too limited; further analysis showed that they had properties which were not shared by the other two groups of tracheobronchial receptor.

On distension and collapse of the trachea and bronchi the receptors discharged for a short time, at the most a second or two (Fig. 16). They had neither the abruptly limited burst of activity of the rapidly adapting endings, nor the smooth decline of discharge over many seconds of the slowly adapting ones. While they might have corresponded to the upper limit of activity of the slowly adapting receptors, there are several indications that this is not so. Increasing the pressure stimulus did not appreciably prolong the time of firing of the endings although the peak frequency increased. The receptors which had

adaptation indices below 100% on inflation of the air passages usually gave a very rapidly adapting discharge (index 100%) on deflation and vice versa. The rate of discharge was often irregular, as was the response of the receptor to stimulation with an endobronchial catheter (Fig. 16*C*). The latter readily excited the endings, but a continuous high frequency discharge was never seen, although it could be obtained with endings of the slowly adapting group which had both a high threshold and a high adaptation index. Very characteristic, too, was the declining response to repeated stimuli, illustrated in

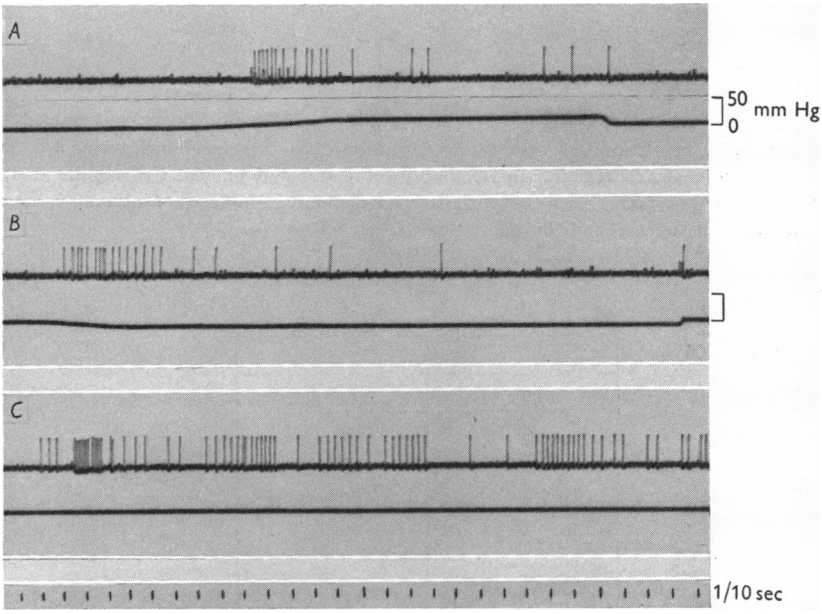

Fig. 16. Cat, 2·6 kg. Pentobarbitone, 32 mg/kg. Response of an intermediate type bronchial receptor. *A*, inflation of the air passages; *B*, deflation; *C*, stimulation of the receptor by touch with an endobronchial catheter.

Fig. 17. For eighteen receptors (out of twenty-eight in which the effect was sought), frequently repeated inflations or deflations raised the pressure threshold, diminished the response and raised the adaptation index. Endings in the slowly adapting group sometimes showed a declining response to repeated stimuli, but it was never of comparable size and there were never appreciable changes in threshold or adaptation index.

The patterns of discharge of the intermediate receptors are drawn in Fig. 18. All but two of the endings were stimulated both by inflation and by deflation of the air passages, and nine of them were also excited by release of the pressures. The latter never caused more than two or three action potentials

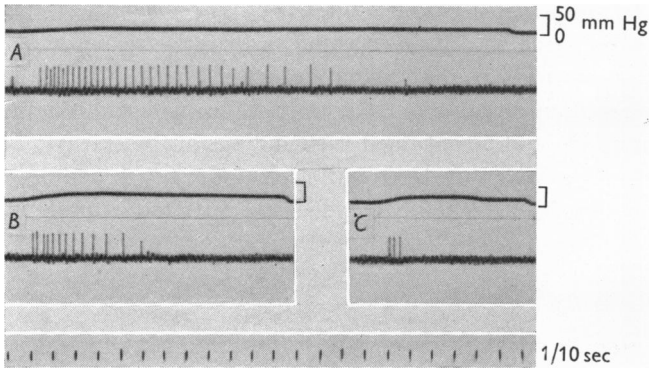

Fig. 17. Cat, 2·4 kg. Chloralose, 60 mg/kg. An intermediate type receptor showing a declining response to repeated stimuli. In *A*, *B* and *C* the tracheobronchial tree was inflated; the response of the receptor decreases with successive stimuli. Half-second intervals between *A* and *B*, and between *B* and *C*.

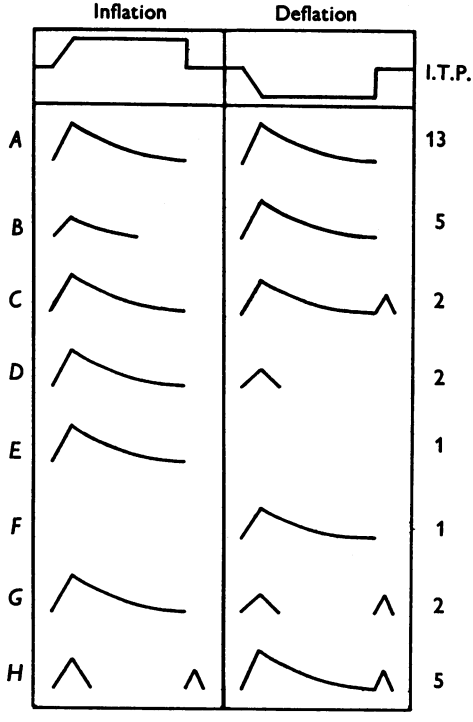

Fig. 18. Diagram of patterns of response of intermediate type receptors, arranged as in Figs. 10 and 15. For description see text.

(Fig. 16*B*) and was always far smaller than the response of receptors in the rapidly adapting group.

General properties of tracheobronchial mechanoreceptors

Localization. Nearly all the receptors were localized in the trachea and main bronchi by passing a polythene catheter into the air passages until it just stimulated the ending; the depth of insertion was measured and compared with post-mortem measurements. The results for the three groups of receptors are expressed in Fig. 19. The tracheobronchial tree has been divided into seven

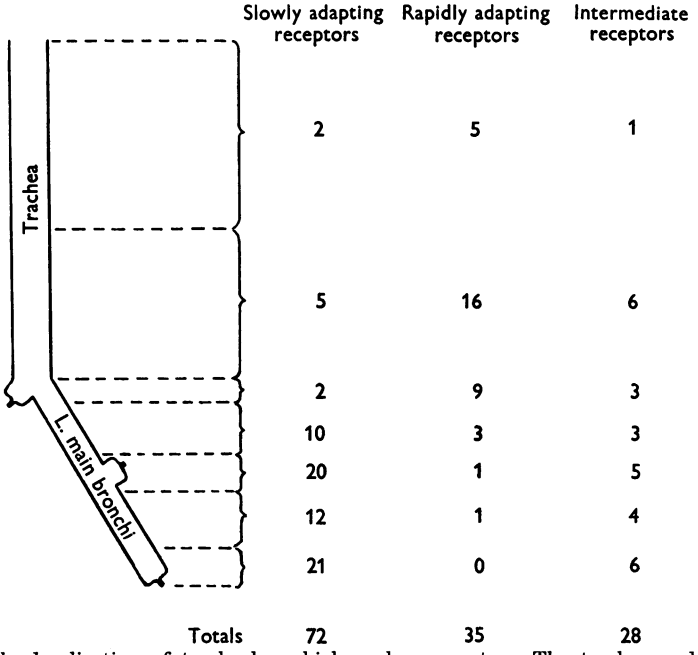

Fig. 19. The localization of tracheobronchial mechanoreceptors. The trachea and left main bronchi are shown diagrammatically on the left; they are divided into seven arbitrary areas indicated by the brackets. Opposite each area is the number of receptors found there for the three types of tracheobronchial ending.

arbitrary areas, and the numbers of receptors localized are shown opposite the appropriate zones. With five exceptions the rapidly adapting endings were restricted to the trachea, and the greatest concentration (although not the greatest number) was found at the carina. By contrast, the slowly adapting receptors were concentrated in the main bronchi, although some also lay in the trachea. Within the bronchi they were most commonly found at two areas, the origin of the bronchi to the left upper lobe and deep in the bronchi to the left lower lobe at the point where that lobe was tied off. This distribution might be because both sites contained branching bronchi, so that the total area of bronchial wall was greater here. On the other hand, only two receptors were

found at the carina. The intermediate endings had a fairly uniform distribution throughout the trachea and bronchi.

The significance of these patterns of distribution will be considered in the Discussion; one point may be mentioned here. The restriction of rapidly adapting receptors to the trachea might have been due to damage to the bronchi, perhaps by the ligatures applied to the lobes of the lungs. But cats in which rapidly adapting tracheal endings were present almost invariably had active slowly adapting and intermediate receptors lying in the bronchi, so the afferent nervous systems there were in good condition.

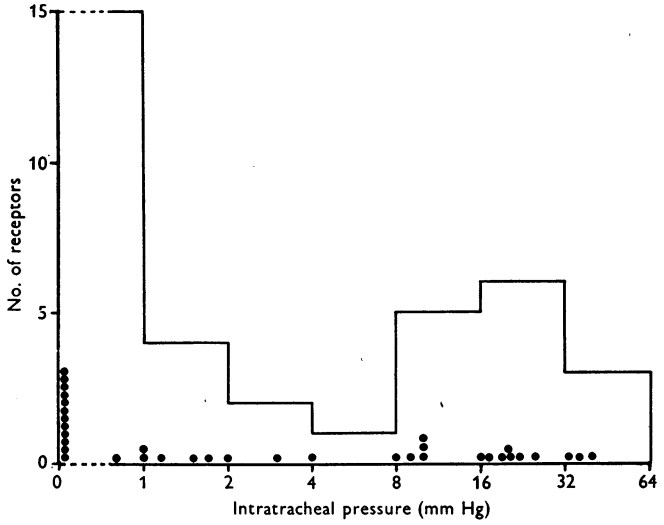

Fig. 20. Pressure thresholds of thirty-six slowly adapting bronchial receptors. Each filled circle shows the threshold for a single receptor, and the histogram the number of receptors for each range of thresholds. The thresholds are for inflations, and are expressed on a logarithmic scale.

Thresholds. Accurate threshold determinations were made for seventy-four of the tracheobronchial receptors. The thresholds are shown in Figs. 20–22 for the slowly adapting, rapidly adapting and intermediate receptors respectively. The thresholds are presented as the least change in intratracheal pressure necessary to excite the endings, and this pressure is plotted along a logarithmic scale on the abscissa. Volume thresholds were not often determined since the pressure figures are more significant for comparison with the natural respiratory cycle, and many cats of different sizes were used.

The thresholds of slowly adapting receptors (Fig. 20) are for *inflations* of the air passages. Although for any receptor the thresholds for inflation and deflation might be widely different the general shape of the deflation threshold histogram was similar to that of Fig. 20. The receptors which are plotted at

threshold zero were firing with the intratracheal pressure atmospheric. A few of these stopped discharging when the pressure was varied slightly, but the majority were like that in Fig. 11 *C*, and were active whatever the intratracheal pressure.

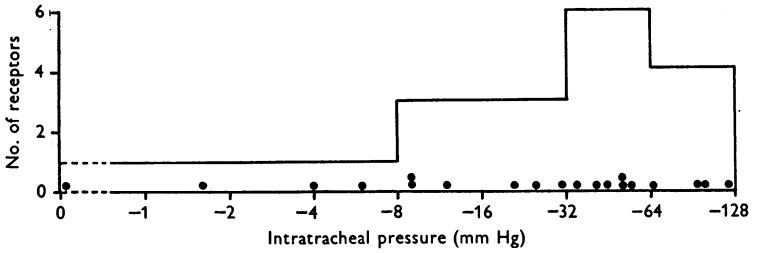

Fig. 21. Pressure thresholds of twenty rapidly adapting tracheal receptors, expressed as in Fig. 20. The thresholds are for deflations of the air passages.

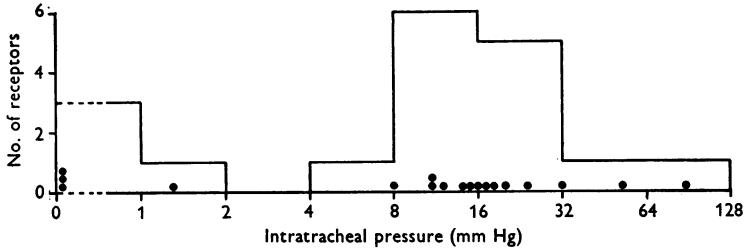

Fig. 22. Pressure thresholds of eighteen intermediate type receptors, expressed as in Figs. 20 and 21. The thresholds are for inflations of the air passages.

For the rapidly adapting endings *deflation* thresholds have been shown (Fig. 21). The histogram for inflation thresholds was similar in shape but contained far fewer points. Fig. 22 shows the *inflation* thresholds of eighteen of the intermediate endings. The receptors plotted at zero atmospheric pressure in Figs. 21 and 22 were firing with a cardiac rhythm before inflation of the trachea.

For the significance of these thresholds to be assessed they must be compared with the intrapleural and intratracheal pressure changes in eupnoea and hyperpnoea. In five cats these two pressures were measured during quiet respiration, during hyperpnoea caused by intravenous injections of nicotine (two cats only) and during coughing produced by mechanical or chemical stimuli to the trachea and larynx. The tracheas were not cannulated, so that the glottis and upper respiratory tract played a part in respiration. The results are shown in Table 1. Four groups of figures are shown: the greatest positive and negative intratracheal pressures, the maximum positive pressure difference (in expiration) and the greatest negative pressure difference (in inspiration) across the tracheobronchial walls. In coughing the intrapleural pressure

reached very high values; the greatest negative intrapleural pressure was −60 mm Hg, and the maximum positive value was +98 mm Hg. The records suggested that these figures were obtained with the glottis closed, since the intratracheal pressure closely followed the intrapleural, and their difference was not so great as might have been supposed. The figures presented here are similar to those of Kroepfli (1950) who used powdered soap to stimulate coughing in cats.

TABLE 1. Respiratory pressures measured in eupnoea, hyperpnoea and coughing

	Max. positive intratracheal pressure (mm Hg)			Max. negative intratracheal pressure (mm Hg)			Max. positive pressure difference (mm Hg)			Max. negative pressure difference (mm Hg)		
Cat	Eupnoea	Hyperpnoea	Coughing	Eupnoea	Hyperpnoea	Coughing	Eupnoea	Hyperpnoea	Coughing	Eupnoea	Hyperpnoea	Coughing
1	0	3	25	0	−4	−16	0	3	10	−4	−10	−5
2	0	2	48	0	−9	−6	0	4	38	−3	−16	−48
3	0	—	25	0	—	−12	0	—	18	−8	—	−18
4	0	—	29	0	—	−15	0	—	10	−4	—	−10
5	0	—	50	0	—	−21	0	—	36	−5	—	−16
Means	0	2·5	37	0	−6·5	−14	0	3·5	22	−5	−13	−19

The maximum positive and negative intratracheal pressures represent the pressure drop across the extrathoracic tracheal wall. The maximum positive and negative pressure differences were obtained by subtracting the intratracheal pressure from the intrapleural pressure; they represent the pressure drop across walls of the intrathoracic but extra-pulmonary air passages.

From Table 1 certain conclusions can be drawn. The *extrathoracic* trachea will be subjected to a pressure drop across its wall equal to the intratracheal pressure; with a closed glottis, as in certain phases of coughing, this pressure may be very high. The *intrathoracic* but extra-pulmonary air passages, however, will be subjected to the difference between intrapleural and intratracheal pressures. In coughing the cat may make a strong expiratory effort against a closed glottis; the intratracheal pressure will rise with the intrapleural pressure, so that the pressure drop across the walls of the air passages may remain small. When the glottis opens the intratracheal pressure drops suddenly, but since the intrapleural pressure remains high a large pressure difference may result.

Comparison between Table 1 and the histograms in Figs. 20–22 suggest that in eupnoea about half the slowly adapting receptors would be stimulated, but that very few of the rapidly adapting and intermediate receptors would be affected. In hyperpnoea more endings of all groups would be brought into play, while in coughing nearly all the slowly adapting endings would be stimulated; but even strenuous coughing would not excite all the rapidly adapting receptors. Some of the thresholds are so high that it is hard to believe that their physiological stimulus can be a general distension or collapse of the air passages.

Vagal cooling. Fig. 5 showed that the afferent nerve fibres from 'rapidly adapting pulmonary stretch receptors' were blocked by cooling the vagus nerves to 6–16° C. This temperature range has been confirmed by cooling the vagi while recording single fibre activity from receptors localized to the tracheobronchial tree. Seventeen fibres from slowly adapting bronchial endings were cooled, and the temperature range was from 7 to 13° C. The range

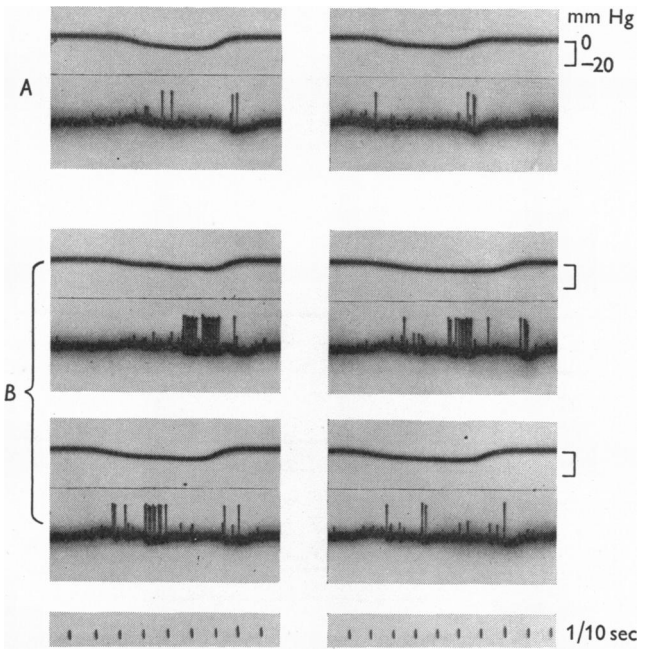

Fig. 23. Cat, 3·4 kg. Chloralose, 60 mg/kg. Effect of inhaled talc on a rapidly adapting tracheal receptor. *A*: two control deflations of the trachea, showing a typical 'double' response. Between *A* and *B* powdered talc was blown into the trachea. *B*: four subsequent deflations showing sensitization of the receptor. Two-second intervals between records.

for fifteen rapidly adapting receptors was from 7 to 15° C. Fibres from three intermediate receptors only have been cooled; these were blocked at temperatures of 10, 10 and 7° C respectively. Cooling the vagi did not, therefore, differentiate between the different afferent nerve fibre groups.

Insufflation of powders. Since the sensory organs being examined might be concerned with the cough reflex, various stimuli which cause coughing were applied to them. One stimulus was the inhalation of powdered talc or starch. These were blown into the trachea and bronchi while afferent nervous activity was being recorded. Of five rapidly adapting tracheal receptors three were clearly sensitized by one or other powder (Fig. 23). After insufflation of the

talc the number of impulses per deflation was greatly increased; the timing of the response was also altered, although the reasons for this are not clear. Four slowly adapting and three intermediate receptors were not appreciably affected by powdered talc or starch.

Irritant gases. The effect of sulphur dioxide and ammonia was observed on a number of receptors. The results with the former are summarized in Table 2.

TABLE 2. The effect of inhaled sulphur dioxide on respiratory mechanoreceptors

Receptor	No.	Sensitized	Sensitized then inhibited	Inhibited	No effect
Slowly adapting bronchial	20	1	2	—	17
Rapidly adapting tracheal	9	1	—	2	6
Intermediate bronchial	15	7	5	—	3
Pulmonary stretch	7	1	3	—	3
Mediastinal	5	—	—	—	5

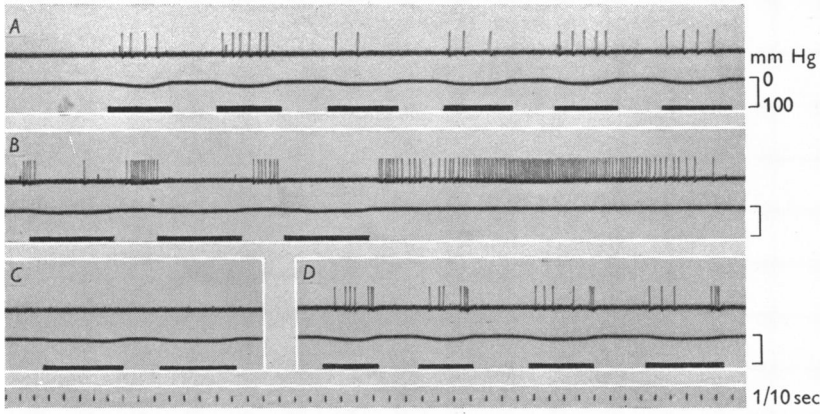

Fig. 24. Cat, 3·1 kg. Chloralose, 60 mg/kg. Effect of inhaled sulphur dioxide on an intermediate type receptor. *A*, six control deflations. Between *A* and *B* sulphur dioxide was blown into the air passages. *B*, three subsequent deflations followed by stimulation of the receptor; *C*, complete inhibition of the ending. Between *C* and *D* the sulphur dioxide was blown out of the air passages. *D*, recovery of activity by the receptor. The periods of deflation are indicated by the wide horizontal lines. Between *A* and *B*: 5 sec. *B* and *C*: continuous. *C* and *D*: 1 min.

Twelve (80%) out of fifteen intermediate endings, three (15%) out of twenty slowly adapting receptors and one (11%) out of nine rapidly adapting receptors were sensitized. No mediastinal endings were affected, but four out of seven pulmonary stretch receptors were sensitized. Of the tracheobronchial receptors, therefore, the intermediate endings were clearly sensitive to sulphur dioxide, while the other two groups were not. The response of an intermediate receptor is illustrated in Fig. 24. The initial change was an alteration in the

pattern of response (cf. Fig. 23) so that the ending fired off *between* deflation stimuli; the receptor suddenly started discharging spontaneously for a second or two (*B*), and was then completely inhibited (*C*). After blowing the sulphur dioxide out of the air passages the receptor recovered its normal activity, giving short bursts of impulses on deflation (*D*). Immediate sensitization of the receptors was more usual.

Ammonia was a less specific stimulant than sulphur dioxide. It almost invariably sensitized pulmonary stretch receptors, was without effect on one rapidly adapting ending and stimulated one intermediate receptor and two out of three slowly adapting receptors.

Anaesthetics. Since 5–10% procaine solution sprayed into the trachea was known to block the cough reflex caused by mechanical stimuli to the trachea, the effect of this drug on tracheobronchial receptors was observed. Five rapidly adapting receptors were completely inhibited; on washing out the trachea with saline and wiping the inside the receptors did not recover, and the cats yielded no more rapidly adapting endings although many slowly adapting, intermediate and mediastinal receptors were still active. Procaine solution was also sprayed into the trachea and bronchi when afferent activity was being recorded from two slowly adapting and one intermediate receptor; these were not affected by the drug.

Ether vapour (7·5–14·5%) completely inhibited nine out of eleven rapidly adapting receptors when the gas was blown into the trachea. Seven out of nine intermediate receptors were also inhibited, but six of these showed a sensitization before the inhibition; this sensitization was not seen with the rapidly adapting receptors. The slowly adapting endings were often partially inhibited (seven out of twelve), but only with stronger concentrations of ether vapour (14·5–21%); complete inhibition was only seen once, and a weak sensitization twice.

Non-vagal nerve fibres; other species. The left recurrent laryngeal nerve was explored for tracheobronchial afferent nerve fibres, before it reached the aortic arch. Fibres from endings of all three types were identified (one slowly adapting, one rapidly adapting and two intermediate). Branches running from the vagus to the sympathetic trunk just below the stellate ganglion have also been examined, and again fibres from the air passages were discovered (three intermediate and two slowly adapting). No extensive investigation of these pathways has been made. Fibre activity from mechanoreceptors situated in the trachea and main bronchi has been recorded in the rabbit and the dog (Dawes & Widdicombe, unpublished).

Mediastinal receptors

Adrian (1933) has reported the existence of receptors which respond to displacement of the mediastinum and to postural changes of the cat's chest; their

nerve fibres ran in the vagus nerves, and they were usually stimulated by inflation of the lungs and by tugging on the trachea. In the experiments described here a large number of these endings have been encountered. A small minority were difficult to distinguish from tracheobronchial receptors, since mediastinal endings may be stimulated by volume changes of the air passages which are large enough to deform the mediastinum, and tracheobronchial receptors may be excited by movements of the mediastinum which also deform the airways. For this reason a rule-of-thumb criterion has been applied; any receptor which was more sensitive to displacement of the mediastinum than to inflation or deflation of the airways or to passage of a catheter down them, has been provisionally classified as a mediastinal receptor.

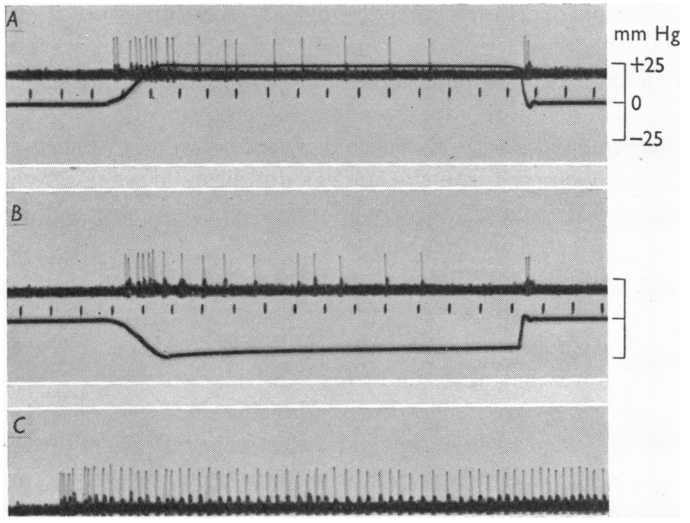

Fig. 25. Cat, 3·3 kg. Chloralose, 60 mg/kg. A mediastinal receptor. *A*, inflation of the air passages; *B*, deflation. The responses are similar to those of intermediate type receptors; *C*, rotation of the cat's thorax causes a slowly adapting response due to mediastinal displacement.

Such endings amount to about one-third of the receptors localized to the airways. The majority of them have been undeniably 'mediastinal'; they could be placed in regions separate from the tracheobronchial tree, and their response to inflation and deflation of the airways was slight compared with that to mediastinal displacement; the latter stimulus always caused a slowly adapting discharge. Those endings around the hila or the trachea were more difficult to define. They often adapted rather rapidly to distension and collapse of the air passages, but the effect of mediastinal displacement clearly distinguished them from the rapidly adapting tracheal endings. Other mediastinal receptors gave a response which was superficially similar to that from inter-

mediate type receptors, sometimes with an additional burst of impulses on release of the deforming stimulus (Fig. 25); these too, were slowly adapting to mediastinal deformation or to thoracic postural changes.

Judging by action potential size and by ease of dissection the mediastinal receptors had relatively large nerve fibres, comparable to the pulmonary stretch fibres and somewhat larger than the tracheobronchial fibres. The vagal trunk was cooled for three mediastinal receptors, and conduction was blocked at 14, 12 and 11° C respectively.

DISCUSSION

The adaptation rates of pulmonary inflation receptors have been considered for two reasons. First, in order to establish that the 'rapidly-adapting pulmonary stretch receptors' (Knowlton & Larrabee, 1946) were tracheobronchial endings; and secondly, to indicate (*contra* Knowlton & Larrabee) that adaptation rate alone does not distinguish between different groups of pulmonary sensory organs. The endings which 'adapted' most rapidly to inflation of the lungs lay in the air passages and the slowly adapting receptors were situated in the pulmonary lobes; no localization of receptors with intermediate adaptation rates to pulmonary distension was made.

The value of the adaptation index is limited. It does not distinguish between the adaptation rates of endings which cease firing within 1 sec, so that stimuli well above threshold must be used and the endings must discharge for 2 sec or more. It is especially dangerous to apply it to receptors which are not being stimulated at constant strength.

A constant volume inflation of the lungs shows a decrease in the intratracheal pressure after the inflation is complete; this is usually assumed to be due to slow continued expansion of pulmonary tissue. Accompanying changes in the calibre of the air passages have not been measured, but there may be a narrowing of the lumen as the intratracheal pressure drops; this would depend on the viscoelastic properties of the trachea and bronchi relative to those of the lungs. This probably explains the fact that a *constant pressure* inflation of the trachea and bronchi caused a more slowly adapting discharge from tracheobronchial receptors than a *constant volume* inflation of the lungs; and that pulmonary deflation excited the receptors at a more slowly adapting rate than inflation.

Three types of tracheobronchial receptor have been described; they have been distinguished on the basis of their localization and the responses to various mechanical and chemical stimuli; their rates of adaptation have been used as a convenient label. In Table 3 are listed the five types of respiratory receptor whose afferent nerve fibres have been investigated.

Rapidly adapting tracheal receptors and the mechanical cough reflex. The following observations suggest that the rapidly adapting tracheal endings were

afferent organs for the mechanical cough reflex; details of the latter in the cat have been given elsewhere (Widdicombe, 1954):

(1) They were stimulated by light touch from within the trachea; the same stimulus caused coughing.

(2) Distension and collapse of the airways excited the endings and caused an expiratory effort; the order of effectiveness of stimuli (release of deflation, deflation, inflation and release of inflation) was the same for both the receptors and for the reflex, and the time relations and thresholds fitted closely.

(3) The localization of the endings corresponded to the pattern of sensitivity of the reflex; for example, the carina was the most sensitive area for eliciting coughing with a mechanical stimulus and the rapidly adapting receptors were concentrated there.

TABLE 3. Afferent nerve fibres from the thoracic respiratory system

Receptor	Localization	Stimulus	Respiratory response	Vagal temperature to block (° C)	Authors
Pulmonary stretch	?Pleura ?air passages	Pulmonary inflation	Inspiratory inhibition	8–19	Adrian (1933)
Slowly adapting bronchial	Trachea and bronchi	Inflation and deflation	Inhibition; broncho-constriction	7–13	This paper
Rapidly adapting tracheal	Trachea	Mechanical stimuli	Cough; broncho-constriction	7–15	This paper
Intermediate bronchial	Trachea and bronchi	Mechanical and chemical irritants	Cough; broncho-constriction	7–10	This paper
Mediastinal	Mediastinum	Mediastinal deformation	Unknown	—	Adrian (1933)

(4) The endings were sensitized by powdered talc, which was a mechanical stimulus to coughing.

(5) Ether vapour paralysed the receptors, and also abolished the mechanical cough reflex by an action on the afferent side of the arc.

(6) The receptors were blocked by 5–10% procaine solution sprayed into the trachea; this inhibited the reflex.

(7) Afferent nerve fibres from the receptors were blocked at temperatures from 7 to 15° C; the cough reflex was blocked by vagal cooling to 8–15° C.

(1), (4) and (5) suggest that the endings lay close to the tracheal epithelium, and this is supported by the fact that an endotracheal mechanical stimulus was more effective than one from outside the airway. Larsell (1921, 1922) has described subepithelial receptors in the trachea and bronchi of a number of species (but not, apparently, the cat) which may be endings for the cough reflex. They had small knoblike terminals, covered a wide area and had large afferent nerve fibres; from their appearance he concluded that they were

tactile organs. They were concentrated at the carina and the points of bifurcation of the bronchi. Elftmann (1943) found similar endings in the puppy and the kitten. Larsell & Burget (1924) investigated the cough reflex in the rabbit, and decided that it was produced through the subepithelial receptors. If these receptors are present in the cat they may well be those examined here. If this is so, it is the first instance of the identification of a respiratory receptor, its afferent nerve fibre and its reflex effect.

The central action of these receptors is to cause coughing. The exact pattern of the response depends on the type and depth of anaesthetic (Widdicombe, 1954) but the primary change is a strong expiratory effort associated with bronchoconstriction. Since the same stimuli cause the expiration and the bronchoconstriction it may be supposed that both motor responses are caused by the same sensory receptors. In the cat the reflex arc for coughing may include a small afferent component in the sympathetic nervous system, and tracheobronchial nerve fibres have been found running there.

In their work on the respiratory effects of electrical stimulation of the vagus nerve, Wyss & Rivkine (1950) described a fibre group of Aβ size ('like tactile fibres') which caused either a weak inspiratory response with a low rate of stimulation or a pure expiratory effect with increased frequency of stimulation. They concluded that a single set of afferent fibres was responsible for these opposite effects, and that they were somewhat smaller than the Hering-Breuer inhibitory fibres (group Aα). While such stimulation experiments are difficult to interpret, it is tempting to suggest that Wyss & Rivkine were stimulating afferent nerve fibres for the cough reflex. The latter are somewhat smaller than the pulmonary stretch fibres (to judge from ease of dissection, action potential size and the temperature needed to block conduction) and their reflex action is to cause expiration, inspiration or both. In addition, Schroeder (1951) has shown that in the unanaesthetized dog with exteriorized vagi the cough afferent fibres are very sensitive to electrical stimuli, although the conditions of his experiments did not allow him to assess the fibre size.

Intermediate endings and the chemical cough reflex. The tracheobronchial receptors with intermediate adaptation rates had several properties which distinguished them from the other two types of receptor; in particular they were the only endings which were consistently sensitized by sulphur dioxide, and at first this observation was rather puzzling. The receptors which seemed to be responsible for the cough reflex (rapidly adapting tracheal receptors) were not affected by sulphur dioxide, which caused coughing. The reason for this discrepancy became clear after a study of the cough reflex; it was shown that the afferent nervous pathways for the mechanical and chemical cough reflexes were different (Widdicombe, 1954), and it is concluded that the intermediate receptors were sensory organs for the chemical cough reflex. The few experiments in which the vagi were cooled were consistent with this conclusion.

The central action of these receptors can be deduced from the reflex effects of sulphur dioxide. The coughing caused by this gas usually started with an expiratory effort, although there were more prominent inspiratory gasps than with a mechanical stimulus; the exact pattern of the motor response must depend on the central mechanisms of coughing (about which little is known) as much as the afferent pathways. Sulphur dioxide also caused bronchoconstriction, but this has not been analysed; if the gas acts in a similar way to ammonia there may be a reflex component to this bronchoconstriction (Banister, Fegler & Hebb, 1949). As with mechanical stimuli, sulphur dioxide acts via the sympathetic nervous system as well as the vagus nerves, and the receptors of the intermediate group have been shown to send fibres to the sympathetic trunk.

The histology of these receptors is not clear. Subepithelial endings were found by both Larsell (1921, 1922) and Elftmann (1943) throughout the bronchi, which are relatively insensitive to mechanical stimuli. The intermediate receptors all responded to mechanical stimuli (which was their means of detection) and the reflex effect of both types of stimuli must be coughing. Probably it is necessary to excite a large number of endings before coughing is caused; a gas would penetrate throughout the lungs whereas a mechanical stimulus would be far more localized and therefore less effective. In this respect the intermediate receptors differ from the rapidly adapting tracheal receptors for which a localized stimulus causes vigorous coughing.

Slowly adapting bronchial receptors. These were the largest group of tracheobronchial receptor discovered. They resembled the 'deflation receptors' of Adrian (1933) in that they were slowly adapting to deflation of the lungs. Adrian stated that 'it was indeed likely that some of the endings which react to suction are those which react normally to inflation. But there is no doubt that deflation calls a new set of endings into play as well.' In the investigation of over 400 respiratory nerve fibres only seven have been found which responded to deflation but not to inflation of the lungs (apart from the rapidly adapting tracheal endings). Knowlton & Larrabee (1946), in an analysis of ninety receptors, did not report any which were not excited by pulmonary distension. It seems probable that Adrian did not use sufficiently large inflations, since many of the airway receptors have very high thresholds to inflation of the lungs, and that his 'deflation endings' were really slowly adapting bronchial receptors. If this is so, specific deflation receptors have yet to be found.

Distension and collapse of the larger air passages of the cat caused a slowing of respiration (Widdicombe, 1954); this was similar to the reflex described by Hammouda & Wilson (1936) for the dog. The reflex thresholds were -10 to -30 mm Hg for deflation, and 25 to 50 mm Hg for inflation. The majority of the slowly adapting receptors would be excited by these pressures, but since they were applied to only a small part of the tracheobronchial tree a large

stimulus might be required for a reflex response. It is more difficult to explain the fact that inflation had a higher reflex threshold than deflation; no such difference was seen with the slowly adapting receptors. Maintained inflation and deflation of the air passages may also cause reflex bronchoconstriction. Apart from these reflexes and coughing, the only reflex response to volume changes of the airways was an acceleration of respiration caused by large negative pressures (threshold -50 to -90 mm Hg). It is probable that the slowly adapting receptors were responsible for the respiratory slowing and possibly the bronchoconstriction; it seems unlikely that the accelerator reflex was mediated by these endings, for not only is the response opposite in nature to the inhibitory reflex, but it could not be produced at all by large inflations of the air passages, but only by deflations.

Histological work on the sensory organs in and around the airways suggests that there are only three main types of receptor. The subepithelial endings which are probably responsible for the cough reflex; smooth muscle spindles and perichrondrial receptors (Larsell, 1921, 1922; Elftmann, 1943). All these endings are said to have 'large' or 'coarse' nerve fibres. If there are no other types of receptor in the bronchial walls it is most likely that the slowly adapting endings were smooth muscle spindles. The following observations support this view:

(1) The receptors were more sensitive to stretch of the bronchial walls than to touching the epithelium.

(2) They were concentrated at the bronchial bifurcations where the greatest area of bronchial wall and the greatest amount of smooth muscle lies.

(3) They were not affected by intratracheal solutions (procaine) and gases (sulphur dioxide and ether vapour) which may be because they lay deep to the epithelium.

(4) Their stretch/response curves were consistent with the view that they lay in the tracheobronchial walls.

Other reflexes. The 'rapidly adapting pulmonary stretch receptors' have been supposed to cause the Hering-Breuer deflation reflex and Head's paradoxical response (Head, 1889; Larrabee & Knowlton, 1946); both reflexes lead to inspiratory activity, the appropriate stimuli being forced deflations and large inflations of the lungs respectively. The 'rapidly adapting' receptors lie in the tracheobronchial tree, but there is no evidence that either the deflation reflex or the paradoxical effect can be elicited from there. The cough reflex often includes an inspiratory component, but this follows the expiratory phase of coughing; the 'accelerator reflex' from the bronchi is only seen when high negative pressures are applied to the air passages, and never with positive pressure. It seems very unlikely, therefore, that the slowly adapting bronchial receptors are responsible for either the Hering-Breuer deflation reflex or the paradoxical response of Head.

The role of tracheobronchial reflexes in normal respiration. The part played by the tracheobronchial receptors in the respiratory cycle can be assessed from their pressure thresholds. In quiet breathing the bronchi show changes in diameter (Ellis, 1936), as they do in coughing (Franklin & Janker, 1938). In eupnoeic inspiration about half the slowly adapting bronchial endings will be stimulated; these receptors probably slow the respiratory cycle. They may, therefore, have a similar effect to the pulmonary stretch receptors. Furthermore, bronchial distension also causes reflex bronchoconstriction in the lobes of the lung, and this bronchoconstriction will cause an increased resistance to inflation and therefore a greater intrapleural pressure for a constant tidal volume; the larger pressure drop across the walls of the extrapulmonary air passages will lead to still greater bronchoconstriction—a 'positive feed-back system'.

The rapidly adapting and intermediate endings can play very little part in eupnoea, but in hyperpnoea, coughing, sneezing and gasping an appreciable number of them will be stimulated. It is difficult to decide what effect these will have on respiration, for their central action is to cause coughing, and this may include both inspiratory and expiratory components. The exact response will depend on central as well as afferent nervous factors. Although the response of the cough receptors to volume and pressure changes in the air passages has been emphasized, they are also sensitive to stimulation by a foreign body in the airways. An endotracheal catheter may excite only a few of the rapidly adapting receptors, while collapse of the trachea excites many, but the reflex responses may be of similar size. If the receptors are subepithelial then deformation of the epithelium (rather than a change in tracheobronchial volume *per se*) would be the natural stimulus; this would explain why many of the pressure thresholds were beyond physiological limits, for the sufficient change in tracheobronchial volume was that which would deform or ruck-up the epithelium where the receptor lay.

Threshold pressure measurements were made on an isolated portion of the extrapulmonary airways. In the intact animal the changes in shape of the air passages are controlled not only by the pressure drop across their walls, but also by the degree of distension of the pulmonary lobes. The intrapulmonary bronchi, for example, are extended during inflation of the lungs, and this must influence considerably their diameter. It is not clear how much the shape of the extrapulmonary air passages is affected by distension and collapse of the lungs, but it is possible that the pressure threshold of the receptors given above do not apply precisely to intact cats. They would apply, however, to the experiments on tracheobronchial reflexes with similar operative conditions.

A further point requires mention. Receptors in the walls of the tracheobronchial tree may respond not only to changes in diameter produced mechani-

cally but also to alterations in smooth muscle tone. Preliminary experiments (unpublished) show that the response of the slowly adapting receptors is affected by the tone of the bronchial musculature. Thus an active bronchoconstriction may influence the tracheobronchial reflexes both by a change in the sensitivity of the receptors lying in the bronchi, and by altering the resistance to inflation of the lungs. It would be interesting to know if these mechanisms were involved in clinical conditions such as asthma and pulmonary congestion when bronchial tone and pulmonary resistance to inflation may be greatly increased.

SUMMARY

1. Respiratory receptors which responded to inflation of the lungs of the cat have been investigated by recording action potentials from their afferent nerve fibres. The receptors which gave the most 'rapidly adapting' responses to maintained pulmonary distension lay in the tracheobronchial tree; their rapid adaptation was often a mechanical artifact.

2. Three types of mechanoreceptor were identified *in the tracheobronchial tree*. They could be distinguished by their responses to various mechanical and chemical stimuli.

3. About half the tracheobronchial receptors adapted slowly to distension and collapse of the air passages. They were found throughout the tracheobronchial tree, being concentrated at the points of bronchial branching. It is suggested that they are smooth muscle spindles, and centrally they may cause respiratory slowing and bronchoconstriction.

4. About a quarter of the tracheobronchial endings gave very short discharges on inflation and on deflation of the trachea, and also on restoration of atmospheric pressure. They are probably subepithelial endings, and cause coughing in response to mechanical stimuli.

5. The remainder of the receptors gave a short discharge on inflation and deflation of the air passages. They were found throughout the trachea and main bronchi, and were sensitized by noxious gases. They are thought to be cough receptors for chemical as well as mechanical stimuli.

6. Mechanoreceptors lying in the mediastinum were also encountered; their central action is not known.

7. The role of tracheobronchial receptors in quiet respiration and in coughing has been discussed.

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