MUSCULAR, BRONCHOMOTOR AND CARDIOVASCULAR REFLEXES ELICITED BY MECHANICAL STIMULATION OF THE RESPIRATORY TRACT

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SUMMARY

1. The effects of mechanical stimulation in the nose, epipharynx, laryngopharynx and tracheobronchial tree, and of chemical irritation of the nasal mucosa, were studied on various somatic and autonomic functions in cats.

2. Action potentials were recorded from the diaphragm and rectus abdominis muscles of spontaneously breathing cats, and from the phrenic and lumbar nerves of paralysed, artificially ventilated cats. Expulsive processes such as sneezing and coughing evoked from the nasal, laryngo-pharyngeal and tracheobronchial mucosae were characterized by strong diaphragmatic and abdominal expiratory discharges; synchronous discharges in these antagonistic respiratory muscles and their motoneurones often occurred especially during laryngopharyngeal stimulation of coughing.

3. The 'aspiration reflex' elicited from the epipharynx was characterized by brief bursts of high-frequency activity in the phrenic nerve and diaphragm, and was usually not followed by any expiratory activity in the rectus abdominis or its motoneurones.

4. In paralysed, artificially ventilated cats stimulation of the laryngeal and tracheobronchial regions caused large increases both in total lung resistance and in tracheal constrictor nerve fibre activity, indicating reflex tracheo-bronchoconstriction; similar stimulation of the epipharyngeal and nasal mucosae decreased both total lung resistance and tracheal constrictor nerve fibre activity, indicating reflex bronchodilation.

5. In paralysed cats, stimulation of each of the four sites in the respiratory tract caused a reflex increase in systemic blood pressure, the largest hypertensive response coming from the epipharynx. Nervous activity in cervical sympathetic efferent fibres was increased by the stimulations, especially those of the epipharyngeal and laryngopharyngeal regions.

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6. There was good correlation in time and magnitude between the changes in total lung resistance and in bronchoconstrictor fibre activity, and also between the changes in blood pressure and in efferent sympathetic discharge, although the mechanical changes lagged behind the nervous ones.

7. In anaesthetized, spontaneously breathing cats stimulation of the respiratory tract evoked large variations in blood pressure accompanying the spasmodic respiratory efforts, probably by mechanical effects.

INTRODUCTION

Defensive reflexes from the respiratory tract, which are important from the physiological as well as from the clinical point of view, have been extensively studied in the past (Bucher, 1952, 1958; Jiménez-Vargas, Miranda & Mouriz, 1962; Widdicombe, 1954, 1964; Tomori, 1965); nevertheless, many aspects of their mechanisms are unclear. In addition to the more obvious respiratory acts such as coughing, sneezing and reflex closure of the glottis, there may also be important pathological reactions such as laryngospasm and bronchospasm. Moreover, two new types of respiratory reaction, evoked from the laryngopharyngeal and epipharyngeal regions of the cat, have been recently described and termed 'laryngo-pharyngeal cough' and the 'aspiration reflex' respectively (Ivančo & Korpáš, 1954; Ivančo, Korpáš & Tomori, 1956; Tomori, 1962, 1965; Tomori & Korec, 1964), or the 'pharyngeal respiratory reflexes' (Takagi, Irwin & Bosma, 1966). These reflexes may have the same underlying mechanism as the 'accelerator respiratory reflex' elicited by stimulation of the palatopharyngeal mucosa or the corresponding afferent nerves (Teitelbaum & Ries, 1934, 1935; Teitelbaum, Ries & Lisansky, 1936). The reflexes may contribute to such processes as sniffing, gasping, retching and hiccough; and their absence could be important in the respiratory control of tracheotomized subjects (Takagi *et al.* 1966); they may be involved in olfactory nervous discharges of purely mechanical origin (Adrian, 1942, 1951; Ueki & Domino, 1961).

Electrophysiological analysis, presented in this paper, is an important part of any detailed investigation of the mechanisms of defensive reflexes from the respiratory tract, and is complementary to results derived from measurements of other parameters such as intrapleural, intratracheal and intra-abdominal pressure changes, glottis calibre and airflow rates and respiratory volume changes (Tomori, Korpáš & Ivančo, 1957; Tomori & Korec, 1964; Tomori, 1965, 1966 *a, b*).

We have used the same type of mechanical stimulation to compare qualitatively and quantitatively the different respiratory reflexes. The

reflex responses have been assessed by (1) electromyography and electro-neurography of the main respiratory muscles and their motoneurones, (2) measurement of reflex changes in total lung resistance and lung compliance with simultaneous recording of action potentials in parasympathetic (constrictor) fibres to the trachea and (3) measurement of reflex changes in systemic blood pressure and analysis of discharges in cervical sympathetic efferent fibres.

METHODS

Twenty cats (weight range, 2·0–3·8 kg) were anaesthetized with pentobarbitone sodium (Nembutal, 32 mg/kg), given intraperitoneally. The trachea was cannulated, usually between the 4th and 5th cartilages; in experiments involving recording of action potentials from tracheal nerves, cannulation was performed just below the cricoid cartilage. An opening (about 1·5 cm long) was made in the right pharyngeal wall, entering just behind the plica pharyngopalatina, to enable mechanical stimulation of the epipharyngeal, mesopharyngeal or epiglottal mucosa with direct observation. Stimulation of the nasal, laryngeal, laryngopharyngeal or tracheobronchial mucosa was achieved through the nares, the tracheal opening above the tracheal cannula, or a small hole in the ventral wall of the trachea, respectively.

Mechanical stimulation was with a thin nylon fibre (0·5 mm diameter). Repeated gentle contacts with the mucosa were made at 1–3 times per second for 10–20 sec. As far as possible the force, duration and repetition rate were identical for all sites in any experiment. In the case of tracheobronchial stimulation, care was taken to ensure that the tracheal opening did not allow a leak of air (by provision of a tissue flap) and the nylon fibre was inserted to and beyond the carina. Signal marks from a foot switch were made on the photographic paper for each touch of mechanical stimulation. Ammonia was administered by bubbling 5 ml. of air through ammonia solution in a conical flask and then into the nose. Occasionally ammonia vapour was also injected into the tracheal tube connexions during an inspiratory effort or during the inflation phase of a pump stroke. A concentration was chosen adequate to cause vigorous but not excessive sneezing or coughing.

The following variables were recorded. Systemic arterial blood pressure from a femoral artery with a capacitance manometer (Southern Instruments) through a polyethylene catheter, the undamped natural frequency of the catheter and manometer system being 22·7 c/s by the method of Hansen (1949); mean blood pressure was obtained from a resistance-capacitance smoothing circuit with 2 sec time constant; intrapleural pressure with an air-filled capacitance manometer (Southern Instruments, range 0–50 mm Hg) through a small polyethylene catheter tied into one of the lower intercostal spaces on the right side, the undamped natural frequency of the system including catheter being 133 c/s; transpulmonary pressure (tracheal minus intrapleural pressure) with an air-filled capacitance differential manometer (Southern Instruments, range 0–50 mm Hg); air flow and tidal volume with a Fleisch pneumotachograph and integrator (Godart); and tidal CO_2 % with an infra-red gas-analyser (Beckman LB-1).

Electromyograms were recorded by means of double twisted silver wire elecrodes tied into the abdominal surface of the diaphragm through a small mid line abdominal incision and into the lateral part of the right rectus abdominis muscle through a small incision of the skin. Electroneurograms were recorded alone or in various paired combinations from efferent single or few-fibre preparations of the following nerves: phrenic, first lumbar, tracheal and cervical sympathetic nerves. Nerve strands were teased out and placed on two platinum electrodes in a dissecting trough (usually 2×1 cm by 0·5 cm deep) containing paraffin oil. Action potentials were amplified with conventional amplifiers (Tektronix 122)

All recordings were from nerves of the right-hand side of the body. Variables were recorded on a twelve-channel ultraviolet recorder (Honeywell UV-31) or photographed from a five-beam oscilloscope (Tektronix 551) with a modified Cossor camera.

Total lung resistance was measured by the subtractor method of Mead & Whittenberger (1953), as modified in several other studies (e.g. Nadel & Widdicombe, 1962 *a*; Colebatch, Olsen & Nadel, 1966; Green & Widdicombe, 1966). This involves displaying the component of transpulmonary pressure required to overcome resistance to flow on the vertical axis of an oscilloscope (Tektronix 502) and tracheal air flow on the horizontal axis to give 'loops'. The pressure required to overcome the 'elastic resistance' of the lungs is assumed to have a linear relation to lung volume and a voltage proportional to lung volume is subtracted from the total transpulmonary pressure signal by passing the volume signal to earth through a potentiometer, the variable centre tap of which is connected to the horizontal axis of the oscilloscope. If the correct proportion of the volume signal is chosen, the result of subtraction is a voltage indicating the pressure producing flow, the relation of which to flow (the slope of the 'loops') is proportional to total lung resistance and can be measured from a protractor mounted on the front of the oscilloscope tube. The accuracy and validity of this method have been discussed elsewhere (Mead & Whittenberger, 1953; Nadel & Widdicombe, 1962 *a*; Green & Widdicombe, 1966). Resistance values include that of the tracheal cannula, the average value of which was 0·05 cm H_2O/l./min.

Lung compliance, essentially 'dynamic compliance' (Mead, 1961), was assessed as the ratio of tidal volume to transpulmonary pressure difference at points of zero air flow, taken from the ultra-violet paper record. At the same time, the readings of the subtraction potentiometer used for assessment of tidal lung resistance were repeatedly recorded, and appropriate calibrations allowed these values to be converted to lung compliance.

Throughout most experiments transpulmonary pressure and tracheal air-flow were also recorded on a tape recorder (Thermionic Products T 3000), with subsequent analysis of the variables (if necessary played back at a slower speed) to allow confirmation and more accurate assessment of values of lung resistance and compliance, and photographic records of 'resistance loops' (e.g. Fig. 9).

Except for electromyographic experiments and a few others with spontaneously breathing animals, cats were paralysed with gallamine (40 mg, I.V.; in two cases with succinylcholine, 5 mg, I.V.) repeated as necessary, and artificially ventilated with a pump volume that kept the end-tidal CO_2 % close to the preparalysis level. The pump frequency was 20–30 cycles/min. Depth of anaesthesia was judged by respiratory movements and reflex responses during periods (approximately hourly) when the effects of the paralytic drugs had declined, and supplementary doses of pentobarbitone (10–20 mg) were given when necessary, before further paralysis.

Unless otherwise stated, results for respiratory variables are expressed as peak responses compared with previous control values averaged over 5–10 respiratory cycles.

RESULTS

Figure 1 shows the changes in blood pressure, mean blood pressure, intrapleural pressure and tidal CO_2 % caused by mechanical stimulation of the various sites. The response from the epipharynx, a series of rapid inspiratory efforts without accompanying active expiratory efforts (the 'aspiration reflex'), may be particularly noted. The subsequent results deal with analysis of the mechanisms of these four types of response and of that due to insufflation of ammonia into the nose.

Electromyography of respiratory muscles

Electromyograms (EMGs) of the diaphragm (inspiratory) and of the rectus abdominis (expiratory) were obtained in eight spontaneously breathing cats. Representative records at slow paper speed of the course of the sneeze, cough and aspiration reflexes are given in Fig. 2. They show a
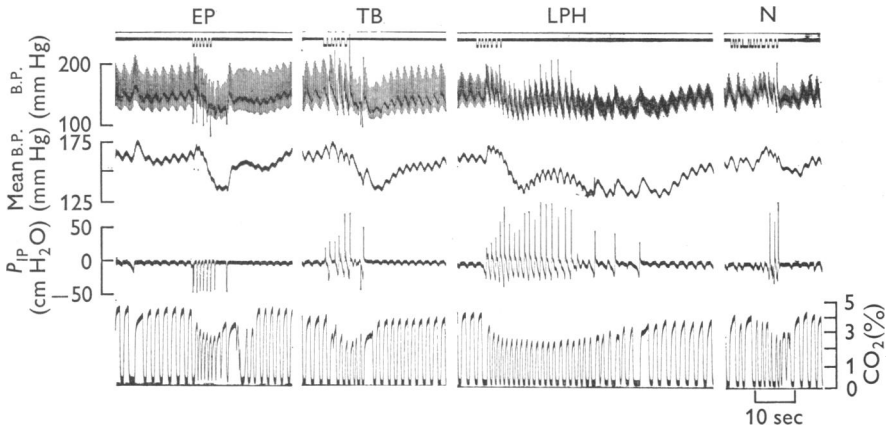

Fig. 1. Changes in systemic arterial blood pressure (B.P.), mean blood pressure (mean B.P.), intrapleural pressure (P_{IP}) and tidal CO_2 % caused by mechanical stimulation of the epipharyngeal (EP), tracheobronchial (TB), laryngopharyngeal (LPH) and nasal (N) mucosae, in an anaesthetized spontaneously breathing cat. Signals for stimulation are at the top of the record. For description see text.

much intensified electrical activity of the diaphragm during these reflexes, compared with the control eupnoeic breaths immediately before, increased expiratory muscle activity for the sneeze and two cough reflexes, with overlap between the inspiratory and expiratory discharges, and the absence of expiratory muscle activity for the epipharyngeal reflex. Figures 3, 4 and 5 illustrate the course of single inspiratory–expiratory cycles of the reflexes from high-speed records (30 cm/sec). During sneezing (Fig. 3) and coughing (Fig. 4) the strong inspiratory discharges in the diaphragm are followed and not infrequently also accompanied by strong activity in the expiratory muscles. In the aspiration reflex (Fig. 5) the electrical activity of the expiratory muscles is usually similar to that during eupnoeic respiration, namely, very weak or absent.

Clear electrical activity occasionally appeared in the abdominal muscle EMG during activation of the epipharyngeal reflex if the nylon fibre, during its insertion or removal, accidentally touched the mucosa of the epiglottis or of the mesopharynx. In these circumstances a single blast of laryngopharyngeal cough, characterized by electrical activity in the expiratory muscles and a clear increase in intrapleural pressure, interrupted

the usual pattern of the aspiration reflex. In one cat (male, 3·8 kg) from
the total number of eight the aspiration reflex was always accompanied
by a small but clear activity in the rectus abdominis.

In an attempt to make an approximate quantitative evaluation of
electromyographic activity of different respiratory reflexes, we counted
from high-speed records (30 cm/sec) the numbers of action potentials in
the diaphragm and abdominal muscle EMGs, and also measured the dura-
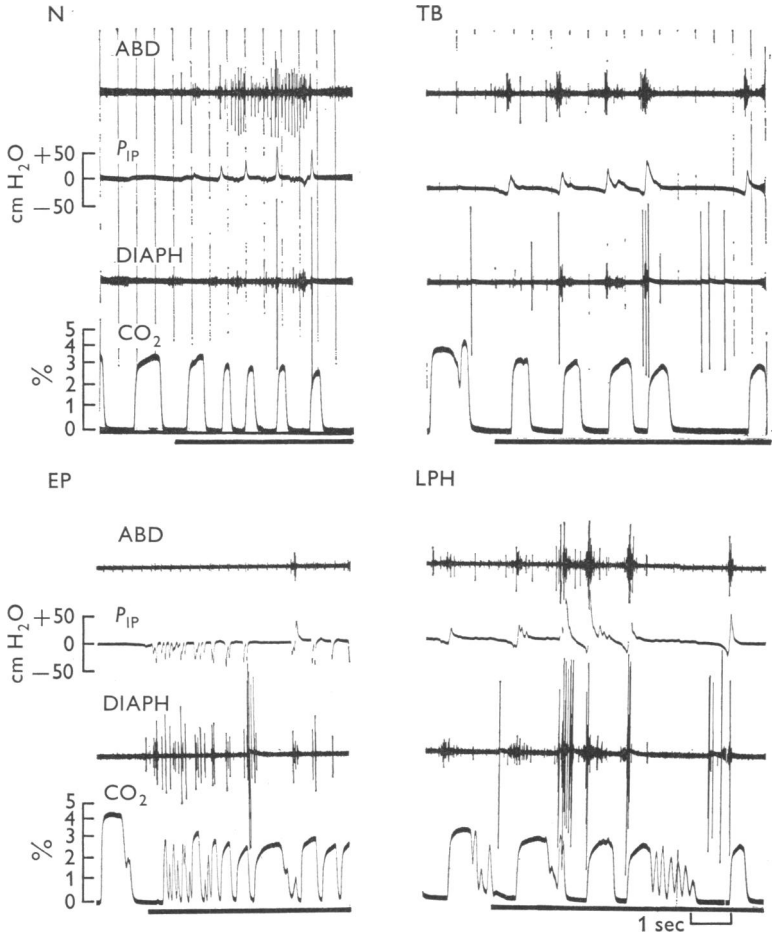tion of the activity of muscles during the inspiratory and expiratory

Fig. 2. Changes in abdominal (ABD) and diaphragmatic (DIAPH) electromyo-
grams, intrapleural pressure (P_{IP}) and tidal CO_2% during sneezing evoked from
the nose (N), coughing from the tracheobronchial (TB) and laryngopharyngeal
(LPH) regions, and the aspiration reflex from the epipharynx (EP) in an anaes-
thetized spontaneously breathing cat. The black bars at the bottom of the records
indicate the periods of repetitive mechanical stimulation.
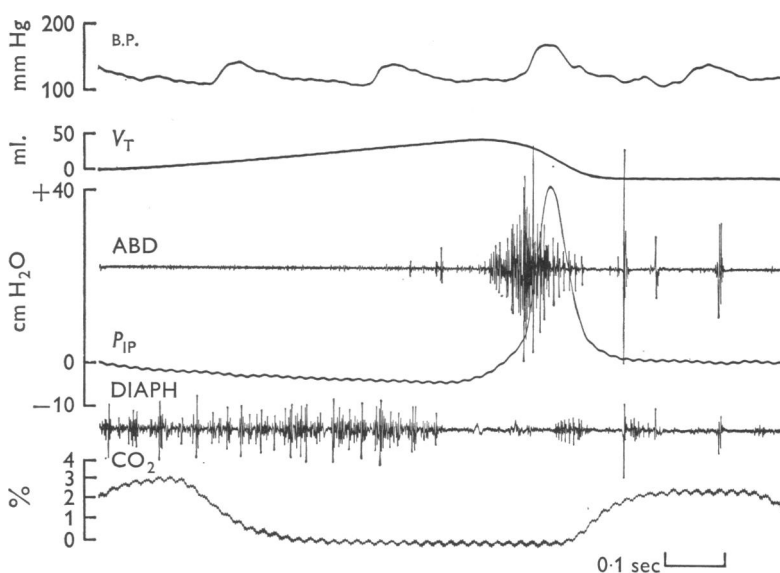
Fig. 3. Changes in abdominal (ABD) and diaphragmatic (DIAPH) electromyograms, blood pressure (B.P.), tidal volume (V_T), intrapleural pressure (P_{IP}) and tidal CO_2 % during a single inspiratory–expiratory cycle of sneezing in an anaesthetized spontaneously breathing cat.
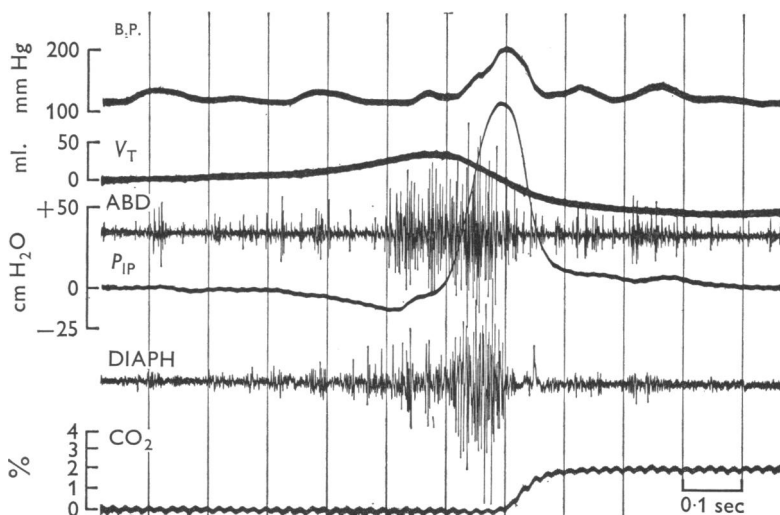

Fig. 4. Changes in abdominal (ABD) and diaphragmatic (DIAPH) electromyograms, blood pressure (B.P.), tidal volume (V_T), intrapleural pressure (P_{IP}) and tidal CO_2 % during a single inspiratory–expiratory cycle of laryngopharyngeal coughing in an anaesthetized spontaneously breathing cat.
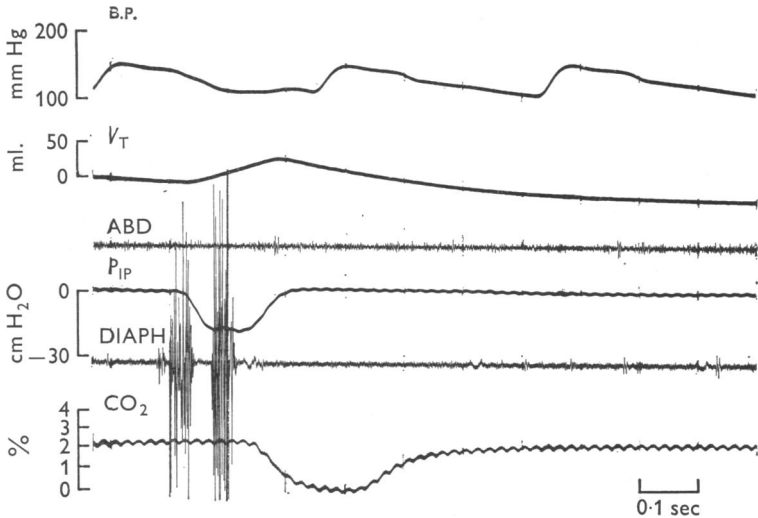
Fig. 5. Changes in abdominal (ABD) and diaphragmatic (DIAPH) electromyograms, blood pressure (B.P.), tidal volume (V_T), intrapleural pressure (P_{IP}) and tidal CO_2 % during a single inspiratory–expiratory cycle of the aspiration reflex in an anaesthetized spontaneously breathing cat.
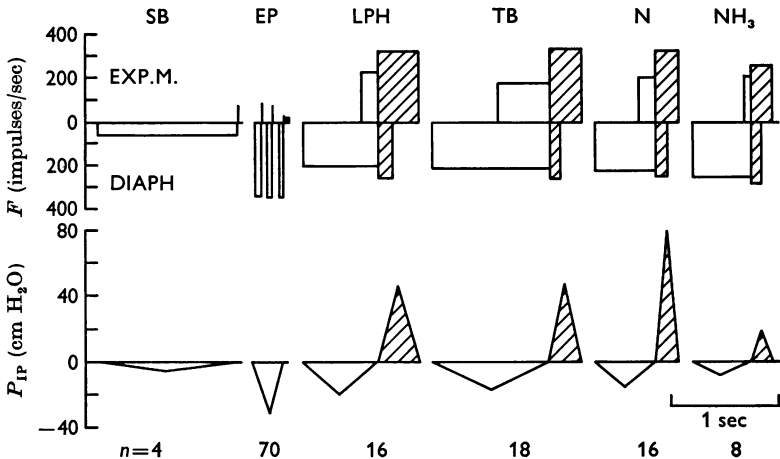
Fig. 6. Electromyographic activity of the diaphragm and the abdominal muscles (above EXP.M.) and maximum intrapleural pressure changes (below) during inspiratory and expiratory phases of reflexes elicited by mechanical stimulation of the epipharynx (EP), the tracheobronchial (TB) and laryngopharyngeal (LPH) regions, the nose (N) and by intranasal insufflation of ammonia (NH_3). SB = spontaneous breathing. EMG values are means from eight cats, with action potential frequencies averaged over the inspiratory and expiratory periods of discharge. Intrapleural pressure changes give peak inspiratory and expiratory changes from the same experiments. The unshaded blocks represent activity during the inspiratory phase and the shaded blocks activity during the expiratory phase; timing was derived from the tidal volume record.

phases of the various reflex responses, taking the tidal volume change as an indication of inspiratory–expiratory transition. Figure 6 summarizes the results, which are presented as if the discharges were of uniform average frequency in the different phases of respiration; one averaged inspiratory–expiratory cycle only is shown diagrammatically for each reflex, except the aspiration reflex where three sequential inspiratory efforts are averaged. The electrical activity of the diaphragm was much greater in all the reflex reactions compared to previous eupnoeic breathing. The activity of the abdominal expiratory muscle was strong during expulsive processes such as coughing and sneezing, but virtually absent in quiet respiration and in the aspiration reflex. Figure 6 also illustrates diagrammatically the overlap of inspiratory and expiratory muscle activity in the former reflexes.

Unlike those of the other reflexes, the inspiratory phase of the aspiration reflex consisted mostly not of one strong single inspiratory effort, but of a set of two (in 74 % of cases) or three (19 %) rapid and brief inspiratory efforts, characterized by irregularities in the inspiratory intrapleural pressure swing, and by separate bursts of activity in the EMGs of the diaphragm (Figs. 5 and 6) and also in electroneurograms (ENGs) of the phrenic nerves, as will be discussed later (Fig. 7). The sniff-like inspiratory efforts lasted from 30 to 66 msec and were repeated at frequencies of 6–12 per second within the inspiratory phase, the values being obtained from the EMG records on fast-moving paper. The frequency of inspiratory efforts was thus far greater than and did not coincide with the frequency of the mechanical stimulations, which was usually 1–3 touches/sec, although the nylon fibre was left in the epipharynx and may have made contact with other receptors. The number of impulses and the duration of successive bursts slowly decreased stage by stage, while the intervals between bursts increased (Fig. 6). The time delay of intrapleural pressure swing after the beginning of the inspiratory EMG discharges of the aspiration reflex was about 20 msec.

Electroneurographic analysis of respiratory motoneurones

The reflexes were further studied after paralysis and during artificial ventilation of the cats, by analysis of the ENGs of single or few-fibre preparations of the phrenic and the first lumbar nerves carrying efferent impulses to inspiratory and expiratory muscles respectively. In these conditions the neuromuscular responses would not be modified by changes in proprioceptive afferent discharge, such as from muscle spindles and tendon organs, as must have occurred in the experiments with EMG recordings described above. Representative records and the average results of measuring impulse frequencies are given in the Figs. 7 and 8. These show that all the reflexes were characterized by increases of phrenic

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activity compared with that in control ventilation and that the phrenic nerve response to epipharyngeal stimulation in the paralysed cat was similar in pattern to the diaphragmatic discharges in spontaneously breathing animals. Furthermore, the expulsive reflexes from the nose and lower
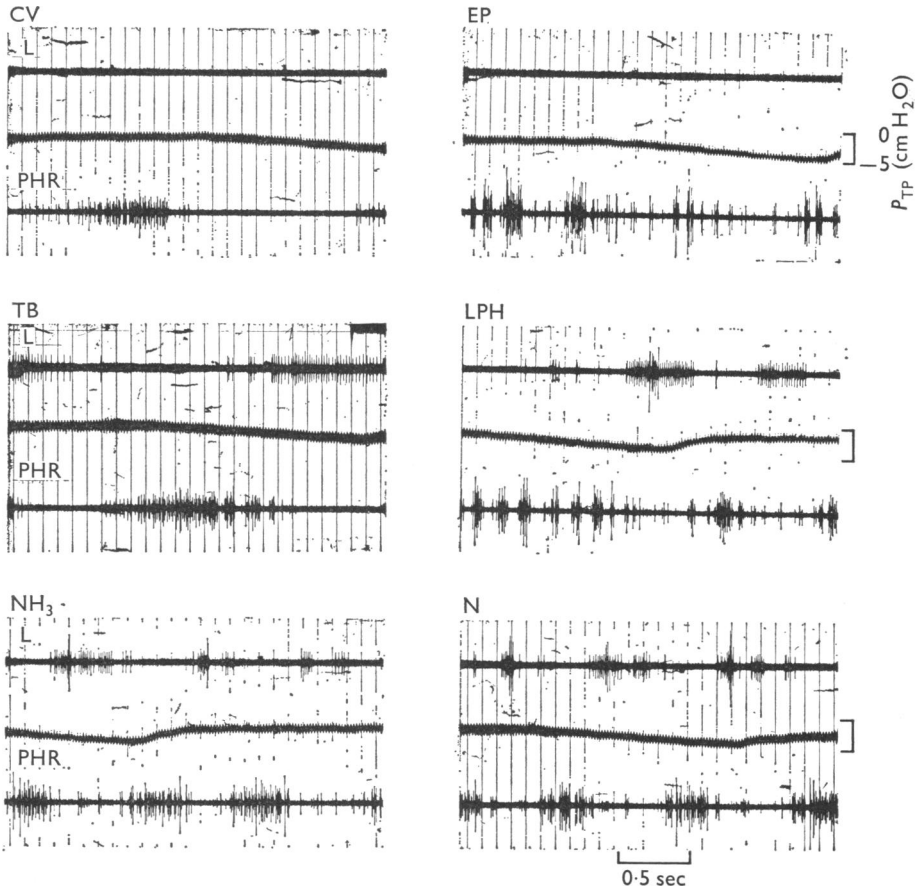

Fig. 7. Records of efferent impulses in lumbar (L) and phrenic (PHR) nerve fibres during mechanical stimulation of the epipharyngeal (EP), laryngopharyngeal (LPH), tracheobronchial (TB) and nasal (N) mucosae, and during intranasal insufflation of ammonia (NH_3) in a paralysed artificially ventilated cat. Middle trace: transpulmonary pressure (P_{TP}). CV = control record without respiratory tract stimulation.

respiratory tract were characterized by strong expiratory motoneurone activity, which was absent in control ventilation and in the aspiration reflex. As with the EMG results, this expiratory discharge frequently overlapped the inspiratory activity (Fig. 7); such overlapping occurred in 53 % of the reflex coughs evoked from the laryngopharyngeal region, in 41 %

of those from the tracheobronchial tree, in 25 % of sneezes and in 18 % of responses to irritation of the nasal mucosa with ammonia vapour.

Bronchomotor responses

Mechanical stimulation of the different sites in the respiratory tract caused parallel changes in total lung resistance and in bronchoconstrictor fibre activity, measured in paralysed artificially ventilated cats. The nature of the response depended on the site of stimulation.
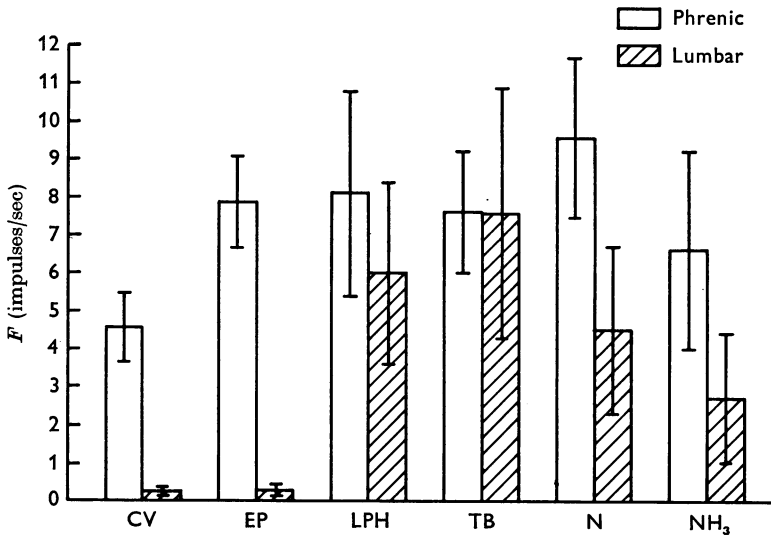

Fig. 8. Impulse frequencies in phrenic (empty columns) and lumbar (hatched columns) single fibre preparations during mechanical stimulation of the epipharyngeal (EP), laryngopharyngeal (LPH), tracheobronchial (TB) and nasal (N) mucosae, and during intranasal insufflation of ammonia (NH_3), compared with control record without respiratory tract stimulation (CV). Values are means ± 95 % probability levels from six anaesthetized, paralysed and artificially ventilated cats.

Total lung resistance. Oscilloscopic records of total lung resistance (Fig. 9) illustrate clear alterations in the slope of the 'loops', due to changes in tracheobronchial calibre during stimulation of the respiratory tract, compared with control values immediately before stimulation. Evaluation of peak bronchoconstrictor and bronchodilator effects of stimulation at different sites in nine cats is summarized in Table 1. The results show that mechanical stimulation of the tracheobronchial or laryngeal mucosa causes bronchoconstriction, and similar stimulation of the epipharynx or nose evokes reflex bronchodilation, as does also insufflation of ammonia vapour into the nose. In further experiments, not included here since they were too few to justify statistical evaluation, it

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was confirmed that inhalation of ammonia into the tracheobronchial tree and lungs causes bronchoconstriction (Banister, Fegler & Hebb, 1950; Widdicombe, 1954).

As shown in Fig. 9, the reflex changes in bronchial calibre sometimes decreased in size during the 10–20 sec period of mechanical stimulation, after reaching a peak value after 5–10 sec.
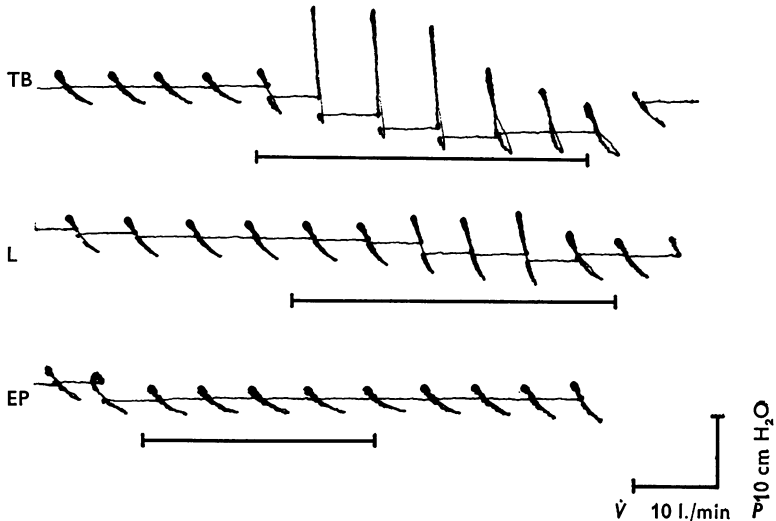

Fig. 9. Oscilloscope records of total lung resistance changes during mechanical stimulation of tracheobronchial (TB), laryngeal (L) and epipharyngeal (EP) mucosae in an anaesthetized, paralysed and artificially ventilated cat. Calibrations are in pressure (P) and flow ($\dot{V}$), and periods of mechanical stimulation are indicated by bars. Each sloping line corresponds to one pump cycle (pump frequency, 30 cycles/min; photographic paper moved horizontally in each expiratory pause), and its slope is proportional to total lung resistance. Thus an increase in slope indicates an increase in resistance, and a decrease in slope a decrease in resistance.

TABLE 1. Changes in total lung resistance and in tracheobronchomotor fibre discharge on stimulation of various sites in the respiratory tract of paralysed artificially ventilated cats

Site	Resistance (cm H_2O/l./min)				Bronchomotor fibre discharge (impulses/sec)			
	n	Control	Change	Change (%)	n	Control	Change	Change (%)
Nose	11	0·51	$-0·09 \pm 0·02$**	-19	8	4·9	$-1·7 \pm 1·2$	-35
Epipharynx	17	0·49	$-0·13 \pm 0·03$**	-25	9	4·8	$-2·5 \pm 0·7$**	-53
Larynx	14	0·45	$+0·38 \pm 0·14$**	$+77$	7	1·9	$+1·6 \pm 0·5$**	$+81$
Trachea-bronchi	11	0·45	$+1·00 \pm 0·26$**	$+156$	11	2·3	$+4·3 \pm 1·0$**	$+196$
Ammonia (nose)	9	0·50	$-0·12 \pm 0·05$**	-24	5	2·3	$-0·2 \pm 0·1$	-9

Total lung resistance (nine cats) and fibre discharge frequency (from four fibres in three cats) are given as means ± S.E. of mean for absolute changes, and as mean percentage changes. ** $P < 0·01$. n refers to the numbers of experimental observations.

Another experiment is illustrated in Fig. 10, where the changes both in lung resistance and in respiratory motoneurone activity, recorded from phrenic and lumbar nerves, are compared during stimulation of the tracheobronchial mucosa. In this experiment adaptation did not occur, and the large increases in resistance seem to correspond with the expiratory motoneurone activity; in those pump cycles where no expiratory activity
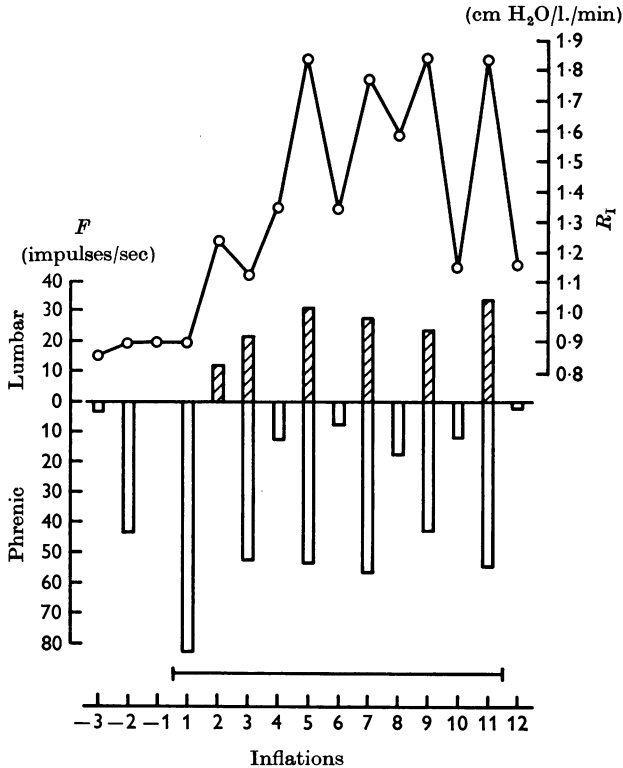

Fig. 10. Comparison of the changes in total lung resistance (——○——) and in nerve impulse frequency of single fibre lumbar (hatched columns, above) and phrenic (empty columns, below) preparations during stimulation of the tracheobronchial mucosa. Each triad of values gives mean resistance and impulse frequencies during a single pump inflation of an anaesthetized, paralysed and artificially ventilated cat. The bar indicates the period of mechanical stimulation.

occurred, the resistance usually fell considerably. However, the average frequency of phrenic motoneurone discharge also increased, and this could similarly be related to the rise in total lung resistance.

Total lung resistance was also measured in seven spontaneously breathing cats before stimulation and during the first eupnoeic breaths after cessation of the respiratory reaction (coughing, sneezing and aspiration reflex)

evoked by stimulation. (Values during the reactions could not be obtained because of the strength of the respiratory efforts, and would in any event have been impossible to interpret in terms of airway muscle tone.) The results showed a decrease in total lung resistance after the aspiration reflex ($P < 0.01$) and sneezing ($P = 0.02$), but no significant changes after tracheobronchial or laryngopharyngeal coughing or after insufflation of ammonia ($P > 0.05$). The absence of significant bronchoconstriction immediately after the coughing attacks may be due to its suppression by the dilatory effect (reflex and mechanical) of deep inspirations, by interference due to simultaneous mechanical stimulation of other sites, and by the dilatory effect of hypocapnia which followed the responses (Fig. 1). Statistical analysis revealed significant decreases in end-tidal CO_2 during and after the respiratory reactions to stimulation of the nasal mucosa chemically ($P < 0.05$) or mechanically ($P < 0.02$) as well as from the other sites in the respiratory tract ($P < 0.01$). The control values of the total lung resistance in non-paralysed cats were between 0.19 and 0.26 cm $H_2O/l./min$, and were significantly lower ($P < 0.05$) than those in paralysed animals (Table 1).

There was no measurable change in lung compliance during stimulation of the nose or epipharynx, and in only one instance from the larynx (compliance decrease, -6%) and twice from the tracheobronchial tree (-21% and -4%); such compliance changes were only seen when the increase in total lung resistance was very great.

Bronchomotor fibre activity. To confirm that the resistance changes described above were due to variations in nervous bronchomotor activity we recorded action potentials from tracheal efferent fibres with discharges and responses characteristic of vagal tracheo-bronchoconstrictor fibres (Widdicombe, 1966). Results of studies on four such single-fibre preparations in three cats are summarized in Table 1 and one is illustrated in Fig. 11. Stimulation of the tracheobronchial and laryngeal mucosae increased the discharge of bronchoconstrictor fibres, while similar stimulation of the epipharynx decreased it. Mechanical or chemical stimulation of the nasal mucosa decreased the constrictor fibre activity, although the mean effects were not statistically significant. In two experiments included in Table 1, for epipharyngeal and nasal stimulation the constrictor fibre discharge was first increased by hypoventilating the cats, in order to make more conspicuous the decrease in activity in fibres which would otherwise have been conducting impulses at a low frequency in the control periods.

We also recorded activity in four fibres with discharges characteristic of 'Type III' tracheobronchial efferent nerves (see Widdicombe, 1966; and Discussion). Discharge in these fibres was increased during and after stimulation of the epipharyngeal and laryngopharyngeal regions by means

of 67 and 127 %, although the results are not statistically significant $(P > 0.05)$.

Simultaneous records of bronchoconstrictor fibre activity and of total lung resistance revealed a considerable correlation in time and magnitude between the two. The parallel reaction of these two variables is clearly seen in Fig. 12, where results are averaged for eight tracheobronchial and five epipharyngeal stimulations. Although there is a lag of resistance change
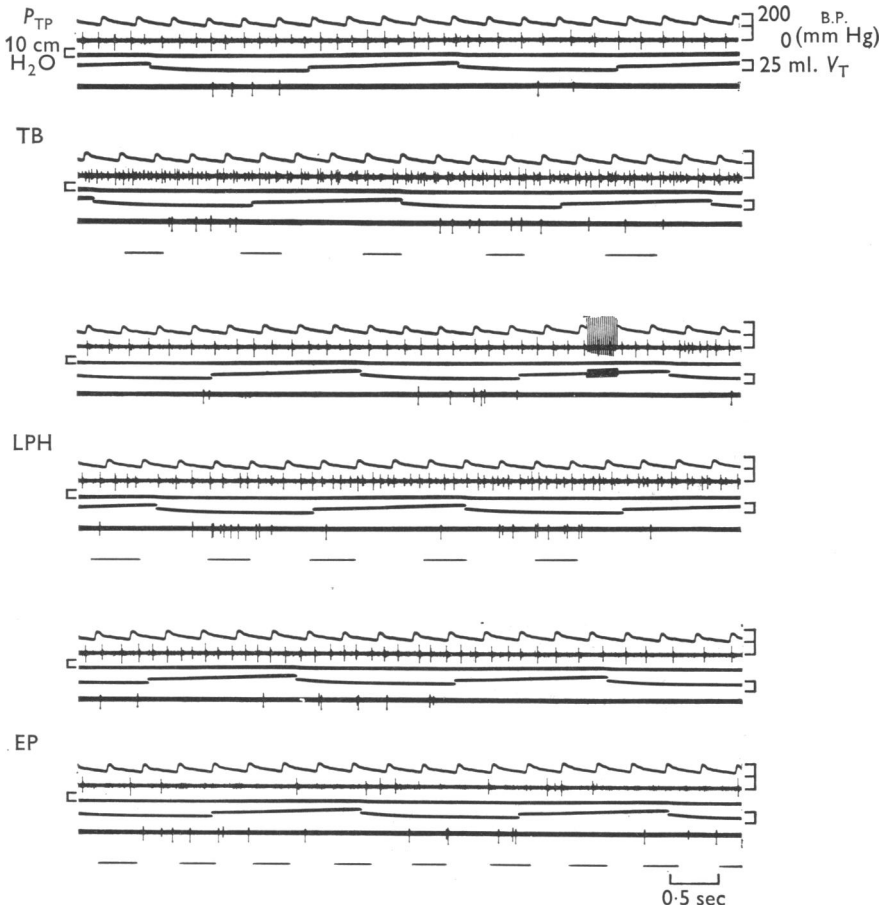

Fig. 11. Records of activity in a tracheal efferent constrictor fibre (upper) and a cervical sympathetic efferent (lower) before (upper records) and during (lower records) stimulation of the tracheobronchial (TB), laryngopharyngeal (LPH) and epipharyngeal (EP) regions. Stimulations are indicated by signal marks at the bottom of the records. Other variables recorded: blood pressure (B.P.), transpulmonary pressure (P_{TP}) and tidal volume (V_T). The artifact in the control before stimulation of the larynx is due to a signal to synchronize the oscilloscope, tape and ultra-violet recorders.

behind bronchomotor fibre change, the responses are very similar in pattern.

Cardiovascular responses

Blood pressure changes. The effect of stimulation at different sites in the respiratory tract on systemic arterial blood pressure was studied in eight paralysed cats. Typical reactions of systolic, diastolic and mean blood pressures in cats are given in Fig. 13. The largest reflex increase in blood
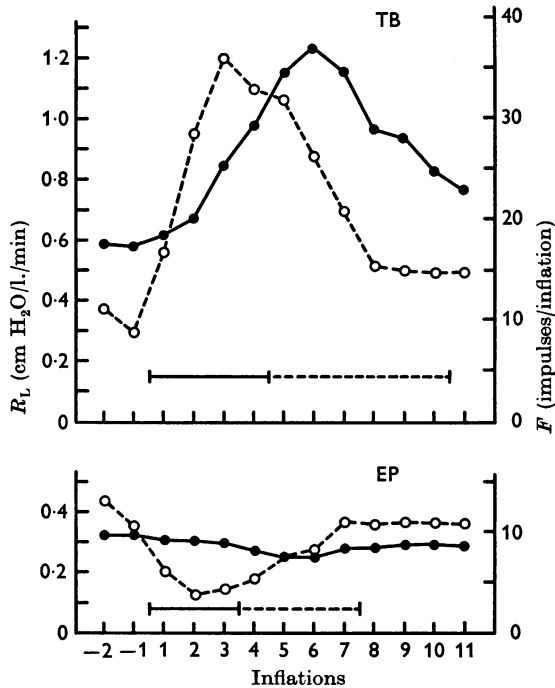

Fig. 12. Comparison of the changes in bronchoconstrictor fibre activity (interrupted lines) and total lung resistance (continuous lines) averaged for eight tracheo-bronchial (TB) and five epipharyngeal (EP) stimulations in three anaesthetized, paralysed and artificially ventilated cats. Stimulus signal: continuous line, common stimulation period in all experiments; interrupted line, stimulation finished in some of the experiments.

pressure was evoked from the epipharyngeal, and the smallest from the tracheobronchial region. Average values (Table 2) show that in paralysed animals all stimulations evoked significant reflex increases in mean blood pressure, the largest response being from the epipharynx. From Fig. 13 it can be seen that there were also increases in pulse pressure and heart rate during the hypertensive reactions from the four sites, the changes being especially conspicuous in the case of epipharyngeal and laryngeal stimulations.

In eight non-paralysed, spontaneously breathing cats, changes in blood pressure would be due to a combination of reflex and mechanical effects. Fig. 1 and Table 3 show that there were clear decreases in diastolic and mean blood pressures during and after the strong ventilatory efforts evoked by all the mechanical stimulations and even greater transient
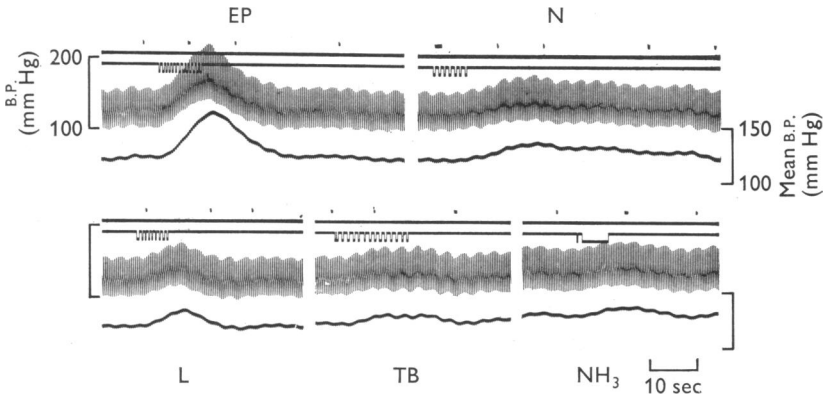

Fig. 13. Representative changes in systolic, diastolic and mean blood pressures on epipharyngeal (EP), nasal (N), laryngeal (L) and tracheobronchial (TB) stimulation, and on intranasal insufflation of ammonia (NH₃) in a paralysed cat.

TABLE 2. Changes in mean systemic arterial blood pressure and in cervical sympathetic efferent fibre discharge on stimulation of various sites in the respiratory tract of paralysed artificially ventilated cats

		Mean blood pressure (mm Hg)				Sympathetic fibre discharge (impulses/sec)		
Site	n	Control	Change	Change (%)	n	Control	Change	Change (%)
Nose	10	136	+22±4·9**	+16	7	2·0	+0·4±0·2	+15
Epipharynx	18	135	+33±3·8**	+26	10	2·0	+1·2±0·4*	+60
Larynx	15	121	+9±1·1**	+8	9	2·4	+1·0±0·4*	+44
Trachea-bronchi	9	109	+10±0·8**	+8	8	1·7	+0·3±0·4	+18
Ammonia (nose)	7	129	+9±1·5**	+7	5	2·1	+0·3±0·4	+14

Mean blood pressure (eight cats) and cervical sympathetic efferent discharge (seven fibres in three cats) are given as means ± S.E. of mean for absolute changes, and as mean percentage changes. ** $P < 0.01$; $P < 0.05$. n refers to the number of experimental observations.

increases both in systolic and mean blood pressures during the strong expiratory efforts of coughing elicited from the tracheobronchial and laryngopharyngeal mucosae, or of the responses to mechanical or chemical irritation of the nasal mucosa. The largest decreases in diastolic and mean blood pressures were in the aspiration reflex, where this was the predominant effect, although there were also first significant increases in systolic and mean blood pressures, occurring usually at the beginning of or during the reaction. In summary, all the respiratory reflexes studied

caused large respiratory variations in blood pressure, which would mask any direct vasoconstrictor hypertension such as was seen in paralysed artificially ventilated cats.

Efferent sympathetic nervous activity. Recordings of action potentials in efferent cervical sympathetic fibres showed that stimulation of all the sites in the respiratory tract enhanced their discharge frequencies (Figs. 11 and 14). These results, for seven cervical sympathetic efferent fibres in

TABLE 3. Changes in systolic, diastolic and mean systemic arterial blood pressures on stimulation of various sites in the respiratory tract of spontaneously breathing cats

Site	Systolic pressure (mm Hg)			Diastolic pressure (mm Hg)		
	Control	Change	Change (%)	Control	Change	Change (%)
Nose	145	$+44 \pm 16 \cdot 1$*	+29	98	$-7 \pm 2 \cdot 7$*	−7
Epipharynx	153	$+15 \pm 4 \cdot 3$**	+10	96	$-27 \pm 6 \cdot 0$**	−27
Laryngopharynx	151	$+47 \pm 3 \cdot 8$**	+32	96	$-11 \pm 4 \cdot 5$*	−9
Trachea-bronchi	146	$+32 \pm 7 \cdot 0$**	+23	95	$-12 \pm 5 \cdot 6$	−11
Ammonia (nose)	150	$+36 \pm 19 \cdot 7$	+22	97	$-8 \pm 2 \cdot 3$*	−8

	Mean blood pressure (mm Hg)				
Site	Control	Maximum increase	Change (%)	Maximum decrease	Change (%)
Nose	115	$+16 \pm 6 \cdot 2$*	+16	$-5 \pm 2 \cdot 7$	−5
Epipharynx	118	$+8 \pm 2 \cdot 0$**	+7	$-23 \pm 3 \cdot 2$**	−20
Laryngopharynx	117	$+15 \pm 4 \cdot 7$*	+13	$-12 \pm 4 \cdot 2$*	−9
Trachea-bronchi	114	$+19 \pm 3 \cdot 2$**	+18	$-11 \pm 4 \cdot 8$	−8
Ammonia (nose)	117	$+16 \pm 3 \cdot 3$*	+14	$-5 \pm 1 \cdot 4$**	−4

Values are from experiments on eight cats. Changes are expressed as means $\pm$ S.E. of mean, and as mean percentage changes. Systolic pressure change refers to the maximum increase during or after stimulation, and diastolic pressure change to the maximum decrease, the two effects not being coincident. For mean blood pressure changes, the maximum and minimum during or after stimulation are given. ** $< P\ 0 \cdot 01$; * $P < 0 \cdot 05$.

paralysed artificially ventilated cats, are summarized in Table 2; they are statistically significant only for the epipharyngeal and laryngeal stimulations. The increase of sympathetic efferent discharge often consisted of bursts of sympathetic activity appearing during or immediately after enhanced phrenic nervous discharges, especially in the case of the aspiration reflex (Fig. 14). Similar reactions to those of the cervical sympathetic nerves were seen in one sympathetic efferent few-fibre preparation of a lumbar nerve.

The reactions of phrenic and cervical sympathetic efferent fibres and of mean blood pressure caused by epipharyngeal stimulation are summarized in Fig. 15 for five experiments on three fibres in one cat. Fibre discharges are averaged over consecutive inflation pump cycles, and phrenic and sympathetic nervous activities show a clear correlation in time and amplitude, indicating a parallel increase both in phrenic and sympathetic

activity. The maximum fibre response was early during the stimulation, and there was a lag in the blood pressure change after the reaction of the sympathetic fibres.
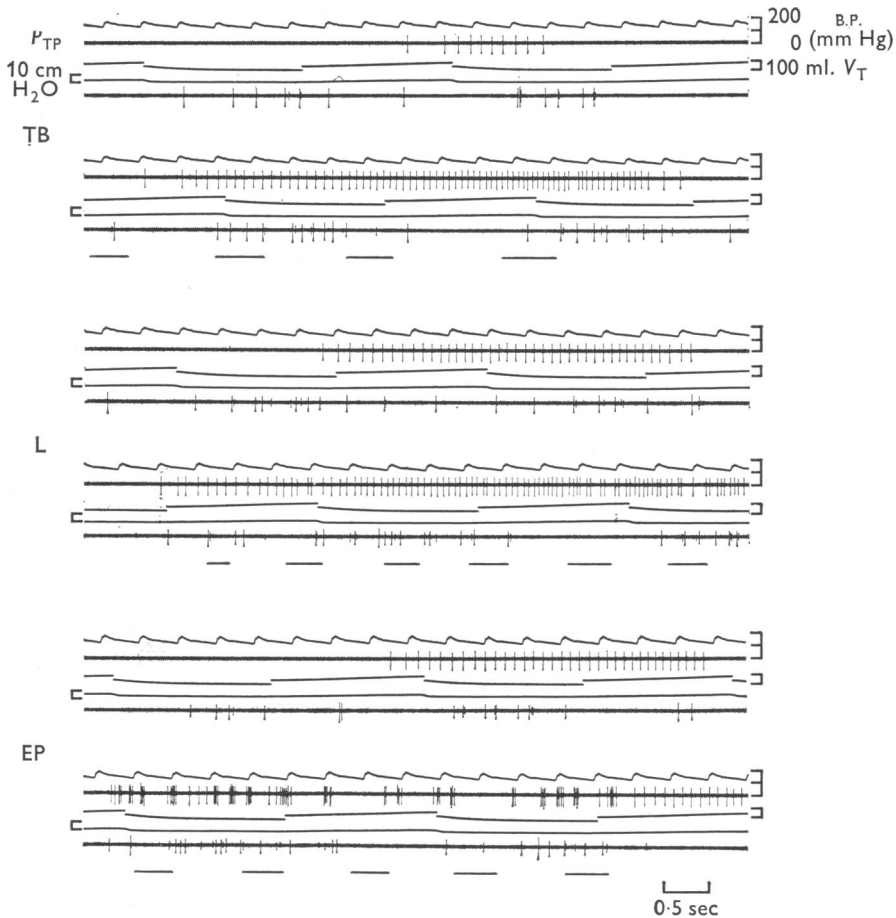

Fig. 14. Changes in activity of a phrenic (upper) and a cervical sympathetic efferent (lower) fibre during tracheobronchial (TB), laryngeal (L) and epipharyngeal (EP) stimulation (lower records) in a paralysed cat compared with controls immediately before the stimulation (upper records). Other variables recorded: blood pressure (B.P.), tidal volume (V_T) and transpulmonary pressure (P_{TP}). Stimulations are indicated by the signal marks at the bottom of the records.

DISCUSSION

EMG and ENG analyses. Analysis of the high-speed EMG and ENG records revealed that the electrical activity of the expiratory muscles and their motoneurones is minimal or absent during the aspiration reflex

elicited by stimulation of the epipharynx in cats. However, introduction of the nylon fibre to touch the mucosa of the mesopharynx or larynx evoked clear electrical activity in the abdominal muscles, as reported also by Korpáš & Kulik (1963). The records confirmed the frequent occurrence of synchronous electrical activity in both inspiratory and expiratory muscles as described for laryngopharyngeal coughing (Korpáš & Kulik, 1963), and
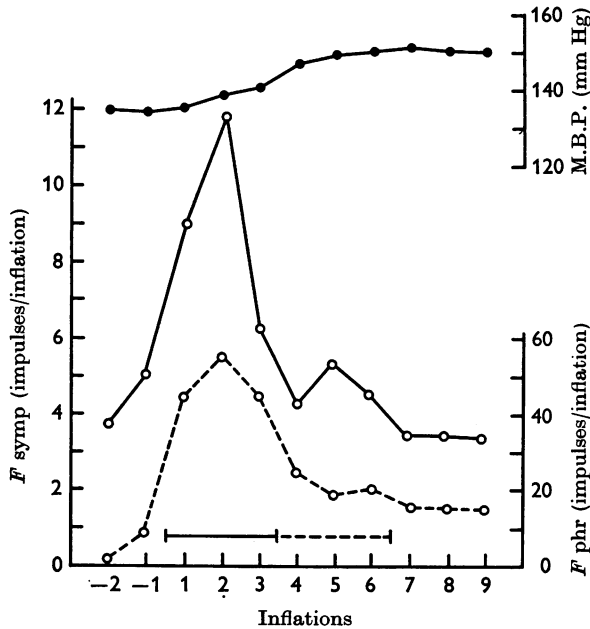

Fig. 15. Reactions of phrenic (- - ◯ - -) and sympathetic (—◯—) efferent fibres and of mean blood pressure (— ● —) on epipharyngeal stimulation averaged from five experiments on three fibre preparations in one paralysed cat. Stimulus signal: continuous line, common stimulation period in all experiments; interrupted line, stimulation finished in some of the experiments.

extended this finding also to the appropriate motoneurones; thus there is presumably a transient but simultaneous activity in both the inspiratory and expiratory half-centres. The same 'overlapping' of the inspiratory and expiratory EMG activities has been described for vomiting (Hukuhara, Okada & Yamagami, 1957; Jiménez-Vargas, Asiron, Voltas & Onandia, 1967); a common factor could be activation of a spasmodic respiratory centre in the region of the nucleus and tractus solitarius (Borison, 1948) which could be excited by afferent discharges in the glossopharyngeal and vagal nerves.

The rapid and strong sniff and gasp-like inspirations of the aspiration reflex have a peculiar character in the diaphragmatic EMG and phrenic

ENG, appearing in short bursts of activity with a frequency as high as 10–12 bursts/second. Similar patterns of diaphragmatic activity were recently reported during electrical stimulation of the pharyngeal wall (Takagi *et al.* 1966), and in medullary inspiratory neurones at the beginning of swallowing (Sumi, 1963). It is possible that, after the primary inspiratory response of the aspiration reflex, some of the later bursts of activity in the phrenic-diaphragmatic units may be evoked or potentiated reflexly from the lungs by the mechanism underlying Head's paradoxical reflex (Head, 1889; Widdicombe, 1967); this may be the same as the inspiratory exciting reflex described by Larrabee & Knowlton (1946) and the respiratory augmenting reflex studied by Reynolds (1962). However, these latter reflexes are all elicited from lung receptors by large or rapid pulmonary inflations, while the aspiration reflex persists after vagotomy (Tomori *et al.* 1957). Other work has shown that the aspiration reflex is present in conscious cats (Tomori, 1960), and that it persists in conditions such as severe hypothermia, hyperthermia, different types and depths of anaesthesia, and in near-dead animals when the pupillary, corneal, cough and swallow reflexes have completely disappeared (Korpáš & Tomori, 1957, 1958; Tomori & Korec, 1964). Single shock electrical stimulation of the pharyngeal branch of the glossopharyngeal nerve which supplies the epipharynx invariably causes a burst of activity in the phrenic nerve of the cat, with a total conduction delay of 15–25 msec (B. S. Nail, G. M. Sterling & J. G. Widdicombe, unpublished).

Bronchomotor reflexes. The results show a clear bronchodilator effect of stimulation in the nose and even more in the epipharynx, with a parallel decrease in tracheo-bronchoconstrictor fibre activity. While the increase in total lung resistance by laryngeal or tracheobronchial stimulation must be mainly an active process controlled by an increase in bronchomotor muscular tone, our results cannot establish whether the bronchodilator effects of stimulation in the upper respiratory tract are potentiated by an increase in adrenal secretion or in sympathetic tracheobronchial efferent activity; however, a clear and probably dominant factor is a decrease in vagal efferent discharge to the airways. Analysis of the balance of influence of vagal constrictor and sympathetic dilator activity on the dog's airway indicates that the former is much stronger (Green & Widdicombe, 1966).

The results illustrated in Fig. 10 suggest that the changes in bronchomotor tone are closely related to the changes in activity of the inspiratory and expiratory motoneurones and therefore probably of the inspiratory and expiratory centres in the medulla; spasmodic expiratory muscle activity such as coughing is accompanied by bronchoconstriction, with an increased activity in vagal bronchomotor 'centres', and the spasmodic in-

spirations during the aspiration reflex are accompanied by bronchodilation. These findings might suggest paired bronchoconstrictor and bronchodilator 'centres' influenced by spasmodic expiratory and inspiratory activities respectively, possibly linked with the expiratory and inspiratory half-centres in the medulla. However, the bronchodilation in sneezing, with prominent expiratory efforts, does not fit this concept, and increased inspiratory motoneurone discharge in hypoxia and hypercapnia is accompanied by vagally mediated bronchoconstriction (Nadel & Widdicombe, 1962a), so there is no consistent correlation between expiratory and inspiratory motoneurone discharge on the one hand, and nervous bronchoconstriction and bronchodilation on the other. The processes, although they can appear linked in some conditions, can also diverge in direction qualitatively.

We did not observe appreciable changes in lung compliance in our experiments, and therefore it is probable that the observed changes in total lung resistance were due to changes in the larger cartilaginous airways, where nervous control appears to dominate (Green & Widdicombe, 1966; Olsen, DeKock & Colebatch, 1967). The dilator effect of airway stimulation was intensified when the control values of total lung resistance and bronchoconstrictor fibre activity had been first increased by hypoventilation which reflexly diminishes bronchial calibre (Nadel & Widdicombe, 1962a).

The bronchoconstrictor effect due to tracheobronchial stimulation cannot be ascribed to the mechanical obstruction of the respiratory tract by the introduced nylon fibre itself, because the latter would only decrease the tracheal cross-sectional area by about 1/60th, because bronchoconstriction resulted also from other types of irritation (e.g. chemical) of this site, and because the increase in total lung resistance persisted after the nylon fibre had been removed.

There was an increase in discharge of vagal 'Type III' fibres, during stimulation of the respiratory tract, especially the epipharyngeal and laryngopharyngeal regions. Indirect evidence suggests that these may be secretomotor fibres to the mucus glands of the respiratory tract (Widdicombe, 1966) and our results are consistent with evidence that stimulation of respiratory tract irritant receptors causes a reflex increase in mucus secretion (Florey, Carleton & Wells, 1932; Boyd, 1954).

Cardiovascular responses. There are several reports of blood pressure changes during stimulation of the respiratory tract, an increase from the nose, larynx and tracheobronchial tree (e.g. Dixon & Brodie, 1903; Allen, 1929; Nadel & Widdicombe, 1962b); the changes may differ in character in anaesthetized and paralysed animals (Kállay & Takács, 1958). Our results indicate that there is a primary hypertensive reaction from the

epipharynx too, and that this reflex in cats is even stronger than that from other regions of the respiratory tract. Moreover, these hypertensive reactions were accompanied by increases in sympathetic efferent fibre discharges, which were frequently grouped into bursts following shortly (usually less than 1 sec) after the beginning of the phrenic discharges, suggesting an increased activity in sympathetic centres driven by the inspiratory centre in a similar pattern to that described for eupnoea or asphyxia (Adrian, Brown & Phillips, 1932; Tang, Maire & Amassian, 1957; Okada & Fox, 1967). Our results in paralysed animals show that this increase in sympathetic activity does not result from mechanical effects or reflexly from respiratory movements. Although the increased impulse traffic in cervical sympathetic efferent fibres need not necessarily have a causative relationship to the hypertension due to stimulation of the respiratory tract (the effector tissues served by the fibres were not identified, and the hypertensions could be due more to release of catecholamines by the adrenals), nevertheless it is a possible indication of enhancement of activity in most of the sympathetic system. We cannot say what change, if any, may have taken place in sympathetic bronchodilator fibre discharge.

In conscious human subjects and in anaesthetized non-paralysed animals stimulation of the respiratory tract has different effects on blood pressure, depending more on mechanical changes secondary to the vigorous respiratory movements rather than on primary cardiovascular reflexes. Intensive respiratory efforts result in great oscillations of the systolic, diastolic and mean blood pressures (Sharpey-Schafer, 1953, 1965; Ivančo & Vereš, 1958). Large increases in systolic pressure, such as those seen in our cats during coughing and sneezing, could have a clinical significance as causative factors in cardiovascular disturbances such as cerebral haemorrhage. On the other hand a mechanically induced decrease in blood pressure after the respiratory reflex response might result in post-tussive syncope (Sharpey-Schafer, 1953).

The bronchodilation and hypertension due to mechanical stimulation of the epipharynx and nose could be partly due to release of catecholamines from the adrenal medulla, but the cervical sympathetic discharge was increased by epipharyngeal stimulation and it is known that this discharge is inhibited by injection of adrenaline (Iggo & Vogt, 1962; Widdicombe, 1966).

We conclude that activation of 'irritant' reflexes from different sites in the respiratory tract causes greatly differing respiratory and bronchomotor effects, and quantitatively different hypertensive responses. The reflexes might be suitable for studies of the interactions between inspiratory and expiratory half-centres, and of the relationships between these complexes and the brain-stem systems controlling bronchomotor tone and sympathetic vasomotor fibre discharge.

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