LARYNGOSPASM DURING GENERAL ANAESTHESIA IN THE CAT

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Miss May Soo typed the thesis.

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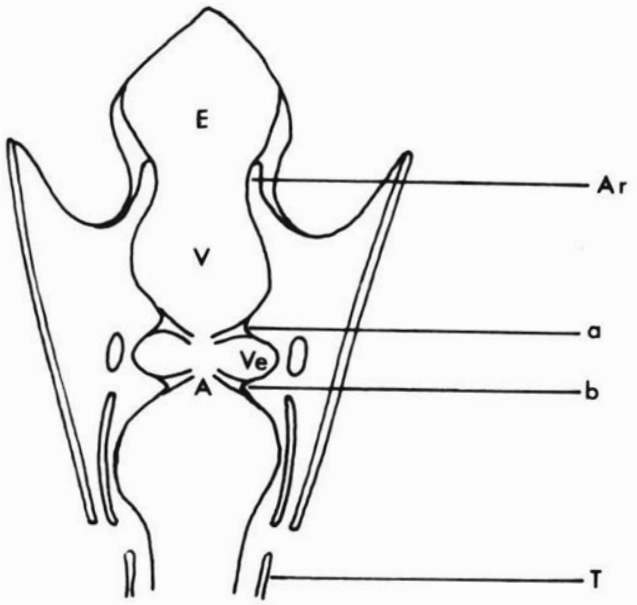
I INTRODUCTION

One of the many hazards of general anaesthesia is spasm of the muscles of the air passages - that is laryngospasm, tracheal spasm and bronchospasm. When any one of these is severe, it can lead to hypoxia or anoxia and death, in addition to less serious sequelae such as the formation of ulcers and granulomata in the larynx and trachea. This thesis is concerned with one of these conditions - laryngospasm, which may be defined as an occlusion of the aditus laryngis by the action of the intrinsic laryngeal muscles.

The investigation has been in the nature of an experimental study on the induction of and the mechanisms involved in laryngospasm. A clearer definition of these mechanisms is essential if the occurrence of this condition during anaesthesia is to be prevented. In particular, attempts have been made to define both the sites of stimulation, and the afferent and efferent limbs of the laryngeal reflex responses stimulated by the inhalation of anaesthetic vapours. The work is an extension as well as a confirmation of preliminary communications (Rex, 1966, 1967), reprints of which are provided as appendices 1 and 2. Interest in this study arose from clinical experience and an awareness of the problem laryngospasm presents in anaesthesia.

Fig. 1 **Diagram of the Larynx**



A schematic diagram of a horizontal section through a larynx to show the main features.

A	Aditus laryngis	a	False cords
Ar	Aryepiglottic folds	b	True vocal cords
T	First tracheal cartilage	V	Vestibule
Ve	Ventricle	E	Epiglottis

II REVIEW OF THE LITERATURE AND AN INTRODUCTION TO THE PROBLEM

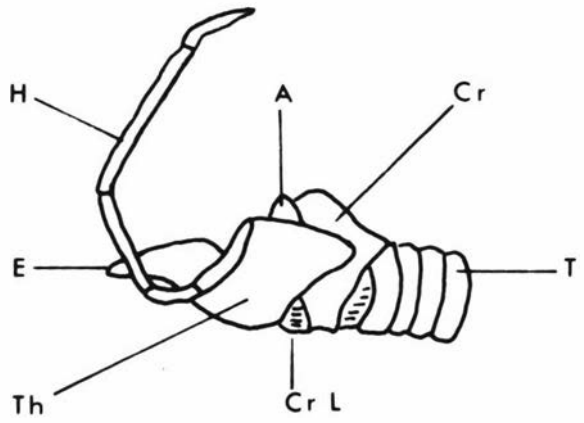
1. A Consideration of the Structural and Functional Basis of Laryngospasm

(a) The gross anatomy of the larynx

Although the detailed internal structure of the larynx varies considerably from species to species (Negus, 1949), a general description of the larynx is possible. The lumen of the laryax may be divided into three areas. The anterior part called the vestibule, extends from the tip of the epiglottis cranially to the false vocal cords caudally. The false cords or ventricular bands are two folds of mucosa (Fig. 1, facing p.2) which stretch from the caudal surface of the epiglottis to the tips of the arytenoid cartilages. Caudal to the false vocal cords, the true vocal cords stretch from the apices of the arytenoid cartilages to the thyroid cartilage near the base of the epiglottis. The middle portion of the larynx is that area between the true and false cords. It has a small sac on each lateral aspect, known as the ventricle. The slit between the true vocal cords is known as the glottis. The width of the glottis can be varied by the action of the intrinsic laryngeal muscles. The caudal portion of the laryngeal cavity is that region between the glottis and the first tracheal cartilage.

In laryngeal spasm in man, either the true vocal cords alone, or the true and false vocal cords are apposed in the midline, completely closing the aditus laryngis (Keating, 1965). Two other types of laryngeal obstruction in man, one where there is spasm of the false cords and the aryepiglottic folds, and the other where adduction of the true cords coincides with inspiration, have also been described (Caiger and Sichel, 1954).

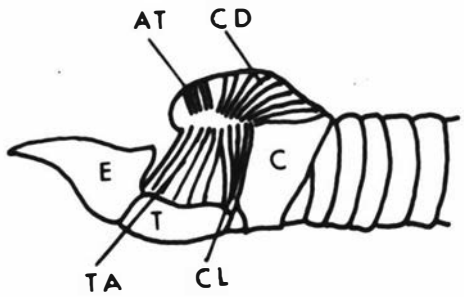
Fig. 2 The Cartilages of the Cat's Larynx



After Elliot (1963). Cartilages of the Cat's Larynx.

A	Arytenoid	Th	Thyroid
E	Epiglottis	CrL	Cricothyroid ligament
Cr	Cricoid	T	Trachea
H	Hyoid apparatus		

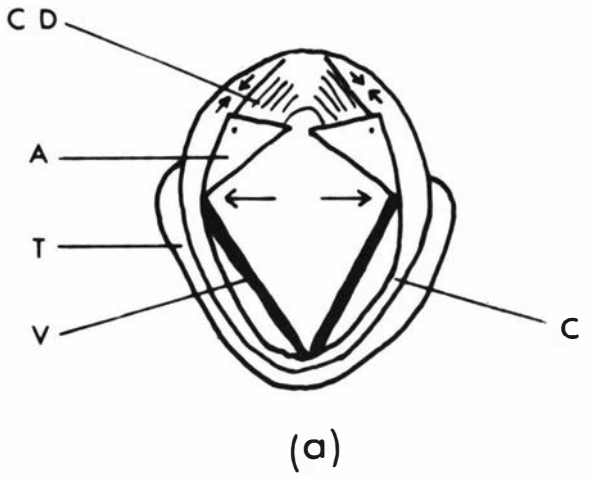
Fig. 3 The Intrinsic Laryngeal Muscles of the Cat



After Elliot (1963). The Intrinsic Laryngeal Muscles of the Cat.
Part of the Thyroid cartilage has been cut away to show the lateral muscles.

AT	Transverse arytenoid	C	Cricoid cartilage
CD	Dorsal cricoarytenoid muscle	CL	Lateral cricoarytenoid muscle
E	Epiglottis	T	Thyroid cartilage (part cut away)
TA	Thyroarytenoid muscle		

Fig. 4 Diagram to show the Mechanism of Laryngeal Closure



(a)

(b)

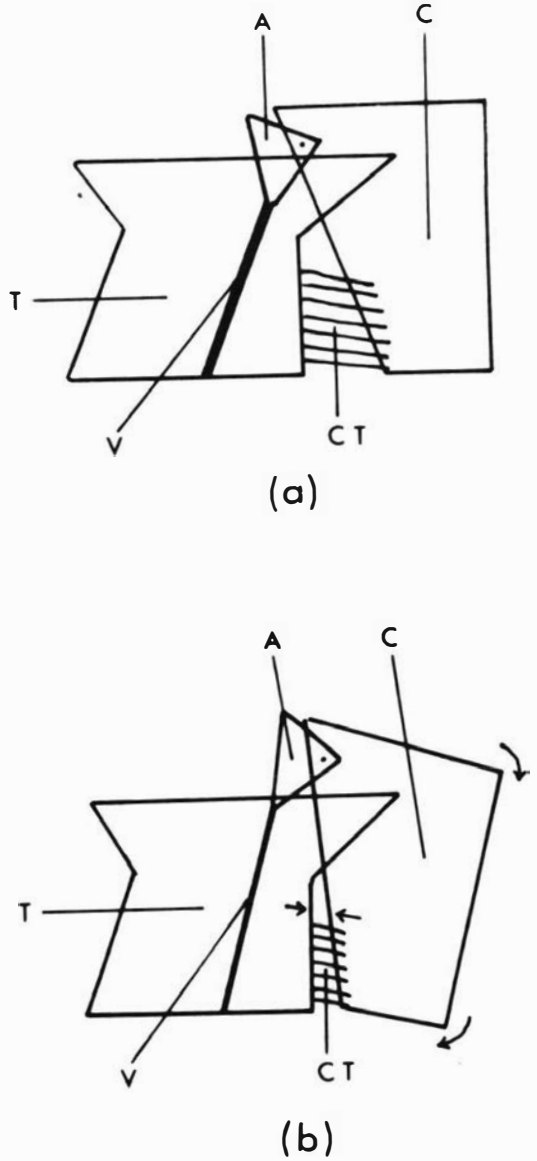
After Miller (1952)

a Action of the dorsal cricoarytenoid muscles as abductors of the vocal cords

b Action of the lateral intrinsic muscles as adductors of the vocal cords

A Arytenoid cartilage
CD Dorsal cricoarytenoid muscle
V Vocal cord
2 Thyroarytenoid muscle
C Cricoid cartilage
T Thyroid cartilage
1 Lateral cricoarytenoid muscle

Fig. 5 Diagram to show the Adductor Action of the Cricothyroid Muscle



After Miller (1952)

a Cricothyroid muscle relaxed - Abduction

b Cricothyroid muscle contracting - Adduction

A Arytenoid cartilage
CT Cricothyroid muscle
V Vocal cord
C Cricoid cartilage
T Thyroid cartilage

The cat's larynx is supported by three unpaired cartilages, the thyroid, cricoid, and epiglottic, and by a pair of cartilages, the arytenoids (Fig. 2, facing p.3). The thyroid cartilage forms almost two thirds of a cylinder and encloses the other cartilages ventrally and laterally. The epiglottic cartilage is attached to the middle of its cranio-ventral border and the whole cranial margin of the thyroid cartilage is connected to the hyoid apparatus. The dorsal border articulates caudally with a point on the lateral aspect of the cricoid cartilage. The cricoid cartilage is annular in shape and its dorsal border is broader than the ventral one. From the caudal aspect of the cricoid cartilage there is a membranous attachment to the first tracheal ring. The arytenoid cartilages are triangular pyramids which articulate with the cranial border of the cricoid cartilage. The lateral cricoarytenoid, thyroarytenoid and dorsal cricoarytenoid muscles are attached to the arytenoid cartilages (Fig. 3, facing p.3). The action of these muscles is to cause adduction and abduction of the vocal cords (Fig. 4, facing p.3). The epiglottic cartilage is attached to the cranial border of the thyroid cartilage and supports the epiglottis. Contraction of the thyrohyoid muscle, stylohyoid muscle and the median and inferior constrictors of the pharynx moves the larynx as a whole cranially. The sternothyroid muscle moves the whole larynx caudally when it contracts. The intrinsic muscles of the larynx (those which move the parts of the larynx in relation to each other) are the ones which are concerned in the production of laryngospasm. In this context, the most important of the intrinsic muscles are the dorsal cricoarytenoid (abductor), the lateral cricoarytenoid, the thyroarytenoid (adductors of glottis) and the cricothyroid which increases the tension of the vocal cords and is therefore considered an adductor (Fig. 5, facing p.3).

(b) The innervation of the larynx and receptor areas which may be involved in the laryngeal reflex

There are considerable differences of opinion expressed in the literature on the innervation of the larynx and it is evident that it varies from species to species.

(i) Motor innervation

Motor innervation of the intrinsic laryngeal muscles is served by the external branch of the superior laryngeal nerve on each side and by the right and left recurrent laryngeal nerves. The external branch of the superior laryngeal nerve is generally considered to be the only motor innervation to the cricothyroid muscle in man (Arnold, 1961; Faaborg-Andersen, 1957; King and Gregg, 1948; Lemere, 1932a, 1932b, 1933; Ogura and Lam, 1953; Pressman and Kelemen, 1955; Tschiassny, 1944; Vogel, 1952) and in dogs (King and Gregg, 1948; Vogel, 1952). Lemere (1932a), however, attributed the motor innervation of the cricothyroid muscle in fifty per cent of the dogs he worked with to a third or median nerve rather than the external ramus of the superior laryngeal nerve, as is usually described.

In cats, Seymour and Henry (1954) state that the cricothyroid muscle receives its motor innervation from the external branch of the superior laryngeal nerve, but Hunt and Kuffler (1954) describe an additional supply to this muscle by a nerve from the pharyngeal plexus. Murray (1957) describes the role of the recurrent laryngeal nerves in the innervation of the intrinsic laryngeal muscles of the cat. These nerves provide the motor innervation to all the intrinsic muscles except the cricothyroid. He did not investigate the superior laryngeal nerves. Murtagh (1945)

used cats with windows cut in the larynx to make direct observations of vocal cord movements in response to nerve stimulation, and a catheter and cuff technique to obtain records of changes in laryngeal volume. In his later experiments, Murtagh used similar techniques in goats, because the small size of the cat's larynx raised technical difficulties. He concluded that the external branch of the superior laryngeal nerve in the goat was the motor nerve to the cricothyroid muscle and that there was no evidence of motor function in the internal branch of that nerve. The cricothyroid muscle was found to be a strong adductor of the vocal cords. In 1954, Murtagh and Campbell published results of experiments in goats in which they used electromyographic techniques to record the activity of the intrinsic laryngeal muscles. Their aim was to secure, if possible, direct evidence as to the nature of laryngeal spasm. The goats were anaesthetized with pentobarbitone sodium and needle electrodes were inserted into the cricothyroid and dorsal cricoarytenoid muscles through a tracheostomy incision between the second and third tracheal rings. The electromyograms of these muscles showed what the authors considered to be a normal respiratory pattern. They also described the production of laryngospasm (high frequency discharge from a greater number of motor units than had been recorded during normal respiration) by mechanical stimulation of the laryngeal mucosa. Observations which they made on the effects of barbiturates and neuromuscular blocking agents on laryngospasm will be considered later in this thesis.

(ii) The afferent pathways

There are a number of afferent pathways which may form part of the reflex arc in laryngospasm and these vary according to the site of

stimulation and the nature of the stimulus. In the respiratory tract itself Kratschmer (1870) described the production of apnoea, closure of the laryax and bradycardia by chemical, electrical, and mechanical stimulation of the nasal mucosa in rabbits, effects which he was unable to elicit after section of the trigeminal nerve roots. This work gave an early indication of the variety of stimuli which act on receptors in the upper respiratory tract. However, the fact that there are great differences between species in the chemoreflexes makes it unwise to transfer observations made in one species directly to another. Ranson (1921), in a discussion of reflex stimulation of respiratory movements by stimulation of various afferent nerves, reviewed the literature and noted that changes in respiratory rhythm resulted from afferent impulses travelling in not only the vagus nerves, but also the superior laryngeal, trigeminal, auditory, phrenic, sciatic, splanchnic and other sensory nerves. He emphasised the fact that it is not always clear what conditions determine the character of an individual response. Strength of stimulus, anaesthetic used, and the particular nerve stimulated are all important in determining what the effect will be. Ranson asserted that afferent branches of the vagus from the larynx, trachea and lungs exert a dominant influence over the respiratory centre.

Other work pertinent to these general observations is reviewed in the following sections:

Stimulation of the nasal mucosa, soft palate and pharynx

Allen (1929a) investigated whether the respiratory and circulatory changes following short inhalations of various vapours in rabbits and cats with their olfactory or trigeminal nerves cut, may be attributed to direct

stimulation of the olfactory and trigeminal nerves, or to stimulation of other sites. All but two of the experiments he reports were carried out on rabbits, but he refers his conclusions to the cat as well as to the rabbit. He considered the possibility of direct stimulation of the chemoreceptors or the medulla by absorbed vapour, and discussed less direct effects which could result in chemoreceptor stimulation such as the anoxia arising in the absence of respiration. He showed that inhalation of odoriferous and irritating substances into the nostrils produced marked changes in respiration and circulation. These reactions could be evoked by stimulating either the olfactory or the trigeminal endings in the nasal mucosa, and could therefore be considered direct effects. The general effect on respiration was one of depression and inhibition. Some volatile agents caused depression and inhibition, or even complete cessation of respiration.

The observations Allen made on the evocation of sneezing by either olfactory nerve or trigeminal nerve receptors emphasises the importance of recognising the identity of these two receptor mechanisms in the nasal mucosa. Odoriferous substances may be present in sufficient concentration to stimulate trigeminal receptors as well as olfactory receptors. Sneezing was demonstrated in conscious or anaesthetised rabbits with trigeminal nerves intact, and olfactory nerves cut. When the olfactory nerves were left intact, and the trigeminals cut, a sneeze could only be evoked when the animal was conscious. Anaesthesia abolishes the sneeze response to olfactory stimulation. Among other compounds, ether, chloroform and ammonia were shown to be almost as effective olfactory stimulants as they are trigeminal stimulants. Division of the depressor, vagus, and cervical sympathetic nerves at the level of the larynx did not interfere with the

strength of the reaction in normal rabbits nor in rabbits with trigeminal or olfactory nerves divided. There is a species variation in the stage of anaesthesia at which the olfactory respiratory reflex disappears. In rabbits it was not inhibited until stage three, whereas in dogs it was abolished during the first stage of anaesthesia (Allen, 1936). Allen found that the trigeminal respiratory reflex from the inhalation of chloroform was obliterated at about the middle of stage three in dogs and rabbits.

Extending his observations to man, Allen (1929b) demonstrated that in normal conscious subjects the inhalation of strong irritants produces marked depression and slowing, or complete arrest of thoracic respiration. An inhibitory respiratory reaction was provoked by the inhalation of some agents in men under ether anaesthesia. This consisted of a shortening, or shortening and slowing of the respiratory excursions. Allen considered that this was an olfactory-trigeminal reflex identical to that seen in rabbits.

Adrian (1953) recorded from units in the olfactory bulb of the rabbit, and was able to infer that receptors were stimulated by a number of volatile substances, for example: xylol, eucalyptus, acetone, pyridine and cedar. The time-course of excitation was determined by the physical and chemical properties of the substance being investigated.

Dixon and Brodie (1903), working mainly with cats, confirmed Kratschmer's observations on the respiratory effects of some inhalation agents. Stimulation of the peripheral end of either of the vagus nerves cut in the neck in the cat was shown to produce an initial slight constriction of the bronchioles followed by recovery. More intense bronchiolar constriction was observed some seconds after the stimulus had ceased. They attributed this effect to the fact that broncho-dilator fibres

in the vagus nerve are particularly well developed in the cat. Anaesthesia with ether or chloroform abolished the effect of the vagus on the bronchioles because the nerve endings were paralysed by direct absorption of the anaesthetic through the mucous membrane. They found that reflex bronchiolar constriction was best obtained by excitation of the nasal mucous membrane and that little or no result was obtained by stimulating the sciatic nerve, central vagus, or the superior laryngeal nerve.

In this thesis, the production of laryngospasm and changes in respiratory rhythm in decerebrate cats has been described when the naso-pharyngeal mucosa was exposed to ether vapour. Methods of modifying or abolishing this response have been investigated.

Teitelbaum, Ries and Lisansky (1936) demonstrated that respiration was markedly accelerated in the anaesthetised cat when the pharyngeal mucosa or soft palate was stimulated mechanically. In some instances, inhibition of respiration occurred and not acceleration. The inhibitory reflex was abolished by section of the greater palatine branches of the maxillary nerve, whereas section of the glossopharyngeal nerve abolished the accelerator response. They also produced evidence that the superior laryngeal nerves mediated a minor portion of the pharyngeal inhibitory reflex, but that the main component was mediated through the pharyngeal branch of the vagus nerve. Andersen (1953) stated that touching the nasal mucosa in rabbits depressed respiration and that the mere passage of a stream of air through the nostrils caused stimulation of breathing, whereas Ramos (1959) reported a complicated response to the passage of an air current, with depression of respiration being followed by increased inspiratory activity.

Stimulation of the epiglottis and larynx

Andrew (1956) carried out a functional analysis of myelinated fibres in the superior laryngeal nerve of the rat. He found that the internal branch of the superior laryngeal nerve (branch 1) contained the largest sensory fibres, as judged by the size of their action potentials. These fibres end in stretch receptors in the intrinsic laryngeal muscles and joint proprioceptors in the joints between the laryngeal cartilages. Nerve fibres from mechanoreceptors in the mucosa of the epiglottis are also carried in this nerve. Afferent fibres of somewhat smaller diameter, travel in the same nerve from chemoreceptors in the mucosa of the epiglottis and larynx anterior to the vocal cords. Andrew suggested that a third branch of the superior laryngeal nerve innervates the larynx, below the level of the vocal cords, as well as the oesophagus, but he only produced evidence for its oesophageal activity.

Pressman and Kelemen (1955), discussing the sensory innervation of the larynx in man, stated that sensory fibres reach the larynx via the internal branch of the superior laryngeal nerve, which innervates it from its superior boundaries to the level of the lower border of the true vocal cords. Stimulation of the central end of the severed superior laryngeal nerve in the cat will frequently result in an inhibition of respiration which may last through the whole period of stimulation, even when this is for as long as thirty to forty five seconds. They cite observations by Ogura and Lam (1953) to substantiate their statements. Below the level of the vocal cords they stated that sensory elements are carried in the recurrent laryngeal nerves, an observation previously reported by Martagh and Campbell (1951). Pressman and Kelemen also suggested that the distribution of sensory receptors throughout the larynx is one suited to

elicit prompt motor reactions in case of need. The degree of sensitivity is greatest around the entrance to the larynx, a distribution which they interpreted to support the theory that these receptors form part of the protective mechanism for the airway. They stated that selective staining techniques had demonstrated that the more compact innervation is on the laryngeal aspect of the epiglottis, the aryepiglottic folds, the interarytenoid area, and lower down in the ventricular folds. In man, the posterior aspect of the true vocal cords, which is more exposed to foreign material than the anterior aspect, is much more generously supplied than the anterior region.

Frankenhaeuser (1948) recorded impulses in large nerve fibres from the epiglottis of the rabbit in time with respiratory air flow; he postulated that there are receptors stimulated by air movement and that they may be involved in the reflex regulation of respiration. Kirchner and Wyke (1965) described afferent discharges from mechanoreceptors in the laryngeal joint capsules of the cat. Their work provides evidence that the principal innervation of the cricothyroid joint is by way of articular branches of the ipsilateral recurrent laryngeal nerve. Pressman and Kelemen cite Cortesi (1949) who found that the effect of stimulation of the superior laryngeal nerve on respiration in cats, dogs and rabbits varies with the intensity of stimulation, whether the stimulus is electrical, mechanical, chemical, or thermal. Strong stimuli decreased the volume and frequency of breathing and even caused temporary paralysis; weak stimuli increased the frequency and volume of respiration. Pressman and Kelemen (1955) describe the sympathetic innervation of the larynx, which is considered to be concerned with vasomotor control and with control of laryngeal secretions. Dirnhuber, Green and Tregear (1965) demonstrated

that afferent impulses from the larynx were transmitted by the recurrent laryngeal nerves when the larynx was stimulated chemically.

Dirnhuber et al (1965), Harrison (1962), Harrison and Vanik (1963), and Harrison, Moir and Vanik (1963), have described chemical stimulation of receptors in the cat's larynx. Dirnhuber et al recorded action potentials from fibres of the recurrent laryngeal nerve in response to stimulation of the laryngeal mucosa by ice-cold saline and irritant chemicals. They found that single cold-sensitive neurones of the cat's larynx can be stimulated by irritant chemicals, whereas only one fibre which was not stimulated by cold responded to chemicals in nine experiments. Previous application of the chemicals did not noticeably alter the response to ice-cold saline, demonstrating that there is no interaction between the different kinds of stimulus. Harrison, Harrison and Vanik, and Harrison et al used inhaled agents as the stimulus for the laryngeal receptors. Laryngeal reflex arcs probably predominate at the cerebral and brain stem level, whereas conscious perception of laryngeal stimulation may rest in the thalamus and cerebral cortex (Lam and Ogura, 1952).

Jackson (1922) reported that the presence of a foreign body in the larynx is capable of stimulating violent coughing. He indicated, however, that a condition of tolerance to mechanical stimulation may be established.

Stimulation of the tracheo-bronchial tree

Brodie and Russell (1900) stimulated the central ends of pulmonary branches of the vagus nerves and observed apnoea, as well as hypotension and bradycardia. They considered that this demonstrated that afferent impulses from receptors in the lungs, travelling up the vagus nerves may produce these reflex effects. Roger (1917), by blowing an inert gas

through a tracheal cannula, produced deep, prolonged and spasmodic inspiration in rabbits, followed by a short period of apnoea and then rapid respiration. Jackson (1922), describing his bronchoscopic observations of the cough reflex in man, recorded the fact that mechanical stimulation of the tracheobronchial mucosa will provoke a violent attack of coughing. Tolerance to the stimulus is established quickly, provided the stimulus, in this case a bronchoscope, is kept in one place and not moved about. Tolerance is quickly lost when the bronchoscope is removed. Larsell and Burget (1924), using rabbits and dogs, confirmed Jackson's observations that mechanical stimulation of the larger air passages elicits a forced expiratory response and that the afferent pathway is in the vagus nerves.

More recently Widdicombe (1954b) has reported three types of mechanoreceptors in the tracheobronchial tree of cats anaesthetized with chloralose. They may be distinguished by their response to various mechanical and chemical stimuli. He noted (Widdicombe, 1954a) that reflex coughing in response to mechanical stimulation may be blocked by intra-tracheal ether vapour or procaine spray and that the pattern of response varied with the type and depth of anaesthetic used. Bucher (1958), discussing the pathophysiology and pharmacology of coughing, includes mechanical and chemical stimulation of the tracheal mucosa as two of the stimuli which may cause coughing.

Work reported in this thesis shows that stimulation of apnoea and laryngospasm occurs when an isolated segment of trachea, with its nerve and blood supply intact, is exposed to ether vapour. It has also been demonstrated that laryngospasm may be stimulated when ether vapour is inhaled into the distal trachea and lung bed, an observation consistent

with Comroe's statement (1965a) that chemoreceptors are present in the lung bed.

Stimulation of the abdominal viscera and diaphragm

Brewer, Luckhardt, Lees, and Bryant (1934) reported a series of experiments on dogs under pentobarbitone, ether or paraldehyde anaesthesia in which adductor spasm of the glottis occurred after electrical stimulation of the splanchnic nerves or traction on the mesentery. Brewer and Bryant (1935) carried out further experiments in dogs under ether anaesthesia before and after section of the splanchnic nerves. They concluded that the splanchnic nerves were the only ones providing an afferent pathway for this reflex from the abdominal viscera.

Reeve, Manson and Rundle (1951) reported that periods of apnoea were common during upper abdominal operations in man, but that they occurred infrequently in other abdominal operations. They were mainly associated with intraperitoneal manipulations of the upper abdominal viscera. Pressure, tension and friction applied to the deep surfaces of the parietal peritoneum were the stimuli which caused this effect and the afferent pathway was said to be in the intercostal nerves. They demonstrated the same reflex in rabbits and dogs. The surgical stimuli were the same as in man but in the rabbit the receptor field was larger. Closure of the glottis occurred in the rabbit at the height of, or during, the last inspiration before the respiratory inhibition. The lungs were then held in inspiration, or the glottis was opened a little to permit a slow expiration. In the dog and the rabbit depression of the diaphragm, caused by traction, slowed or arrested respiration and increased the functional residual air. This reflex was abolished by section of the

vagus nerves in the cervical region and the authors suggest that it may be the inflation Hering-Breuer reflex. An equally plausible explanation is that it may be the result of stimulation of receptors in the diaphragm. It was not seen in man, and they suggested that this may be because there is less traction applied to the diaphragm during operation. They suggested that the inhibitory respiratory reflex may be best abolished by local anaesthesia of the parietal peritoneum. In their experiments, respiratory records were obtained by the use of a spirometer in both rabbits and dogs. In rabbits they had observed the behaviour of the larynx directly by cutting an 8 mm hole in the anterior wall of the pharynx just above the thyroid cartilage and gently pulling the epiglottis through the wound, or the size of the laryngeal orifice was measured indirectly by measuring the resistance of the larynx to a stream of air blown through it from below.

(c) Laryngeal closure and its function

Theories of laryngeal closure were suggested by a number of workers in the nineteenth century. Wyllie (1866) carried out experiments on the human larynx obtained at post mortem examinations and concluded that there is a double valve mechanism within the larynx which is capable of controlling both the entrance and exit of air. He postulated that when the true vocal cords were in apposition they would prevent the entrance of air, but not its exit, whereas apposition of the false vocal cords was capable of preventing even a powerful current of air passing through from below. Brunton and Cash (1883) carried out experiments which confirmed Wyllie's work on the action of the true and false cords.

Semon (1890a) made observations on the action of the larynx in quiet

respiration in man. He concluded that in man the dorsal cricoarytenoid muscles (dilators of the larynx) are normally in a state of partial contraction, that this contraction is tonic in nature and that the afferent impulses involved in the reflex are mainly conducted along the vagi. The adductor muscles of the vocal cords have primarily nothing to do with respiration and are limited to assisting in the protection of the lower air passages against entry of foreign bodies and in the mechanism of the modified forms of expiration, coughing and laughing. Later in 1890, Semon and Horsley published the results of an experimental investigation of central motor innervation of the larynx. They believed that the stimulus for phonatory laryngeal movements may originate in the cortex and the stimulus for respiratory laryngeal movements in the bulbar region. By stimulating the floor of the fourth ventricle, they localised areas whose stimulation resulted in adduction and abduction of the vocal cords respectively. They noted that results varied when intensity of stimulation was not kept constant, or when an even depth of anaesthesia was not maintained. Differences in response between species, and even differences between different animals within a species were observed.

Semon (1890b) published more details of the work leading to his conclusions about the reflex tonus of the abductor muscles and the function of the adductors. His conclusions were based on evidence from "trustworthy observers", direct comparative measurements of the width of the glottis during quiet respiration and after death, and on the results of animal experiments. When he stimulated the cut end of the recurrent laryngeal nerve, in most species the corresponding vocal cord was drawn towards the midline. He stated that the cat proved to be an exception to this general observation, but gives no details of any experiments on cats. When the

adductor and abductor muscles were stimulated equally strongly, the overall effect was adduction. He commented that this observation was incompatible with theories which had been expressed previously that there is a dominance of abductor over adductor tone in the larynx.

More recently, Rattenborg (1961) has postulated that in man the larynx plays an important part in the regulation of frequency and depth of breathing. He has shown that the resistance of the larynx decreases when resistance to expiration is increased. He compared free exhalation through the mouth with exhalation through the nose and graded resistances. He suggests that the larynx is the primary site of, or at least an important contributor to intrinsic adjustments of airway resistance.

The current opinion of the majority of anaesthetists has been put forward by Keating, who states that the primary purpose of the intrinsic adductor muscles of the larynx is to protect the airway and prevent foreign material reaching the lungs (Keating, 1963). He stresses the importance of recognizing that blood, saliva, mucus and vomitus provide a stimulus for laryngospasm if they are allowed to accumulate in the region of the anterior larynx. The fact that irritant inhalation anaesthetics may produce the same effect is noted. When the laryngeal aperture is diminished, but not obliterated, a "crowing" noise is heard at inspiration and respiratory effort is increased. Complete spasm is indicated by a silent state, in which no gases may pass the tightly closed glottis, despite considerable respiratory efforts in those cases where the spasm is not accompanied by apnoea. Laryngospasm presents a potential hazard, which too frequently becomes a real danger to the maintenance of a clear airway during general anaesthesia.

The present review of some of the more important contributions to

the literature on respiratory reflexes makes it clear that reflex laryngospasm, bronchospasm, coughing and changes in respiratory rhythm may be stimulated by the response of various types of receptors in a broad distribution throughout the body. A major part of this investigation has been concerned with the definition of sites of stimulation, types of receptor, and nerve pathways involved in the production of these reflexes.

2. The Clinical Significance of Laryngospasm

Laryngospasm has been defined as an occlusion of the aditus laryngis by the action of the intrinsic laryngeal muscles. It was considered essentially to be a protective reflex by Keating (1965) and is supposed to prevent foreign material reaching the tracheobronchial tree and lungs. Bronchospasm, a condition in which contraction of the bronchial musculature causes constriction of the smaller air passages, may be associated with laryngeal spasm in some circumstances. Edwards, Morton, Pask, and Wylie (1956) state that "bronchospasm" is a term often used by anaesthetists to denote a state in which inflation of the lungs becomes increasingly difficult or impossible. In all sixteen cases listed in their report it was possible to define a cause or a stimulus which was responsible for the bronchial constriction and they emphasise the likelihood of the occurrence of "bronchospasm" when protective reflexes are inadequately suppressed. The exact nature of the mechanism of "bronchospasm" has not been determined and it is interesting to note that in some cases it may be relieved in dogs by the intravenous injection of a muscle relaxant (Rex, 1963). Evans and Gray (1965) report that bronchospasm may be relieved when complete muscle paralysis is produced and draw attention to the apparent connexion between what seems to be bronchial spasm and a lack of complete muscular

relaxation. These observations are particularly interesting because the muscle around bronchioles and alveoli is smooth (Macklin, 1929).

(a) The importance of laryngospasm and bronchospasm in man and animals

There are many references to the fact that laryngospasm and bronchospasm add to the hazards associated with anaesthesia in both man and animals. In 1949, the Association of Anaesthetists of Great Britain and Ireland undertook a project encouraging the voluntary reporting of anaesthetic deaths (Anaesthesia, 1949). The response was such that by 1955 one thousand reports had been received. These were studied by a committee and the results published (Edwards et al, 1956). The report shows that during the period under consideration one in twenty of the deaths was the result of respiratory obstruction of one sort or another. Of these fifty deaths, laryngospasm alone occurred in three, widespread spasm of the respiratory muscles including those of the larynx during expiration, occurred in nine, sixteen were reported as displaying bronchospasm, in sixteen complications of endotracheal intubation occurred, and six had an "upper respiratory obstruction" in the form of a neoplasm or oedema of the glottis associated with the clinical condition. Other authors to comment on this problem are Bamforth and Siebecker (1963), who state that laryngeal spasm is potentially the most frequent source of respiratory obstruction during inhalation anaesthesia in man, and Lewis and Swerdlow (1964) who report that cardiac arrest is a hazard of endotracheal intubation.

In a discussion of the laryngeal sequelae of endotracheal intubation, Wolfson (1958) mentioned laryngeal granuloma formation as one of the major complications encountered. In some cases this was a result of difficulty

in intubation through attempting the procedure when there was partial or complete laryngeal spasm. Another cause may be clamping of the cords against the tube during anaesthesia. Wylie (1950), and Lewis and Swerdlow (1964) have also reported trauma during direct laryngoscopy for intubation when muscle relaxation and reflex suppression were incomplete.

Lamb (1963a), Westhues and Fritsch (1965a) and Hall (1966a) state that laryngeal spasm has been reported during general anaesthesia in all species of domestic animals, but that the condition occurs most frequently in cats, especially when they are subjected to high concentrations of ether vapour or when there is excessive mucus, saliva, or blood in contact with the larynx before the protective laryngeal reflexes have been subdued. Bronchial spasm is also mentioned as a hazard of general anaesthesia in all species by these authors.

(b) Conditions under which laryngospasm occurs

Guedel (1951) considers that two separate mechanisms contribute to the occurrence of laryngeal spasm during clinical anaesthesia. The first, in which there is direct irritation of the vocal cords, occurs when there is a sudden increase in the concentration of the irritating vapour at the mask when the depth of anaesthesia is insufficient to suppress the vocal cord reflex; once such a direct spasm is established, it may be difficult to relieve, and thirty to forty five minutes may elapse before "free respiration" is established again. The second mechanism he considers is damage to the tissues, with traction on abdominal or pelvic viscera being the most important stimulus involved.

That the inhalation of irritant vapours and anaesthetic agents may produce laryngeal spasm, apnoea, coughing or bronchospasm in man and

animals is supported by the work of Allen (1929a, 1929b), Comroe (1965b), Harrison et al (1963) and Rex (1966, 1967). Allen used seventeen volatile substances as well as ether and chloroform on unanaesthetised human subjects, sleeping subjects, and one who was anosmic. He also carried out inhalation tests on anaesthetised subjects at the end of operation, but in this case he used only five of the volatile agents and included neither ether nor chloroform. Comroe records the occurrence of reflex apnoea, laryngeal closure, and bronchoconstriction as possible results of chemical or mechanical irritation of the nasal passages of some animals. He states that in the rabbit, the reflex apnoea following inhalation of ether or chloroform may be so prolonged as to cause death. Comroe emphasises the need for more information about the immediate response of man to a variety of gases and vapours used in clinical anaesthesia. The same statement may be applied to the situation in animal anaesthesia. Harrison (1962) compared the duration of active respiratory responses to irritation of the respiratory tract during anaesthesia with different agents. The irritant stimulus he used was a puff of cigarette smoke. Harrison suggested that the differences in duration of response are determined by the strength and duration of the stimulus and by the effect of the anaesthetic agent. His proposition was that the anaesthetic agents may sensitize receptors, act on the respiratory centre, or even modify respiratory muscle activity.

Laryngospasm produced by high concentrations of irritant vapours may reduce the amount of these vapours reaching the lung. Inert dusts, smoke and low concentrations of gaseous irritants increase airway resistance in man, even when the concentration is too low for the subject to be aware of it, or too low to elicit the cough reflex (Comroe, 1965b).

The second mechanism mentioned by Goodal is well supported by the

report by Reeve et al (1951) referred to earlier in this literature review. The technique used in the upper abdominal operations they describe was "morphine-thiopentone-d-tubocurarine anaesthesia" (that is, thiopentone administered after a morphine premedication and using d-tubocurarine as a muscle relaxant). Periods of apnoea also occurred in patients under other combinations of anaesthetic drugs and they were mainly associated with intraperitoneal manipulations to the upper abdominal viscera.

Laryngeal spasm has also been reported as being produced by mechanical stimulation of the epiglottis during attempts at intubation, when the glottic reflex was not abolished by deep anaesthesia, a muscle relaxant, or a local analgesic spray of the pharynx and anterior larynx (Bamforth and Siebecker, 1963). Under conditions of light thiopentone narcosis, Dundee (1965) states that there is an apparent increase in the sensitivity of the laryngeal reflexes, with an increased incidence of laryngospasm over that observed when inhalation techniques are used. He suggests that this is probably due more to a failure of the barbiturates to depress the laryngeal reflexes, than to any stimulant action. Coughing, sneezing, hiccup or bronchospasm are also stated to be common with the barbiturates. The presence of excess mucus or foreign bodies in the upper respiratory tract are predisposing causes. Dundee considers that this may be because thiopentone depresses the sympathetic nervous system more than the parasympathetic system.

(c) Methods suggested for preventing laryngospasm

Rosen (1960) states that severe laryngeal spasm in man is less common than it was formerly. This is probably due to the wider use of muscle relaxant drugs, whereas formerly atropine, used in pre-anaesthetic medication

was the only agent which would contribute to the control of laryngospasm. Rosen discusses the rationale of the use of atropine in both prevention and treatment of laryngospasm. Harrison and Vanik (1963) have also discussed the effect of atropine on the incidence of laryngeal spasm. The consensus of opinion seems to be that atropine does not prevent laryngospasm, although it may remove some of the predisposing causes by suppressing the secretion of saliva and mucus. Effects of atropine are considered in more detail at a later stage in this study. Lamb (1963a) stated that atropine may be used as pre-anaesthetic medication to prevent laryngospasm and he considers that it may be used in the treatment of the condition once it develops.

Other methods which have been advocated to help in the prevention of laryngospasm are the use of an increased depth of anaesthesia, muscle relaxants, or local analgesic sprays (Guedel, 1951). Among the precautions Lewis and Swerdlow (1964) suggested for avoiding cardiovascular hazards of endotracheal intubation were the maintenance of adequate oxygenation, prevention of laryngeal spasm, coughing and bucking, use of a muscle relaxant or deep anaesthesia, and blocking of autonomic reflexes by application of a topical analgesic to the laryngo-tracheal mucosa.

III EXPERIMENTAL PREPARATIONS EMPLOYED AND THE ACTIVITY OF THE LARYNGEAL MUSCLES AND THE DIAPHRAGM DURING QUIET RESPIRATION AND INFLATION AND DEFLATION OF THE LUNGS

1. The Experimental Preparation

The cat was chosen for this study of laryngeal reflexes because it was easily available and relatively easy to handle. Laryngospasm is more common during anaesthesia in the cat than in other species of domestic animals. There is a fair background of anatomical study on the cat and a considerable body of evidence on respiratory reflexes has been accumulated in this species. The animals used were clinically healthy and had not been submitted to anaesthesia for a period of at least one month before they were used in an experiment. One hundred and fifty two cats were used in the study of which sixty four were males and eighty eight females. They were a variety of ages and their weights ranged from 1.2 to 5.9 kg.

It was considered necessary to have a record of the activity of the laryngeal muscles and diaphragm during quiet respiration in each preparation before any stimuli were applied. It was also essential that the activity of the larynx and diaphragm should not be complicated by the addition of maintenance doses of anaesthetic agent during the course of an experiment. In an attempt to provide such conditions, the following techniques were considered:

(a) The administration of chloralose intravenously after induction of anaesthesia with halothane by mask.

(b) The production of a decerebrate animal after induction of anaesthesia with a volatile

anaesthetic, for example halothane by mask.

(c) Maintenance of anaesthesia with other agents.

These are discussed in detail in the following sections.

(a) Maintenance of anaesthesia with chloralose

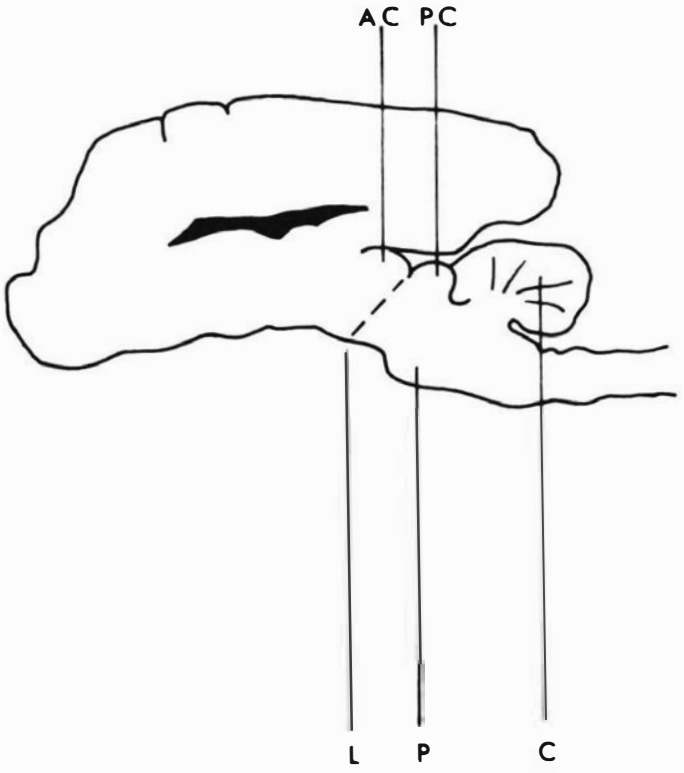
Heffter (1889) was the first to isolate and describe chloralose. This publication included an account of the chemical rather than the pharmacological properties of the drug as it was written for a chemical journal. A description of the pharmacology of chloralose by Hanriot and Richet in 1893 stimulated Heffter to publish an account of his experiments in frogs, dogs and rabbits (Heffter, 1893). Hanriot and Richet (1893), working with dogs and cats, reported that when chloralose was injected intravenously or administered either intraperitoneally or by mouth, it produced loss of consciousness and analgesia. Spinal reflexes were not abolished and the animals showed hyperexcitability to mechanical stimuli. The blood pressure was raised and the drug appeared to produce no disturbances of cardiac rhythm. Respiratory movements tended to be rather irregular. Temperature control was lost and the animals tended to shiver. They considered that chloralose was a useful drug for physiological experimental work because it rendered animals unconscious and free from perception of pain without interfering with reflex activity. The only disadvantage they reported, was that because of its low solubility a large volume of solution had to be injected to provide an effective dose. Heffter (1893), using the drug in frogs, dogs and rabbits, demonstrated excitability of reflexes in all three species during loss of consciousness. He considered that chloralose provided paralysis of the cerebrum and that higher doses produced paralysis of the respiratory centre. The trembling reported by

Hanriot and Richet (1893) was also observed by Heffter. Blood pressure was maintained unless there was a considerable reduction in respiratory rate. Heffter considered that when overdosage with chloralose occurred, death was due to paralysis of the respiratory centre.

Chloralose has been used extensively in the cat for experimental work in which a prolonged period of anaesthesia without depression of reflexes is required. Westhues and Fritsch (1965b) recommend a dose rate in cats of 50-70 mg per kg given intravenously, Lumb (1963b) recommends a dose rate of 79 mg per kg. Widdicombe (1954a, 1954b, 1954c) used chloralose at a dose rate of 60 mg per kg to anaesthetise cats for the investigation of respiratory reflexes originating from the stimulation of receptors in the trachea, bronchi and lungs. Green and Neil (1955) used a mixture of chloralose and urethane intraperitoneally in an investigation of the respiratory function of the laryngeal muscles. Wang and Nims (1948) reported that chloralose depressed respiration in cats, and that the drug also depressed the stimulating action of carbon dioxide on respiration.

Chloralose has the advantage that it allows the neuraxis of the animal to remain intact while a relatively stable state of anaesthesia can be maintained over a long period. If induction of anaesthesia is achieved with an inhalation agent before the chloralose is administered, the inhalation agent may be largely eliminated via the lungs before the experiment is started. Disadvantages of chloralose are a tendency for the animal to be hyperexcitable and a possibility that the drug may interfere with, depress, or augment reflex effects during an experiment. This leads one to ask if the responses observed during the course of an experiment are a true result of the stimuli used, or an indication of the action of the stimulus in relation

Fig. 6 Diagram to show the Level of Transection of the Neuraxis in a Decerebrate Preparation prepared by Intercollicular Section



After Lovatt Evans (1949c) Longitudinal section of a cat's brain.

AC Anterior colliculus
L Level of transection of neuraxis
PC Posterior colliculus
C Cerebellum
P Pons

to chloralose. Chloralose was used in twenty four cats in this study, it was administered intravenously at a dose rate of 65 or 70 mg per kg after induction of anaesthesia with halothane by mask. No substantial conclusions have been derived in this thesis from experiments performed under chloralose alone. Similar experiments have either been done in decerebrate preparations or conclusions have been supported by work done under conditions other than chloralose anaesthesia.

(b) The decerebrate preparation

Section of the brain stem at a midbrain level leaves both the pons and medulla oblongata intact and connected with the spinal cord through their descending pathways. A state of hyperactivity of the stretch reflexes ensues, giving rise to "decerebrate rigidity". The rigidity of the decerebrate preparation was described clearly by Sherrington (1898). He regarded "decerebrate rigidity" as the result of releasing the lower brain stem from the control of the higher centres of the forebrain. Decerebration by intercollicular section involves the transection of the neuraxis anterior to the bony tentorium, with the animal under an inhalation anaesthetic (halothane in the case of experiments described in this thesis). Fig. 6 (facing p.27) shows the level at which the neuraxis is transected.

An alternative method of decerebration in cats by the production of ischaemia of the forebrain was described by Pollock and Davis (1923). They achieved this by ligating the basilar artery with the cat under ether anaesthesia. The basilar artery was exposed by trephining through the base of the skull in the midline between the tympanic bullae. The dura mater was exposed, and the basilar artery ligated. The common carotid arteries

Fig. 7 Diagram to show the Level of Decerebration of the Neuraxis in the Ischaemic Technique

After Pollock and Davis (1923)
Methylene blue has been injected intravenously before death. That part of the neuraxis with an intact blood supply is stained, the ischaemic area remains unstained.

were then ligated and a decerebrate preparation resulted. Fig. 7 (facing p.28) shows that decerebration by ischaemia causes loss of function of the anterior half of the cerebellum, the cerebral hemispheres, and the whole of the neuraxis anterior to the mid-pons. Pollock and Davis (1923) argued that operations for the production of decerebrate preparations by transection of the brain stem were attended by a high mortality and considerable shock. They suggested that frequently some part of the brain, anterior to the point of section, remained intact and that haemorrhage was uncontrolled and immeasurable. They stated that shock would alter the properties of the preparation and that other untoward symptoms might be seen because of haemorrhage causing compression of brain tissue caudal to the section.

Pollock and Davis' technique of ischaemic decerebration was attempted in twenty three cats during the course of this study. Although successful decerebration was achieved in fifteen of the twenty three cats, their behaviour as experimental preparations was not consistent. In the author's hands, the technique took much longer than that of intercollicular section and the results were not predictable. The survival times of these preparations varied from thirteen minutes to over eleven hours. In seven cats, profuse haemorrhage occurring during attempts to ligate the basilar artery caused the abandonment of the experiment. Pollock and Davis suggested that the area of the brain rendered ischaemic might be mapped out by injecting methylene blue solution intravenously. This procedure was carried out in six of the twenty three cats. Staining was identical with that illustrated in Fig. 7, except in the case of one cat, in which a large branch of the basilar artery supplying the forebrain was noted just posterior to the ligature. Although fifteen of the twenty three cats

exhibited decerebrate rigidity, they also exhibited hyperexcitability when the pharynx and larynx were stimulated and proved unsatisfactory preparations for an investigation of the laryngeal reflexes.

The majority of experiments whose results are reported in this thesis were performed on decerebrate preparations which had been produced by intercollicular section. These preparations had the advantage that no further anaesthetic was needed once section of the neuraxis had been carried out. Anaesthesia during the process of decerebration was provided in the earlier experiments by halothane and ether, and later by halothane alone. These volatile anaesthetics were almost completely excreted via the lungs before each experiment was started. There was thus unlikely to be a significant pharmacological effect continuing through the experiment. This represented an advantage over chloralose anaesthesia. A major disadvantage, is the possibility of haemorrhage and shock occurring during the process of decerebration. This may be avoided by careful technique and the judicious use of warm saline, cotton wool packs, and suction. Gentle surgery and the control of haemorrhage resulted in the majority of preparations being satisfactory for experiments on the laryngeal reflexes. Although it was not possible to define the exact level at which the neuraxis would be sectioned, the use of a standardized technique ensured that section was at approximately the same level in every preparation. The fact that experimental results were repeated without difficulty in different preparations suggests that accurate section of the brain at a particular level is not important in relation to these reflexes.

(c) Maintenance of anaesthesia with other agents

Workers in the field of laryngeal and respiratory physiology have used

a number of agents other than chloralose for the maintenance of anaesthesia in cats. For example, Fink and Ngai (1959), Milojevic and East (1964), Floyd, Negus and Neil (1957) and Kirikae, Hirose, Kawamura, Sawashima and Kobayashi (1962) have used pentobarbitone sodium by the intravenous or intraperitoneal route. Burstein and Rovenstine (1938) anaesthetised cats with various short acting barbiturates (including pentobarbitone) which they administered intravenously. They demonstrated adduction of the vocal cords and hyperactivity of the laryngeal reflex during this type of anaesthesia. The findings of Burstein and Rovenstine suggest that barbiturates may cause a sensitization of the laryngeal reflex. For this reason, barbiturates were not used to anaesthetize cats in this study.

Urethane has been used by many workers for prolonged anaesthesia in the cat. It produces a long period of light anaesthesia, but it has undesirable side effects such as emesis and excitement. It has also been suggested that urethane may have carcinogenic effects (Wood, 1956). For this reason care must be taken to avoid contact with urethane or its solution.

Teitelbaum et al (1936) and Nanjo (1955) used ether to anaesthetize cats for the investigation of respiratory reflexes and respiratory muscle activity respectively. Ether was used as an adjunct to halothane in the earlier experiments in this study. Its use was discontinued, to eliminate the possiblity of sensitization of chemoreceptors by ether.

In the work reported here, both decerebration and the intravenous administration of chloralose were found to produce stable preparations. Experiments of up to nine hours duration were carried out with consistently reproducible results. For these reasons, therefore, preparations anaesthetized with chloralose, or decerebrate preparations were used

throughout this study.

2. Methods Used to Investigate the Activity of the Laryngeal Muscles

The larynx can be observed directly if the cat's jaws are held open with a gag. This method of observation proved unsatisfactory because a permanent record of vocal cord activity could not be obtained. Cine photography of the cords was considered to be impractical because of limited access and expense. Even if records of the movements of the vocal cords during quiet respiration could have been obtained, it would have been impossible to film cord activity during administration of inhalation agents by mask.

Electromyographic records of the intrinsic muscles of the larynx may be obtained with needle electrodes (Adrian and Bronk, 1929) inserted into these muscles. The muscle activity can be monitored from leads from the needle electrodes to the input of an amplifier by feeding the signal to a loudspeaker. This technique may be combined with direct observation of the laryngeal muscles. Permanent records of such muscle action potentials can be obtained by photographing the display produced when the signal from a needle electrode is amplified appropriately and displayed on a cathode ray oscilloscope. Another method of obtaining a permanent record is to feed the signal into a multi-channel recorder. The recording of action potentials from muscles during their activity is known as electromyography, in its most precise form it involves the use of high speed recording systems such as an oscilloscope and recording camera. This was the method selected for recording muscle activity in this study.

(a) A historical consideration of electromyography

In the eighteenth century, Galvani had observed that skeletal muscles

produce a detectable voltage when they contract. He also showed that they would contract if they were stimulated electrically. Neurophysiologists and anatomists in the twentieth century, notably Adrian and Bronk, Basmajian, and Denny-Brown, developed techniques for recording the electrical potentials produced by active muscles. The introduction of the concentric needle electrode by Adrian and Bronk (1929) was a considerable step forward. Weddell, Feinstein and Pattle (1944) were the first to report on electromyographical investigations of the muscles of the larynx in man. Their records of laryngeal activity formed a small section of work on the body musculature as a whole. Since Weddell et al (1944) published the results of their work, many papers have appeared describing the use of electromyography for the investigation of laryngeal activity in man (for example: Buchthal, 1959; Faaborg-Andersen, 1957, 1965; Faaborg-Andersen and Buchthal, 1956; Faaborg-Andersen and Edfeldt, 1958; Faaborg-Andersen and Vennard, 1964; Katsuki, 1950; Portmann, 1956, 1957; Portmann, Humbert, Robin, Laget and Vannier, 1955; Portmann, Robin, Laget and Duncombe, 1959; Roasier, Mieporent, Pipberger and Kalin, 1956; and Spoor and van Dishoeck, 1958) and in animals (for example: Doty and Boamm, 1956; Feesard and Vallancien, 1956; Kirikae et al, 1962; Milojevic and East, 1964; Murtagh and Campbell, 1954; and Nakamura, Uyeda and Sonoda, 1958).

(b) Techniques for electromyography

The two main types of electrode used in electromyography are surface electrodes and electrodes inserted into the muscles being studied. The latter have usually been needles. Localised recording from a single small muscle is not possible using a plate electrode unless the electrode can be placed directly on the muscle in question. The record is complicated

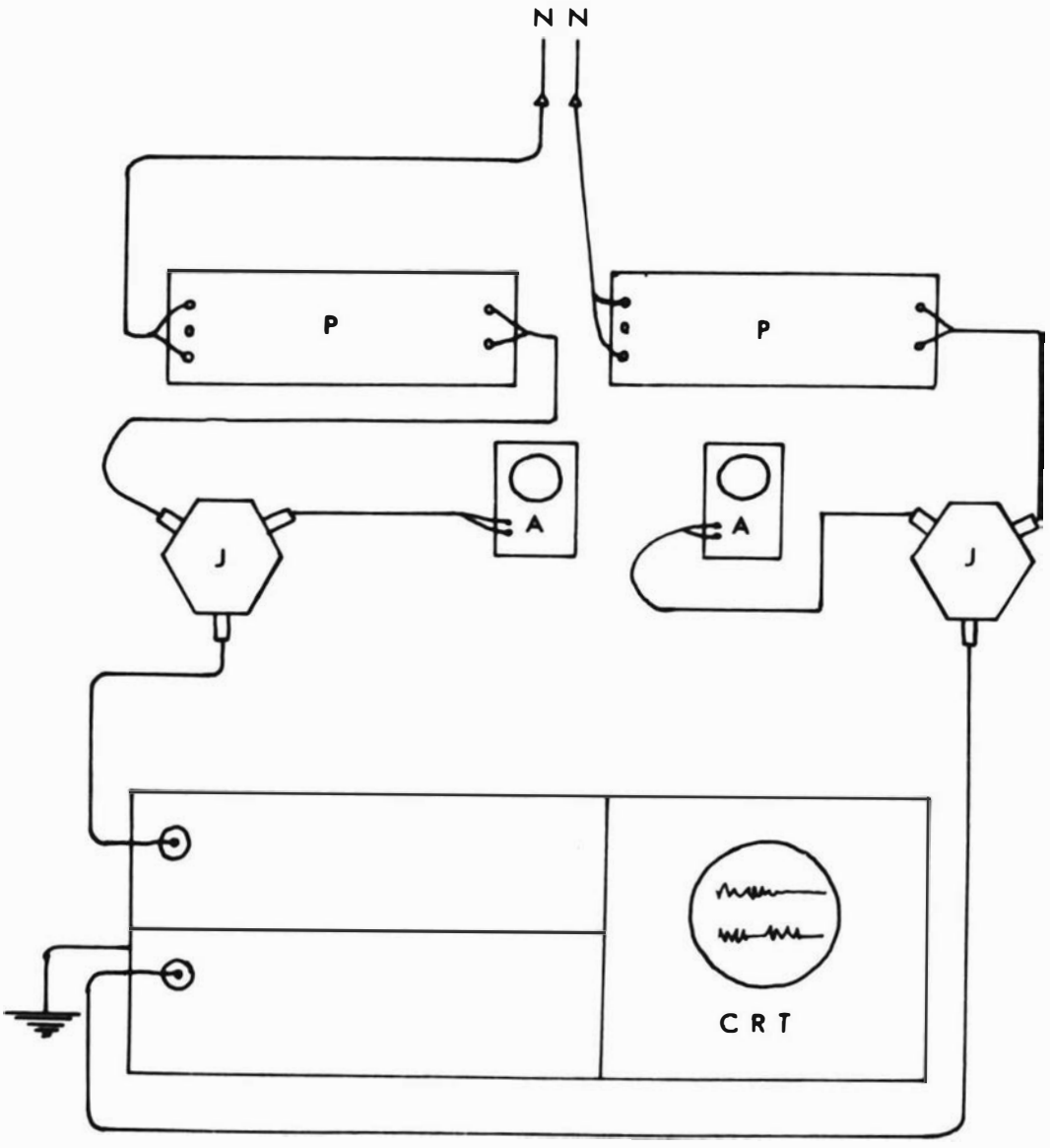
by the activity of other muscles in the vicinity. For this reason, plate electrodes were not used at any stage in this investigation.

The most commonly used needle electrodes are the concentric type first described by Adrian and Bronk (1929), and these were used throughout the work reported in this thesis. These concentric needle electrodes consisted of a stainless steel hypodermic needle of outer diameter 0.018" which contained an insulated 0.005" diameter stainless steel central core. The angle at the needle tip is 22°. Action potentials are measured between the tip of the central core and the surrounding needle shaft. The concentric needle electrode has advantages over the surface and unipolar types in selectivity, frequency response, and noise level (Becker and Chamberlin, 1960). In the acute experiments which form the basis of the work reported here, few problems were encountered in retaining electrodes in position during an experiment. In future work, however, when it is envisaged that electrodes will be implanted in chronic preparations, stainless steel wire loop electrodes (Basmajian, 1962a) or something similar will have to be used.

Basmajian (1962b) recommends that the leads from needle electrodes should be connected to a high gain amplifier with a selectivity for frequencies in the range from ten to several thousand cycles per second. Buchthal, Guld and Rosenfalck (1954) considered that a range of 2 to 10,000 cps was necessary to prevent distortion. The signal from the amplifier can be fed into one or more cathode ray oscilloscopes and the traces recorded photographically.

Other methods of recording, involving the use of ink-writing or hot stylus recorders, have the important disadvantage that their mechanical systems are not responsive enough for electromyographic work. These

Fig. 8 Block Diagram of the Recording System used for Electromyography



A Audio monitor
J Junction box
P Pre-amplifier
CRT Two channel cathode ray oscilloscope
N Needle electrode

recorders are not capable of reproducing signals of over 100 cps accurately. Ultraviolet recorders may provide a satisfactory alternative to photographic recording.

(c) Development of a recording technique

In this investigation a method of recording was required which would both provide accurate records of the activity of the laryngeal muscles and record the respiratory cycle simultaneously. The activity of the laryngeal muscles could then be related to events in the respiratory cycle. This was achieved by placing a second needle electrode in the diaphragm. In the early "pilot" experiments, the electromyograph was followed from the output of an audio-amplifier. No record was obtained. The next step was to feed the signals from two needle electrodes into the amplifiers of a two beam D33R Telequipment oscilloscope and into two audio-amplifiers (Fig. 8, facing p.34). A continuous record of the oscillations in the Y axis of stationary beams (no sweep) could be obtained by using a camera (Telequipment) which moved film past the beams at a constant speed. Agfa ARP2 paper was used in the camera whose film transport speed could be varied from 0.1 inches per second to 9.0 inches per second. The camera cassettes hold 25 feet of 35 mm film or paper.

A satisfactory record was not obtained with this apparatus. In an attempt to overcome the problems introduced by noise and interference (which will be discussed more fully later), a pair of balanced pre-amplifiers was introduced between the preparation and the oscilloscope. These pre-amplifiers were battery powered, and of the design of the Queens Square National Hospital, each had a 1 mV calibrator incorporated in its circuit. The time marker was a mechanical one provided in the camera

Fig. 9 The Effect of Excessive Intensity of the Oscilloscope Trace

Anaesthetized cat 3.0 kg. Chloralose (60 mg per kg) after halothane/ether induction. Electromyogram from diaphragm during inspiration.

from a flash of light every one fifth of a second. For this a synchronous clock motor was used to drive a rotating disc which had a slot cut in it so that a flash of light occurred every one fifth of a second. This was directed towards the camera by a perspex rod. Later in the study a large screen monitor was added to the circuit. This made both photographic recording and continuous visual monitoring possible.

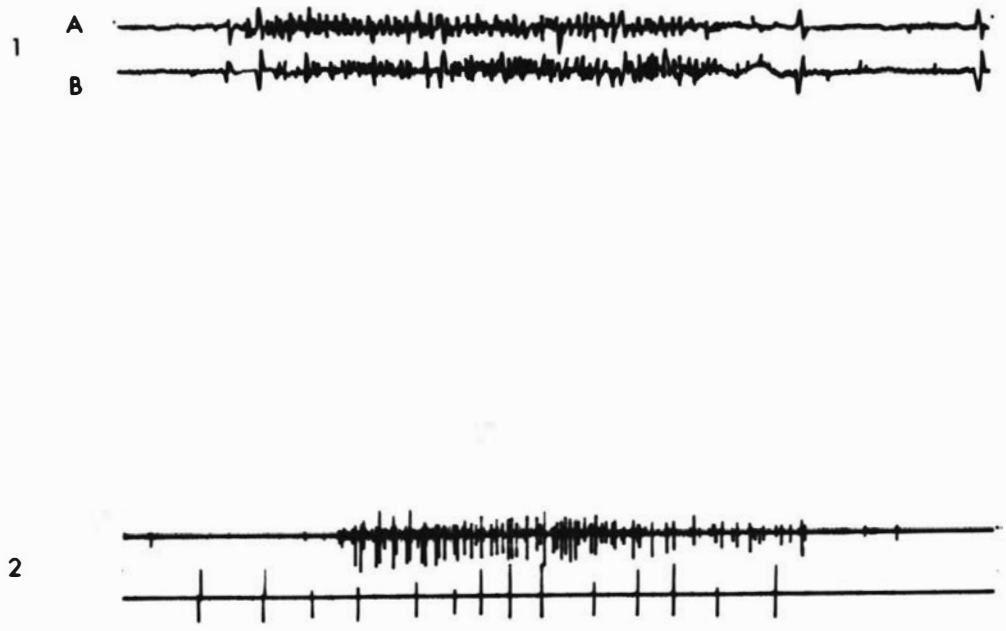
(d) Difficulties encountered in obtaining a satisfactory record

Too great an intensity of the oscilloscope trace in relation to the camera aperture, caused an increase in width, and blurring of the photographic record of the trace (Fig. 9, facing p.35). This problem was overcome by adjusting the oscilloscope intensity and the camera stop.

Care was needed to ensure that the paper or film transport speed was such that a clear record of action potentials was obtained on a length of film which could be handled easily and which avoided the problems of interpretation which arise when the resting trace is too short or when traces are cut in the middle of a response. After using a number of different speeds in the early stages of the investigation, a paper speed of approximately half an inch per second was chosen.

When potentials of 1 mV or less are being recorded, the elimination of background noise and interference becomes extremely important. Whitfield (1959) defines "noise level" as the degree of random movement of the base line due to spontaneous fluctuations in the system. Source noise is a function of the impedance and the temperature of the signal source. This is unavoidable, but it can be limited by using an instrument which does not respond to frequencies over 10,000 cps. Amplifier noise is introduced by the recording apparatus and should be capable of reduction,

Fig. 10 The Elimination of Noise and Unwanted Signals



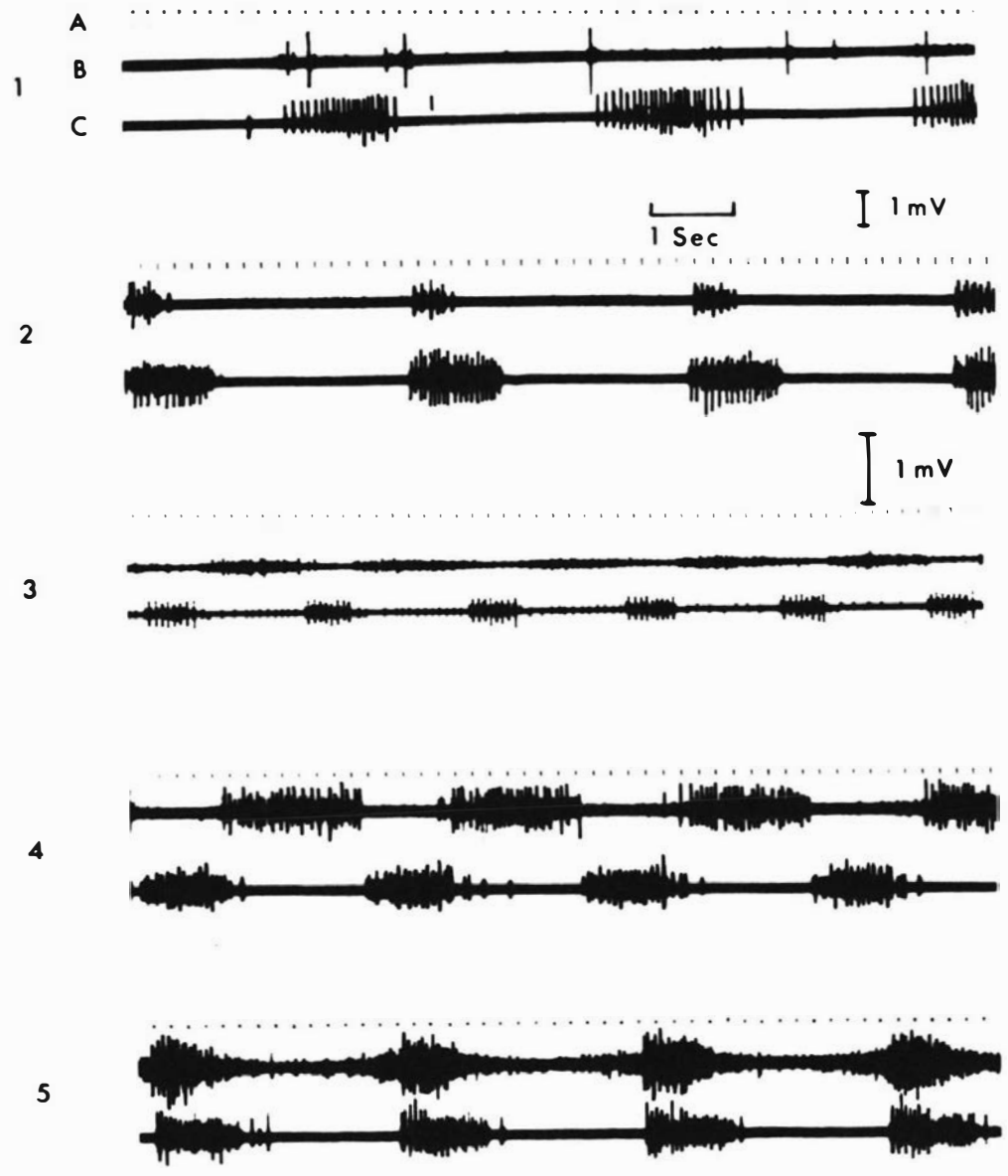
Trace 1: Decerebrate cat, adult female. Decerebration under halothane/ether anaesthesia.
A Electromyogram from dorsal cricoarytenoid muscle.
B Electromyogram from diaphragm.
Trace 2: Decerebrate cat, adult male. Decerebration under halothane/ether anaesthesia.
A Electromyogram from diaphragm.
B Electromyogram from cricothyroid muscle.
(Spikes retouched)

if not complete elimination, by proper design of equipment. It is of most significance in the first stage of a system, as there it is usually several times as large as the intrinsic source noise. In order to approach the theoretical minimum, careful first-stage adjustment is necessary and it is unwise to use maximum gain on a first stage amplifier.

Interference occurs as a result of the apparatus picking up unwanted signals either from the preparation itself or from the environment. Theoretically, this interference should be completely avoidable; in practice it may prove impractical to eliminate it completely. The most common type of interference is that emanating from the wiring of the 50-cycle mains supply. The mains supply to the apparatus itself is usually adequately smoothed, but other instruments working from the mains should be kept at a distance or, better still, switched off when recording is in progress. Other less important sources of interference are electrostatic interference and broadcast radio interference.

By working inside a screened cage lined with an earthed wire mesh, most interference can be eliminated, but this method is expensive to set up and presents some practical problems. Interference is reduced by the use of screened cable for the power supply, co-axial cable for instrument leads, and a common earth lead in the system. Earth loops, caused by the use of more than one earth lead, may introduce more interference than is present with no earth lead. It is not possible to generalise about the elimination of interference. The optimum signal can only be obtained by a system of trial and error in which the positions of the preparation, leads and components of the apparatus are altered until a satisfactory signal is obtained. Fig. 10 (facing p.36) shows a record of diaphragmatic activity and the activity of the dorsal cricoarytenoid muscle in which

Fig. 11 Resting emg Activity of the Diaphragm and Intrinsic Laryngeal Muscles of the Cat



Records from decerebrate cats. Decerebration under halothane or halothane/ether anaesthesia.
A: All traces. Time marker 0.2 sec.
B: Traces 1, 2 and 3. Electromyogram from cricothyroid muscle.
Trace 4. Electromyogram from lateral cricoarytenoid muscle.
Trace 5. Electromyogram from dorsal cricoarytenoid muscle.
C: All traces. Electromyogram from diaphragm.
(Spikes retouched)

there is source noise and an unwanted electrocardiogram (ecg) signal (Trace 1). The second trace in this figure shows a record of diaphragm and cricothyroid muscle in which noise and ecg have been eliminated (Trace 2).

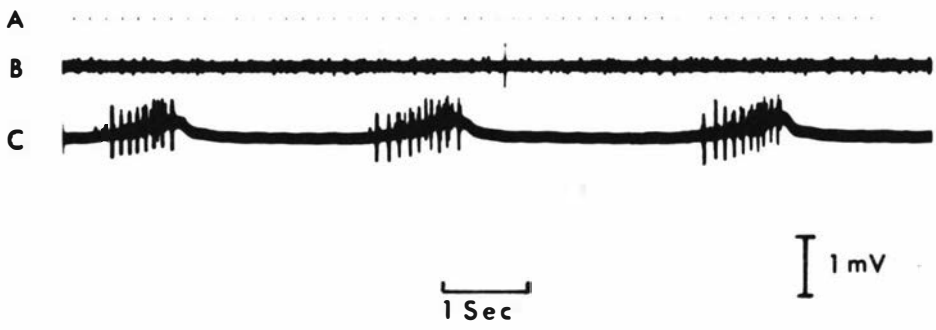
(e) Section and stimulation of nerves

In some experiments, nerves were cut and their central and peripheral ends stimulated. The object of cutting and stimulating nerves was to attempt to define the afferent and efferent pathways concerned in the production of laryngospasm. Action potentials from the diaphragm and the intrinsic laryngeal muscles were recorded before and after nerve section, and during electrical stimulation. Details of the experiments and the methods used are presented in chapters V and VI of this thesis.

3. Results of Investigations into the Resting Activity of the Diaphragm and the Intrinsic Laryngeal Muscles

Before an attempt was made to record the activity of the diaphragm and the intrinsic laryngeal muscles during laryngospasm, the types of activity which occur during quiet respiration had to be established. Fig. 11 (facing p.37) shows records of action potentials from the diaphragm, cricothyroid muscle, lateral cricoarytenoid muscle and dorsal cricoarytenoid muscle during quiet respiration. Rhythmic bursts of action potentials were recorded from the diaphragm on each inspiration during normal quiet respiration (All Traces, Fig. 11). Two types of resting activity of the cricothyroid muscle were commonly detected. One of these consisted of intermittent spontaneous activity of relatively few motor units unrelated to the diaphragmatic rhythm (Trace 1, Fig. 11). The

Fig. 12 A Record of Intrathoracic Pressure Superimposed on the Diaphragmatic emg Signal



Decerebrate cat 1.8 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec.
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm with intra-thoracic pressure record superimposed. (Spikes retouched)

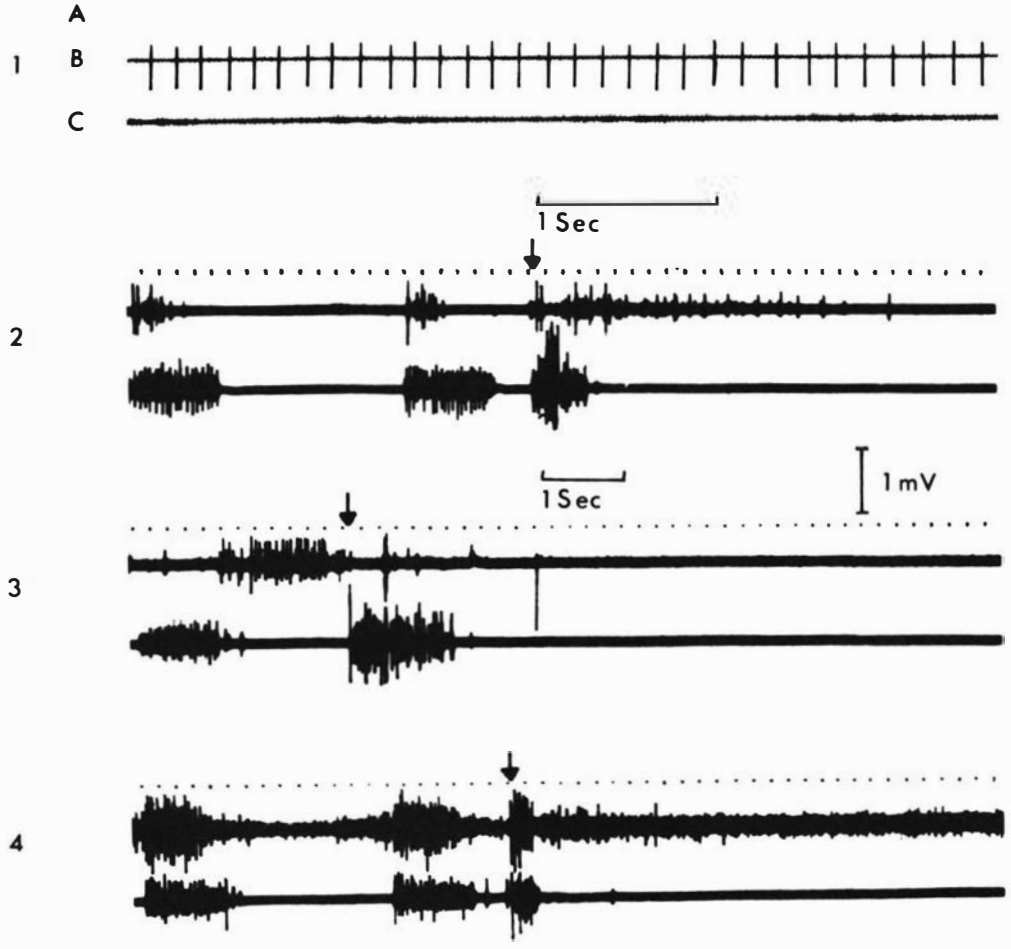
other was of phasic activity, again of relatively few motor units; the phasic activity was related to the inspiratory activity of the diaphragm (Trace 2, Fig. 11). A third type of activity of the cricothyroid muscle was observed occasionally. This was also phasic in character, but the activity was related to the expiratory phase of the respiratory cycle (Trace 3, Fig. 11).

Early in the study, records were obtained from two of the other intrinsic laryngeal muscles, the lateral cricoarytenoid muscle and the dorsal cricoarytenoid muscle. The lateral cricoarytenoid muscle is an adductor of the vocal cords. The recordings from this muscle showed phasic activity related to the expiratory phase of the respiratory cycle (Trace 4, Fig. 11). The dorsal cricoarytenoid muscle shows phasic activity starting slightly before the start of inspiration and continuing through the inspiratory phase of the cycle (Trace 5, Fig. 11). In one cat a record of intrathoracic pressure was obtained, through a transducer, from a tube attached to a balloon in the oesophagus. In the same cat a better pressure record was obtained by attaching tubing from a needle in the pleural cavity to a manometer and recording through a transducer. On both occasions the pressure record was superimposed on that of the diaphragmatic emg. It was possible to show, by this means, that electrical activity of the diaphragm extended very slightly into the expiratory phase in some cycles (Fig. 12, facing p.38).

4. <u>The Activity of the Diaphragm and Some of the Intrinsic Laryngeal Muscles during Inflation and Deflation of the Lungs</u>

A glass cannula was tied into the trachea at the junction of the larynx and the first tracheal ring. This had a piece of rubber tubing attached to its external end so that the airway could be clamped. Responses

Fig. 13 The Effects of Lung Inflation on the Activity of the Diaphragm and Intrinsic Laryngeal Muscles of the Cat



Records from decerebrate cats. Decerebration under halothane or halothane/ether anaesthesia.
A: Time marker 0.2 sec in traces 2, 3 and 4. (In trace 1 the lungs were inflated throughout, in traces 2, 3 and 4 arrows indicate the start of inflation).
B: Traces 1 and 2. Electromyogram from cricothyroid muscle.
Trace 3. Electromyogram from lateral cricoarytenoid muscle.
Trace 4. Electromyogram from dorsal cricoarytenoid muscle.
C: All traces. Electromyogram from diaphragm.

to inflation and deflation of the lungs have been well documented (Widdicombe, 1954b and 1954c). The object of these experiments was to show that cats which had been given chloralose or decerebrated display normal respiratory reflexes.

(a) Inflation

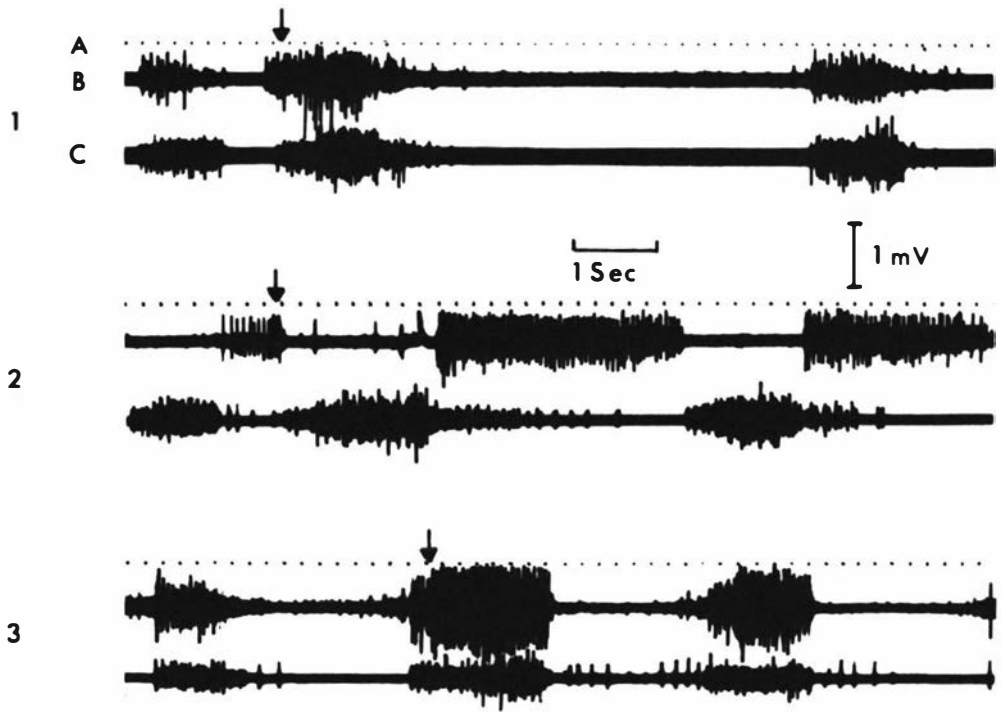
Inflation of the lungs was achieved by blowing air into the tube at the time of a normal inspiration. The lungs were over-inflated and the airway was then clamped. After a burst of action potentials at the time of inflation, no activity was recorded from the diaphragm during the 30 sec for which the lungs were held in the inflated position (All Traces, Fig. 13, facing p.39). The cricothyroid muscle displayed two patterns of activity on lung inflation. In the first type (Trace 1, Fig. 13) a continuous discharge was observed during the period of diaphragmatic inactivity. In the second type, the cricothyroid muscle activity was depressed or abolished during the period of inflation (Trace 2, Fig. 13). The lateral cricoarytenoid muscle showed a cessation of activity when the lungs were inflated (Trace 3, Fig. 13). Later, when the airway clamp was removed the muscle returned to its normal resting phasic rhythm at once. This is not shown in the figure.

The dorsal cricoarytenoid muscle showed depression of activity during the period of inflation (Trace 4, Fig. 13). Phasic activity of the dorsal cricoarytenoid muscle started again when the airway clamp was removed.

(b) Deflation

Deflation of the lungs was achieved by sucking air out from the tracheal cannula at the end of a normal expiration and clamping the rubber tube. Activity of the diaphragm was augmented, as judged by its emg.

Fig. 14 The Effects of Lung Deflation on the Activity of the Diaphragm and Intrinsic Laryngeal Muscles of the Cat



Decerebrate cat 2.25 kg. Decerebration under halothane anaesthesia.
A: All traces. Time marker 0.2 sec (arrows indicate start of deflation).
B: Trace 1. Electromyogram from cricothyroid muscle.
Trace 2. Electromyogram from lateral cricoarytenoid muscle.
Trace 3. Electromyogram from dorsal cricoarytenoid muscle.
C: All traces. Electromyogram from diaphragm.
(Spikes retouched)

Each inspiratory effort was of longer duration than in normal quiet respiration and more motor units were involved (All Traces, Fig. 14, facing p.40). The cricothyroid muscle also showed an increase in activity on deflation which was simultaneous with that of the diaphragm (Trace 1, Fig. 14). The lateral cricoarytenoid muscle maintained its phasic activity, alternating with that of the diaphragm. Activity of this muscle increased during deflation as judged by an increase in the frequency and in the number of motor units involved (Trace 2, Fig. 14). The dorsal cricoarytenoid muscle showed greater contraction during deflation and also maintained its phasic activity related to inspiration (Trace 3, Fig. 14).

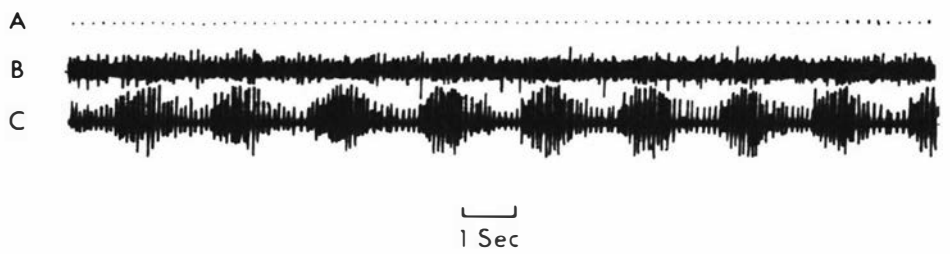
5. A Discussion of the Records Obtained during Quiet Respiration and on Inflation and Deflation of the Lungs

(a) Activity during quiet respiration

Fink and Ngai (1959) observed that in decerebrate cats electrical activity could be recorded throughout the diaphragm during inspiration. Basmajian (1962c) stated that many of the studies of electrical activity of the diaphragm have been conducted under highly unphysiological conditions. He quoted as an example an emg study by Di Benedetto, Siebens, Cincotti, Grant and Glass (1959) which was conducted on hepatectomised dogs whose abdomens were open during recording. Basmajian's aims and those of the present author differ in that the normal diaphragmatic record required in this investigation is that obtained during quiet respiration in the anaesthetized or decerebrate preparation, whereas he was interested in muscle activity in the conscious animal. Electromyographic recordings from conscious animals were not obtained in the present study.

There is general agreement that action potentials may be recorded from the diaphragm during inspiration. Pauly (1957) presented the simple

Fig. 15 Tonic Activity of the Diaphragm during Quiet Respiration



Decerebrate cat 2.5 kg. Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec.
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
(Spikes retouched)

Table 1. Activity of the diaphragm and laryngeal muscles during quiet respiration

	Diaphragm	Cricothyroid	Lateral cricoarytenoid	Dorsal cricoarytenoid
Inspiration	Active	Active	Inactive	Active
Expiration	Inactive *	Variable **	Active	Inactive

* Tonic activity was observed in the diaphragm in one preparation (Fig. 15, facing p.41) and in the other muscles on a number of occasions.

** Active in some cats, but inactive in others.

view, based on electromyography, that in man the diaphragm is active during inspiration and inactive during expiration. Murphy, Koepke, Smith, and Dickinson (1959), however, reported that there is a carry-over of electrical activity of the diaphragm into expiration in man even during quiet respiration. They noted that this did not occur during forced expiration. They postulated that the diaphragmatic contraction and that of the intercostal muscles during expiration served as a "braking force" against the elastic forces of the lung during passive expiration.

In this study diaphragmatic activity has been observed during inspiration. By obtaining a record of intrapleural pressure on the same trace as the diaphragmatic emg it was possible to show that electrical activity of the diaphragm extended very slightly into the expiratory phase in some cycles (Fig. 12, facing p.38). There was only one instance of truly continuous or tonic activity of the diaphragm during quiet respiration in the one hundred and fifty two cats used in the study (Fig. 15, facing p.41). Table 1 (facing p.41) summarizes the activity of the diaphragm, the cricothyroid muscle (adductor), the lateral cricoarytenoid muscle (adductor), and the dorsal cricoarytenoid muscle (abductor) during quiet respiration.

The cricothyroid muscle has been identified as an adductor of the vocal cords (Faaborg-Andersen, 1957; Seymour and Henry, 1954). In the present study its activity was found to be representative of that of the vocal cord adductors during laryngeal spasm. Therefore in most of the experiments the activity of the cricothyroid muscle and the diaphragm was recorded. A number of authors have reported activity of the cricothyroid muscle during inspiration in various species: Armstrong and Smith (1955) in dogs; Andrew (1955) in rats; and Faaborg-Andersen (1957)

in man. Arnold (1961) reported inactivity of the cricothyroid muscle during expiration in man. In contrast, Martagh and Campbell (1954) in the goat and Tschiassny (1944) in the dog had reported electrical activity of the muscle during expiration. There appear to be few reports of the activity of the cricothyroid muscle in cats apart from those of Seymour and Heary (1954) and Martagh (1945) that it has a marked adductor function. During expiration, in this study, the cricothyroid muscle has been observed in some cats to be inactive and in others to be active (Fig. 11, facing p.37). In some cats, continuous tonic activity has been observed in the muscle (Fig. 11, facing p.37). Tonic activity has also been reported by Faaborg-Andersen (1957) in man and by Nakamura et al (1958) in dogs.

The general consensus of opinion in the literature is that the lateral cricoarytenoid muscle (one of the chief adductors of the larynx) is inactive during inspiration and active during expiration in man (Portmann, 1957), dogs (Nakamura et al, 1958), and cats (Green and Neil, 1955). Faaborg-Andersen (1957), however, reported increased activity of this muscle during inspiration in conscious man. In the present study from fifteen experiments in which an electrode was placed in the lateral cricoarytenoid muscle in cats, it was found to be inactive during inspiration and active during expiration (Fig. 11, facing p.37).

The dorsal cricoarytenoid muscle has been reported as active during inspiration in man, cat, dog, and goat respectively by Portmann (1957), Green and Neil (1955), Nakamura et al (1958), and Martagh and Campbell (1954). Faaborg-Andersen (1957) reported inhibition of activity of this muscle during inspiration in man. In the present study, in twelve cats in which records were obtained from the muscle, it showed activity

during inspiration and was inactive during expiration (Fig. 11, facing p.37).

It has been possible, by recording the action potentials from the cricothyroid muscle of cats anaesthetized with chloralose and decerebrate cats, to identify three types of activity which occur in cats breathing quietly. Observations of other workers on the activity of the diaphragm during quiet respiration have been confirmed. A small number of records was obtained from other intrinsic laryngeal muscles. The divergent reports as to the activity of the intrinsic laryngeal muscles indicate that there may be some species differences in their patterns of activity. They also add weight to Basmajian's comment (1962d): "we can only hope that renewed and vigorous emg research will soon eliminate the controversy about this important region".

(b) Activity during maintained inflation of the lungs

Widdicombe (1954c) confirmed the occurrence of the Hering-Breuer inhibito-inspiratory reflex in the cat: during maintained inflation of the lungs the diaphragm is relaxed (Fig. 13, facing p.39). He also identified another reflex in response to large pulmonary inflations. This was an inhibition of respiratory activity of short duration. Widdicombe considered that this was distinct from the Hering-Breuer reflex. These observations have been confirmed during the course of this study.

In this investigation when the lungs were inflated the cricothyroid muscle has been observed to show continuous activity of a higher frequency than that recorded during normal quiet respiration. The lateral cricoarytenoid muscle displayed increased activity in some cats, but decreased activity in others (for example in the experiment illustrated in Fig. 13, facing p.39). The dorsal cricoarytenoid showed decreased

Table 2. Activity of the diaphragm and laryngeal muscles during maintained inflation and maintained deflation

	Diaphragm	Cricothyroid	Lateral cricoarytenoid	Dorsal cricoarytenoid
Maintained Inflation	Inactivity (Apnoea)	Active Continuous, and of higher frequency than normal.	Variable *	Decreased activity
Maintained Deflation	Increased activity	Bursts of activity synchronous with inspiration.	Activity maintained with increased frequency.	Activity maintained with increased frequency.

* Activity increased in some cats but decreased in others.

activity during inflation of the lungs and clasping of the tracheal cannula. These observations, summarized in Table 2 (facing p.44), do not agree completely with those of Green and Neil (1955).

(c) Activity during maintained deflation of the lungs

Comroe (1965c) stated that maintained deflation of the lungs increased the frequency and force of respiratory effort, that the vagus nerves probably form the pathway for the reflex and that different receptors are involved from those stimulated in the inflation reflex. Lumsden had reported the existence of this reflex in cats in 1923. It was possible to demonstrate this reflex in preparations used in this study (Fig. 14, facing p.40).

During maintained deflation, the cricothyroid muscle showed bursts of action potentials of a higher frequency than in quiet respiration, and these were synchronous with diaphragmatic activity. The lateral cricoarytenoid muscle maintained its phasic activity related to expiration, and there was an increase in the frequency of action potentials. The dorsal cricoarytenoid muscle also showed continued phasic activity of increased frequency. Activity of the diaphragm and laryngeal muscles during maintained deflation is summarized in Table 2 (facing p.44).

(d) Conclusions drawn from electromyographic records obtained during inflation and deflation of the lungs

The records of activity of the diaphragm obtained in experiments during this study confirm previous work by Green and Neil (1955), Lumsden (1923) and Widdicombe (1954c). The effects of inflation and deflation of the lungs on the activity of the intrinsic laryngeal muscles, however,

differed in some experiments from those reported by Green and Neil. This emphasises once more Basmajian's comment that more research is needed into laryngeal muscle activity (Basmajian, 1962d). Widdicombe used cats anaesthetized with pentobarbitone sodium or decerebrate cats. Lumsden used both anaesthetized and decerebrate cats for his experiments. Green and Neil's cats were anaesthetized with a mixture of chloralose (50 mg per kg) and urethane (250 mg per kg) administered by intraperitoneal injection.

Because it was possible consistently to repeat observations on diaphragmatic activity which had been recorded by earlier workers in anaesthetized and decerebrate cats, it was concluded that the preparations used in this study were suitable for the investigation of respiratory reflexes.

IV THE RESPONSES OF THE LARYNGEAL MUSCLES AND DIAPHRAGM TO MECHANICAL AND CHEMICAL STIMULATION OF THE RESPIRATORY TRACT

The cricothyroid muscle in the cat is the most accessible of the intrinsic muscles of the larynx and is a representative member of the group of vocal cord adductor muscles in this species (Martagh, 1945; Seymour and Henry, 1954). For these reasons, recordings were taken from the cricothyroid muscle in the majority of the experiments. Its activity was compared with that of other intrinsic laryngeal muscles in some preparations.

The types of emg activity which were recorded from the diaphragm and intrinsic laryngeal muscles during quiet respiration have been described in chapter III of this thesis. The next step was to record electromyograms from the adductor muscles of the larynx when laryngeal spasm was stimulated mechanically or chemically. A dramatic change in the pattern of activity of the adductor muscles from that which had been recorded during quiet respiration was observed. The discharge was of a much higher frequency, and involved a large number of motor units which had been inactive previously. This is the type of discharge characteristic of laryngospasm. Whenever laryngospasm occurred, it was accompanied by a cessation of the regular rhythm of the diaphragm.

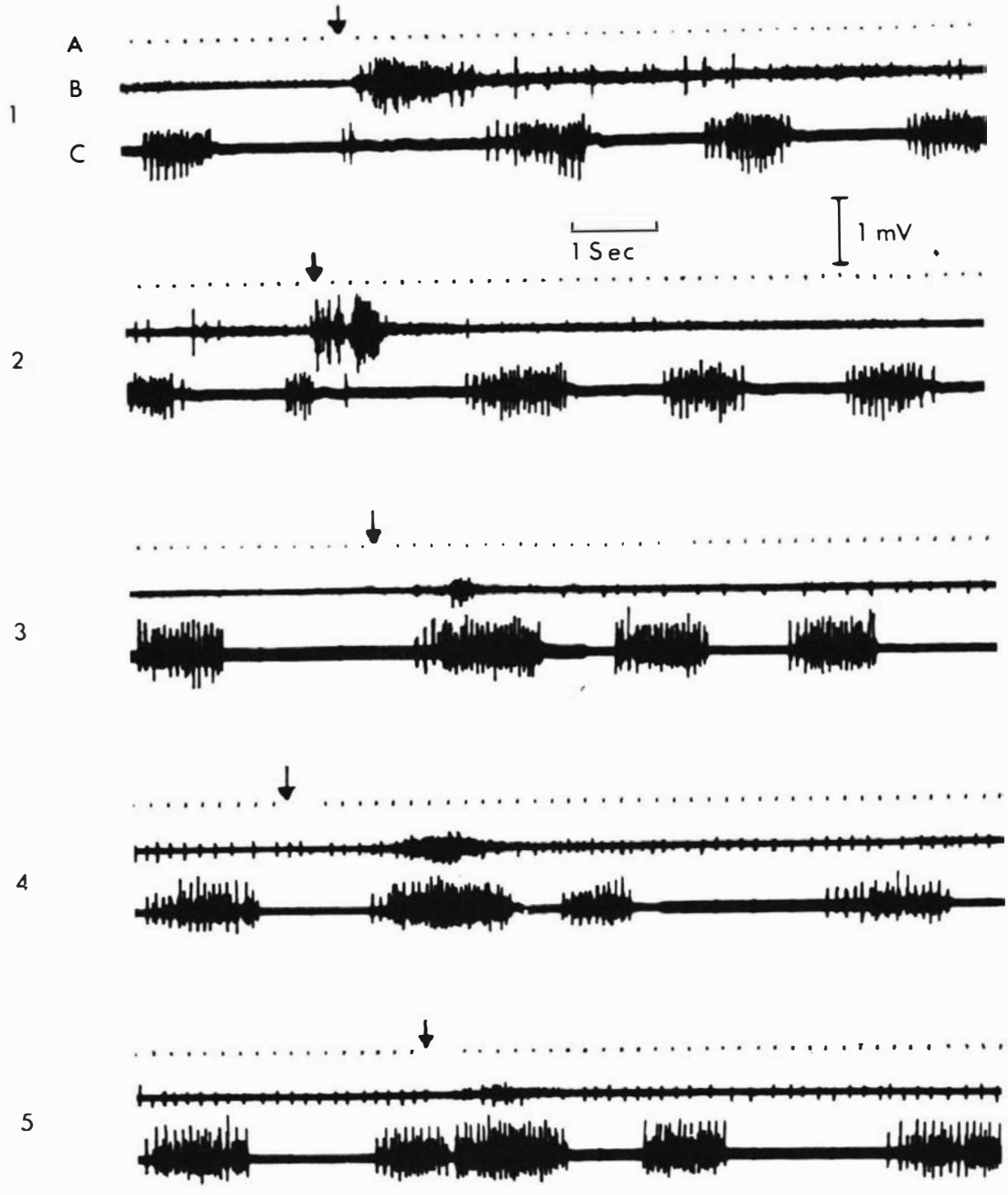
1. Experiments to Record the Responses of the Laryngeal Muscles and Diaphragm to Mechanical and Chemical Stimulation of the Respiratory Tract and the Effects of Some Other Drugs on These Responses

(a) The effects of mechanical stimulation of the pharynx, soft palate, larynx and trachea

In the early experiments on mechanical stimulation, cats anaesthetized with chloralose were used. The cat's mouth was held open with a gag and a polythene tube was used to provide the stimulus. Stimulation of the soft palate resulted in movement of the soft palate in an anterior direction, breath-holding, and increased activity of the lateral cricoarytenoid muscle which was synchronous with the soft palate movement. The activity of the lateral cricoarytenoid muscle was recorded by means of a needle electrode inserted from the oral cavity. When the vocal cords were stimulated mechanically a cough was provoked together with a simultaneous increase in the activity of the lateral cricoarytenoid and cricothyroid muscles. In one cat, anaesthetized with chloralose, the dorsal cricoarytenoid (abductor) became more active during mechanical stimulation of the soft palate. This was a rather paradoxical observation indicating that in some instances stimulation of the laryngeal reflex may result in spasm of the abductors as well as the adductors - total intrinsic muscle spasm.

Decerebrate cats whose soft palates or vocal cords were stimulated with a polythene tube also exhibited breath-holding, changes in respiratory rhythm and increased activity of both cricothyroid and lateral cricoarytenoid muscles, which were recorded as changes in their electromyograms. Increased activity of the lateral cricoarytenoid muscle could be demonstrated throughout the respiratory cycle, in contrast to its rhythmical activity

Fig. 16 The Response of the Diaphragm and the Cricothyroid Muscle to Mechanical Stimulation of the Larynx and Trachea

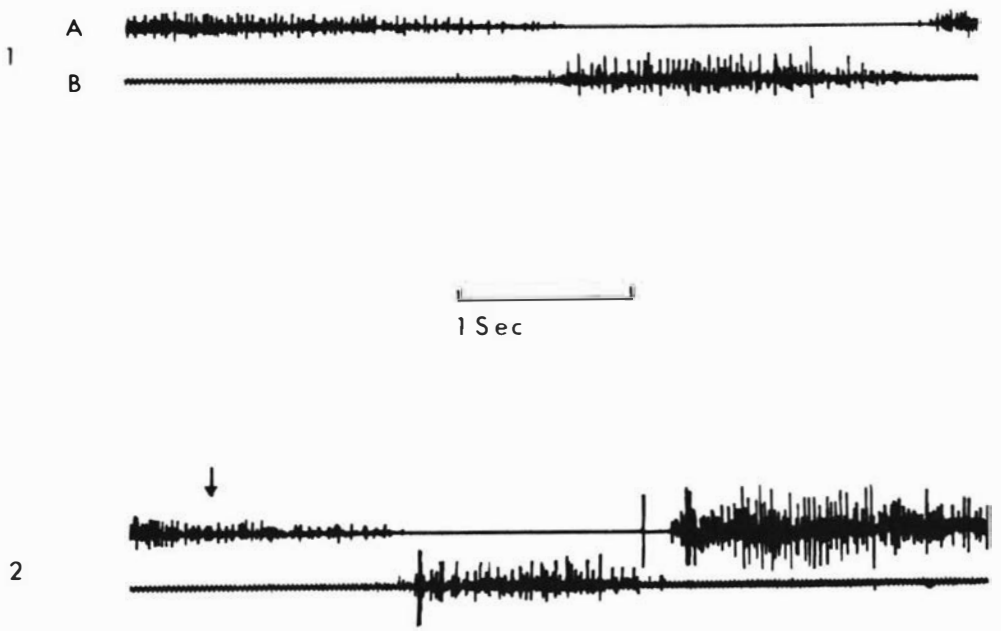


Decerebrate cat 3.4 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate mechanical stimulation).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Traces 1 and 2: Response to mechanical stimulation of the anterior larynx.
Trace 3: Response to endotracheal intubation after analgesic spray of pharynx and larynx.
Trace 4: Response to pushing the endotracheal tube into the distal trachea.
Trace 5: Response to pushing the endotracheal tube, lubricated with analgesic cream, into the distal trachea.
(Spikes retouched)

associated with expiration recorded during quiet respiration. The bursts of increased activity of the lateral cricoarytenoid muscle in response to mechanical stimulation were followed immediately by a return to the normal rhythm of the muscle's activity. The response to mechanical stimulation was temporary closure of the glottis, during which the whole larynx was observed to move cranially.

In a 3.4 kg decerebrate cat (Fig. 16, facing p.48) records were obtained of the activity of the cricothyroid muscle and the diaphragm when the tip of an unlubricated 5.0 mm endotracheal tube was pushed against the anterior larynx. Traces 1 and 2 show bursts of action potentials from the cricothyroid muscle indicative of laryngeal closure, and a disturbance in the regular rhythm of the diaphragm. Trace 3 shows a less vigorous reaction from the cricothyroid muscle as the non-lubricated endotracheal tube was inserted into the trachea after spraying the pharynx and larynx with 40 mg of lignocaine hydrochloride. This reaction occurred as the tube passed down the trachea and not during its passage through the glottis. Diaphragmatic rhythm was altered very slightly at the time of intubation but there was no apnoea. When the endotracheal tube was pushed to the distal trachea a burst of activity from the cricothyroid muscle lasting 1 sec occurred (Trace 4). This compared with activity of 0.3 sec on initial insertion of the tube to the trachea as shown in Trace 3. There was an increased frequency of action potentials from the cricothyroid muscle when the tube was pushed into the distal trachea as compared with the frequency when the tube was first introduced into the trachea. This tends to confirm the clinical observation that the trachea is more sensitive at its distal end. After lubricating the tube with 2 per cent amethocaine cream the reaction of the cricothyroid muscle, as judged by

Fig. 17 The Response of the Dorsal and Laterel Cricoarytenoid Muscles when the Pharynx and Anterior Larynx are Sprayed with Ether



Decerebrate cat, adult female. Decerebration under halothane/ether anaesthesia.
A: Electromyogram from lateral cricoarytenoid muscle.
B: Electromyogram from dorsal cricoarytenoid muscle.
Trace 1: Quiet respiration in resting state.
Trace 2: Effects of spraying the pharynx and larynx with ether (arrow indicates start of spray).

(Spikes retouched)

its electromyogram (Trace 5), was lessened, but the respiratory rhythm of the diaphragm was still altered.

In the series of 9 experiments on mechanical stimulation, closure of the glottis and changes in respiratory rhythm could be provoked consistently by tactile stimulation of the soft palate, pharynx, larynx and trachea. A smooth endotracheal tube of the type used in clinical anaesthesia was as effective as a piece of polythene tubing in producing the response.

(b) The effects of spraying the pharynx and anterior larynx with volatile anaesthetic agents

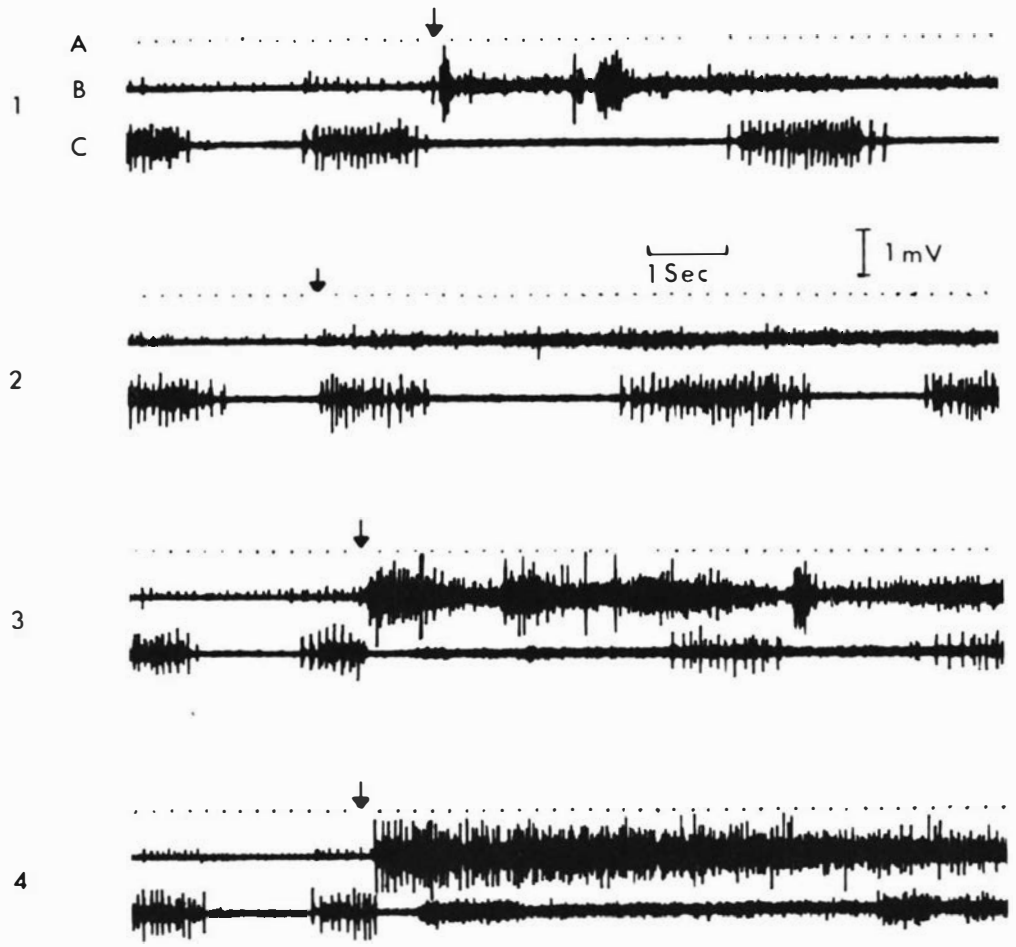
Volatile anaesthetic agents were sprayed from a simple nebulizer onto the pharynx and anterior larynx. During the procedure, the cats were positioned in dorsal recumbency and a gag used to hold their mouths open. Needle electrodes were placed in the cricothyroid muscle and the diaphragm in 15 of the experiments, but in 3, electrodes were placed in the dorsal and lateral cricoarytenoid muscles.

In the first experiments in which ether was sprayed onto the pharynx and larynx, the spray from the nebulizer lasted for 30 sec, but later the time of exposure to ether was reduced. This was because it was noted early in the investigation that less reaction was stimulated if the interval between successive sprays was short, or if the previous exposure had been of long duration. As the bulb of the nebulizer was squeezed and each cloud of ether spray impinged on the pharynx and anterior larynx, the cat gasped and a burst of action potentials could be recorded from the lateral cricoarytenoid and cricothyroid muscles. Traces from one of the early experiments of this type are reproduced in Fig. 17 (facing p.49). This was a decerebrate prepration, and the needle electrodes were placed

in the dorsal and lateral cricoarytenoid muscles. During quiet respiration, the activity of these muscles alternated, the dorsal cricoarytenoid being active on inspiration and the lateral cricoarytenoid active on expiration (Trace 1). Trace 2 shows that shortly after the start of the ether spray which lasted 12 sec, there was a continuous discharge from the lateral cricoarytenoid of high frequency. This lasted for 14 sec. It contained action potentials from more motor units than had been active in quiet respiration. During this period of laryngospasm there was apnoea and the only activity from the dorsal cricoarytenoid muscle was 3 bursts of action potentials each of which lasted 0.5 sec (this compares with 2 sec duration of activity when the muscle was showing rhythmic contraction during quiet respiration). The first relatively normal discharge from the dorsal cricoarytenoid muscle after stopping the ether spray was 3 times the duration of those occurring during quiet respiration and exhibited a greater frequency of action potentials. In the same cat, when halothane was sprayed on to the pharynx and anterior larynx in a similar manner, continuous activity was stimulated in the lateral cricoarytenoid muscle, but no activity was recorded from the dorsal cricoarytenoid except for a 0.5 sec burst of activity approximately 2 sec before the end of the halothane spray. The first relatively normal discharge from the dorsal cricoarytenoid after the withdrawal of halothane was $2\frac{1}{2}$ times the duration observed during quiet respiration and of greater frequency. This increased activity of the dorsal cricoarytenoid muscle (abductor) after spasm caused by an ether spray may be interpreted as a compensatory mechanism providing an increased airway diameter.

The effect of ether and halothane sprays may be due merely to tactile stimulation of receptors in the area. Another possibility is that the

Fig. 18 A Comparison of the Effects of Spraying the Pharynx and Larynx with Saline, Ether, and Halothane



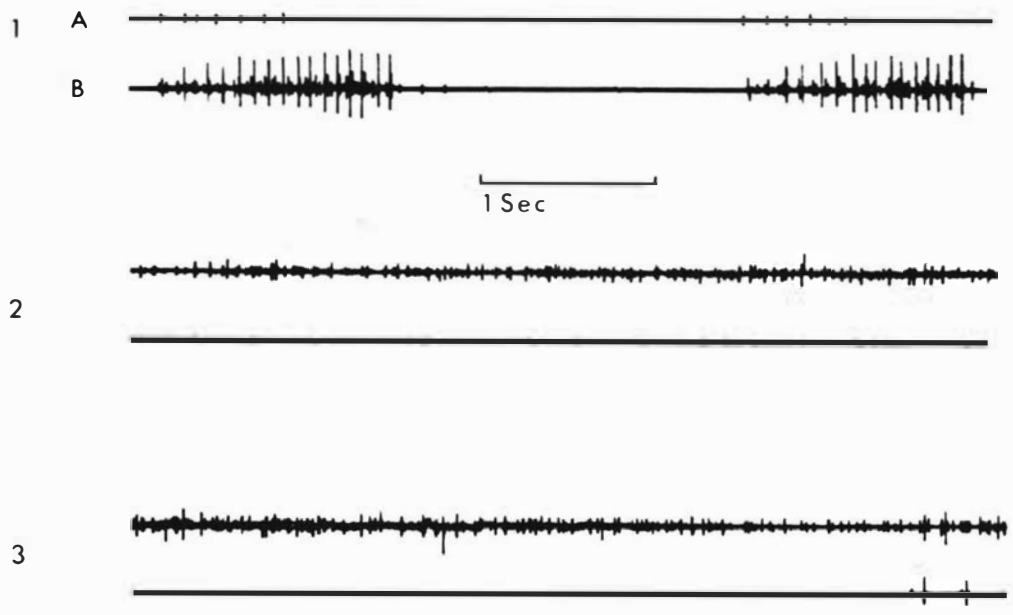
Decerebrate cat 2.7 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of spraying).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of spraying the pharynx and larynx with saline at 37°C.
Trace 2: Effects of spraying the pharynx and larynx with saline at 26.5°C.
Trace 3: Effects of spraying the pharynx and larynx with ether.
Trace 4: Effects of spraying the pharynx and larynx with halothane.
(Spikes retouched)

spray may stimulate cold-sensitive receptors. The effects of spraying 0.9 per cent saline were therefore compared with the effects of spraying ether and halothane. A decerebrate cat weighing 2.7 kg had needle electrodes placed in the diaphragm and left cricothyroid muscle. Saline at 37.0°C was sprayed on the pharynx and anterior larynx for 2 sec. This resulted in some increase in cricothyroid activity and a change in the respiratory rhythm over the period when spraying was in progress (Fig. 18, Trace 1, facing p.51). Five minutes later, spraying with saline at 26.5°C for the same time resulted in less alteration in the respiratory rhythm and produced a smaller increase in cricothyroid activity (Trace 2). Five minutes after the second saline spray, the pharynx and anterior larynx were sprayed for 2 sec with ether. A discharge of much higher frequency, involving a greater number of motor units was stimulated in the cricothyroid and there was more disturbance of the respiratory rhythm than there had been with saline (Trace 3). Spraying the area with halothane for 1.8 sec 5 min later stimulated a cricothyroid reaction of even greater frequency than had the ether spray, and the diaphragm went into a state of spasm for 17 sec (Trace 4). The conclusion to be drawn from this experiment is that chemoreceptors are more important in this reflex than receptors sensitive to tactile or cold stimulation.

(c) The effects of the inhalation of volatile anaesthetic agents, administered by mask, into the intact respiratory tract

In the next series of experiments, ether and halothane were administered as vapours through a conical latex rubber mask (Hall, 1957) to decerebrate cats or cats anaesthetized with chloralose. Ether was administered from a standard Boyle ether vaporiser with the lever in the full-on position and the plunger up. The concentration of ether vapour obtained from the

Fig. 19 The Effects of Administering Ether and Halothane by Mask to the Intact Respiratory Tract



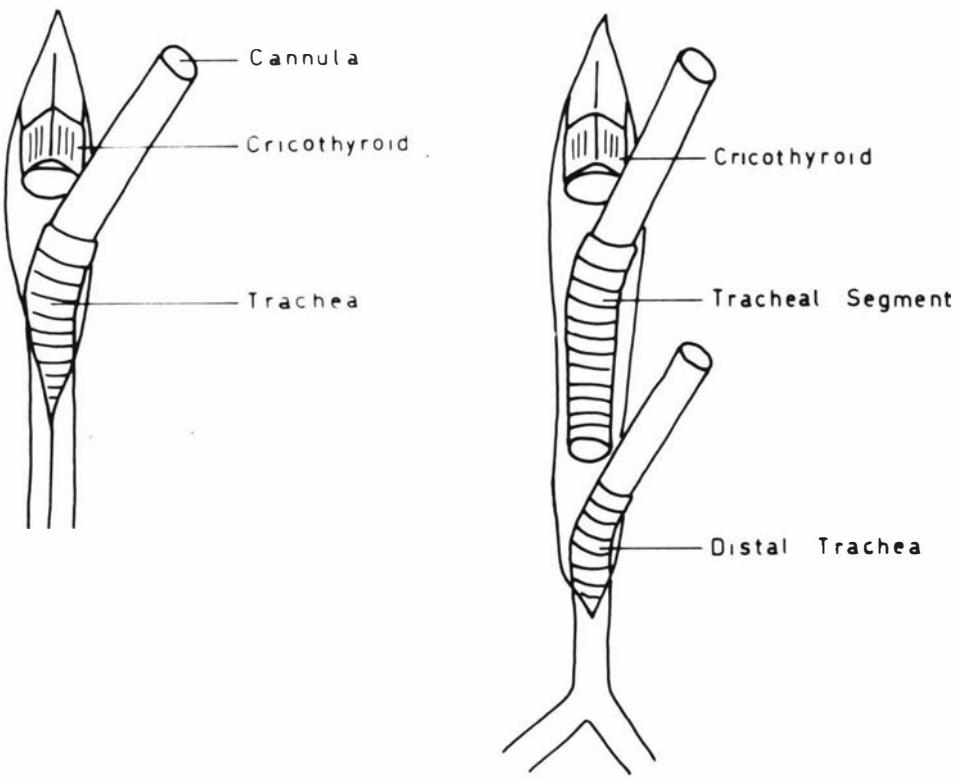
Decerebrate cats. Decerebration under halothane/ether anaesthesia.
(Traces 1 and 2 are from the same cat).
A: Electromyogram from cricothyroid muscle.
B: Electromyogram from diaphragm.
Trace 1: Quiet respiration, breathing oxygen through the mask.
Trace 2: Effects of inhalation of ether by mask.
Trace 3: Effects of inhalation of halothane by mask.
(Spikes retouched)

vaporizer in these conditions was between 10 and 20 per cent (Macintosh, Mushin and Epstein, 1963). In clinical practice, concentrations as high as 20 per cent may be required for the induction of anaesthesia in man (Wood-Smith and Stewart, 1962). Halothane was administered from a modified trichloroethylene vaporizer (Hillard, 1957). The concentration, taken from the calibration curve (British Oxygen Co.), was in the range 6 to 8 per cent. This is within the range used by Johnstone (1961) for his high percentage induction technique in man.

Fig. 19, Trace 1 (facing p.52) shows activity of the cricothyroid muscle and the diaphragm in a decerebrate cat during quiet respiration. Trace 2 shows continuous activity of the cricothyroid of high frequency involving large numbers of motor units (laryngospasm) and apnoea during the administration of 10 to 20 per cent ether by mask. Trace 3, taken from the record of another decerebrate cat, shows the activity of the cricothyroid muscle and the diaphragm at the end of 48 sec inhalation of 6 to 8 per cent halothane by mask. Decreasing activity of the cricothyroid muscle was occurring at the end of a period of spasm, and the start of action potentials from the diaphragm can be seen following apnoea.

It is clear that volatile anaesthetic agents, when administered as a spray from a nebuliser (as in section (b)) or via a standard anaesthetic mask, can provoke laryngospasm, apnoea, and changes in respiratory rhythm. These effects may be the result of stimulation of receptors in the nasopharynx and larynx, the trachea, the lungs or to action at other sites after absorption of the volatile agents to the blood stream. Further experiments were devised in an attempt to define more exactly the sites of stimulation.

Fig. 20 The Positions of Tracheal Cannulae in Experimental Preparations



a. Diagram to illustrate the site of introduction of a cannula into the first tracheal ring to isolate the nasopharynx and larynx.

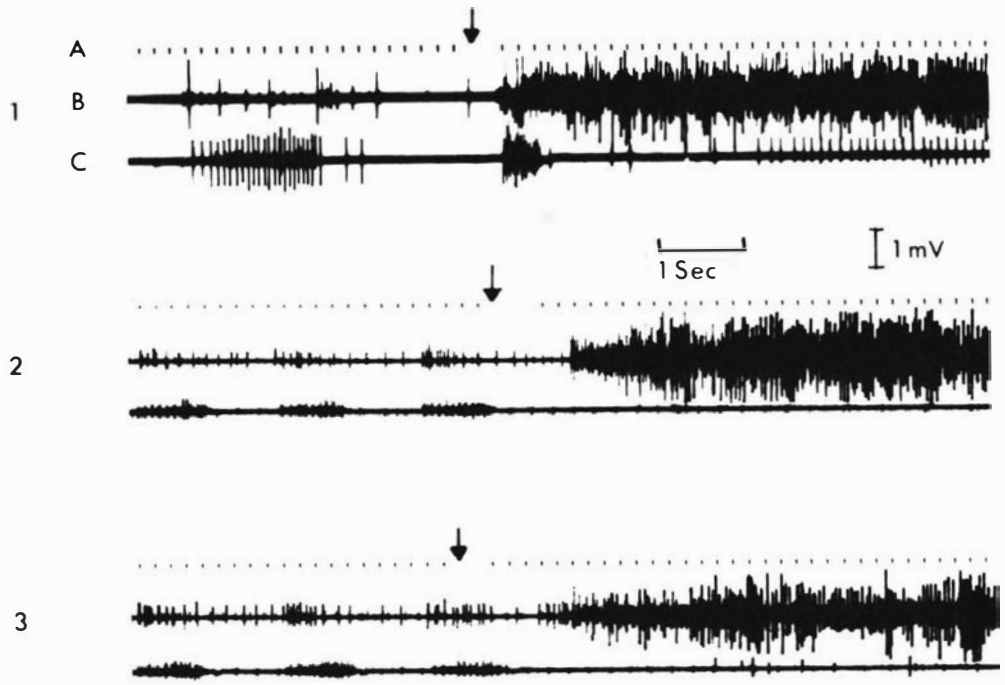
b. Diagram to illustrate the sites of introduction of cannulae into the first tracheal ring and into the distal trachea to isolate a segment of cervical trachea as well as the nasopharynx and larynx.

(d) The effects of the passage of volatile anaesthetic agents into isolated areas of the respiratory tract: the nasopharynx and larynx; the trachea; the distal trachea and lungs

At the end of section (c), it was suggested that there may be a number of sites at which volatile anaesthetic agents act to stimulate laryngospasm. This series of experiments was designed to determine whether stimulation occurs at different levels of the respiratory tract itself. The larynx and nasopharynx were isolated by inserting a cannula into the anterior end of the trachea. Oxygen and an inhalation agent could then be passed through the nasopharynx and larynx without entering the trachea and lungs (Fig. 20a, facing p.53). Although the effects of stimulation of the respiratory tract by ether, halothane and methoxyflurane were investigated, the main part of the work was concerned with the administration of ether. In 2 experiments, a segment of trachea, with its nerve and blood supply intact was isolated by inserting a second cannula into the distal trachea (Fig. 20b). In these preparations, the inhalation agent could be passed through the nasopharynx and larynx only, through the isolated tracheal segment, or into the distal trachea and lungs. Records were obtained from needle electrodes placed in the cricothyroid muscle and in the diaphragm.

During quiet respiration, rhythmic bursts of action potentials were detected from the diaphragm on each inspiration. The most common form of record obtained from the needle electrode in the cricothyroid muscle was intermittent spontaneous activity unrelated to the diaphragmatic rhythm. Other forms of cricothyroid activity, described in chapter III, were recorded in some preparations.

Fig. 21 The Effects of Exposing the Isolated Nasopharynx and Larynx to Ether, Halothane and Methoxyflurane



Decerebrate cats 3.0 kg (Trace 1,) 1.6 kg (Traces 2 and 3). Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of administration of inhalation agent).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of ether by mask.
Trace 2: Effects of administration of halothane by mask.
Trace 3: Effects of administration of methoxyflurane by mask.
(Spikes retouched)

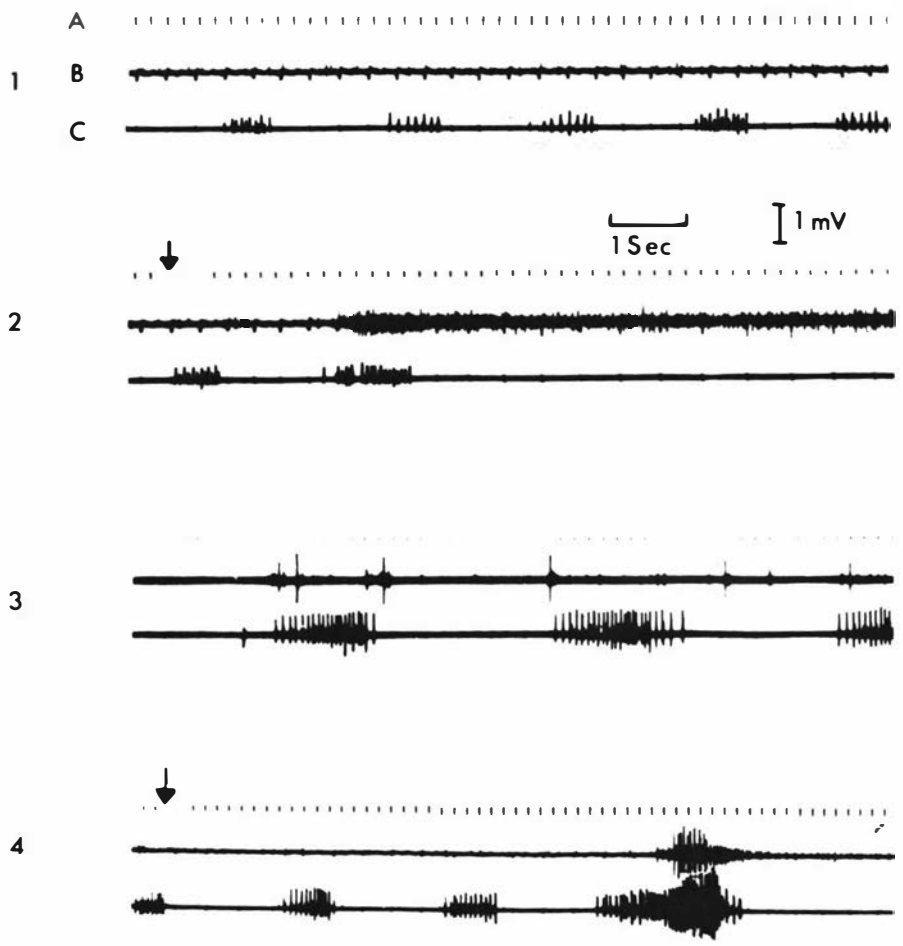
(i) Passage of volatile anaesthetic agents through the nasopharynx and larynx

Ether, halothane and methoxyflurane were passed through the isolated nasopharynx and larynx by means of a latex rubber mask (Hall, 1957). The mask was strapped onto the cat's face and leaks were prevented by inserting cotton wool padding between the mask and the face. During the exposure of the nasopharynx to the volatile agent, the cat breathed oxygen or air through a tracheal cannula. When 10 to 20 per cent ether or 6 to 8 per cent halothane were administered in these conditions, a prolonged high frequency discharge in the cricothyroid muscle was stimulated. In some experiments this response occurred within 0.2 sec of the start of ether administration (Fig. 21, Trace 1, facing p.54), and within 0.6 sec of the start of halothane (Trace 2) or 2.9 per cent methoxyflurane (Trace 3) administration. The period between the start of administration of the inhalation agent and stimulation of a cricothyroid muscle discharge varied from 0.1 to 2.4 sec for ether (47 experiments), from 0.6 to 4.0 sec for halothane (15 experiments), and from 0.6 to 8.0 sec for methoxyflurane (4 experiments).

(ii) Passage of volatile anaesthetic agents through an isolated tracheal segment with nerve and blood supply intact

The effects of passing ether vapour through an isolated segment of the trachea were demonstrated in consecutive experiments on 2 decerebrate cats. In both cats, when 10 to 20 per cent ether vapour was passed through the nasopharynx and larynx, apnoea and a continuous high frequency discharge from the cricothyroid muscle were recorded. When ether vapour of the same concentration was passed through the isolated tracheal segment,

Fig. 22 **The Effects of Passing Ether Vapour Through an Isolated Tracheal Segment**



Decerebrate cats 2.8 kg (Traces 1 and 2), 3.0 kg (Traces 3 and 4). Decerebration under halothane/ether anaesthesia.

A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).

B: Electromyogram from cricothyroid muscle.

C: Electromyogram from diaphragm.

Trace 1: Quiet respiration with oxygen passing through an isolated tracheal segment.

Trace 2: Effects of administration of ether into an isolated tracheal segment.

Trace 3: Quiet respiration.

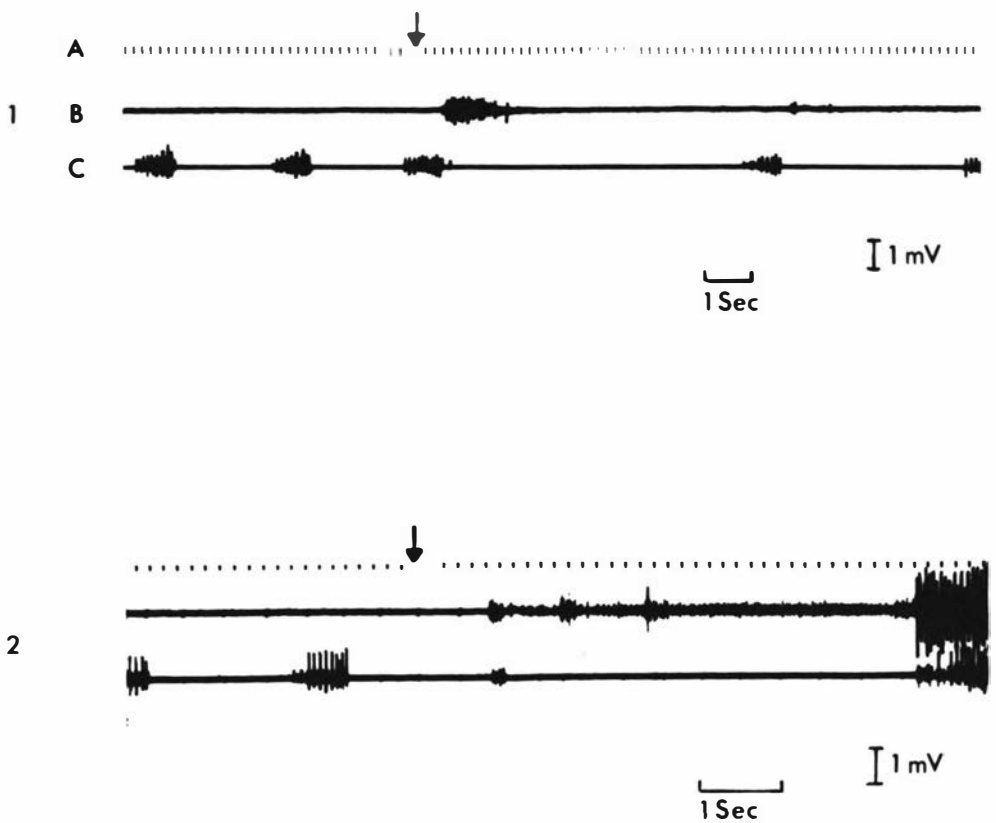
Trace 4: Effects of administration of ether into an isolated tracheal segment. (Spikes retouched)

a similar result was obtained. Fig. 22, Trace 1 (facing p.55) shows the record obtained when oxygen alone was passed through an isolated tracheal segment. Intermittent spontaneous activity was present in the cricothyroid muscle, and the electrocardiogram is visible on both the cricothyroid and the diaphragm emg record, the heart rate being recorded as 240 per min at this time. Trace 2 shows the effects of passing 10 to 20 per cent ether vapour through the tracheal segment for 10 sec. Apnoea and a continuous high frequency discharge from the cricothyroid muscle were stimulated. At the same time, the heart rate fell from 240 per min to 180 per min. Apnoea persisted for 13 sec, but increased cricothyroid activity was still apparent after 23 sec. In the second cat, intermittent spontaneous activity was also present in the cricothyroid muscle (Trace 3). In this experiment, ether was passed through the isolated tracheal segment for 21 sec. Laryngospasm was stimulated, but did not occur until 7.5 sec after the start of administration of ether (Trace 4). Spasm of the cricothyroid muscle only lasted 2 sec in this cat, but, after a brief stimulation of inspiration, apnoea lasted for 10 sec. A further period of continuous increased cricothyroid activity occurred following the cessation of ether administration (not shown in Fig. 22).

(iii) Passage of volatile anaesthetic agents into the distal trachea and lungs

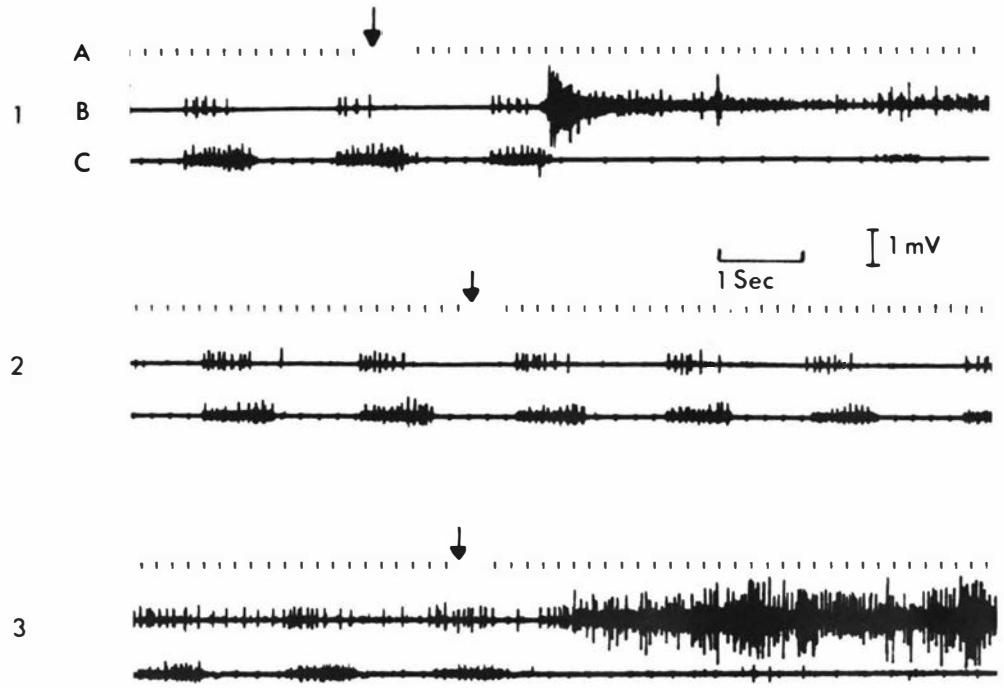
It had been noted during pilot experiments, that the inhalation of low concentrations of ethyl chloride, ether, and halothane through a tracheal cannula resulted in an increase in the frequency of action potentials from the cricothyroid muscle, and changes in the respiratory rate. When ethyl chloride was inhaled, the respiratory rate decreased in some cats and increased in others. Administration of halothane resulted

Fig. 23 The Effects of Administering Ether Vapour to the Distal Trachea and Lungs



Two decerebrate cats 1.5 kg (Trace 1) and 3.0 kg (Trace 2). Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of ether into the distal trachea and lungs.
Trace 2: Effects of administration of ether into the distal trachea and lungs (showing biphasic response).
(Spikes retouched)

Fig. 24 A comparison of the Effects of Halothane and Methoxyflurane, Administered to the Trachea and Lungs



Decerebrate cat 1.6 kg. Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of administration of inhalation agent).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of halothane into the distal trachea and lungs.
Trace 2: Effects of administration of methoxyflurane into the distal trachea and lungs.
Trace 3: Effects of administration of methoxyflurane by mask to the nasopharynx and larynx.
(Spikes retouched)

in marked slowing of the respiratory rate. When, however, ether and halothane were administered at higher concentrations, laryngospasm, accompanied by apnoea or a cessation of the regular respiratory rhythm, was recorded. In this series, therefore, ether was administered at a concentration of 10 to 20 per cent and halothane at 6 to 8 per cent. When ether vapour was administered into the distal trachea and lungs (Fig. 23, Trace 1, facing p.56), a short burst of cricothyroid activity lasting 2 sec was stimulated. An interruption of the rhythm of the diaphragm for 7 sec occurred simultaneously. Trace 2 shows a different pattern of response when ether was administered in the same way. In this cat, the cricothyroid activity which was stimulated, occurred as a biphasic response. Within 1 sec of starting the administration of ether there was an increase in frequency of action potentials and inspiration was inhibited. Greater cricothyroid activity, similar to that provoked when ether was administered by mask, occurred after 6 sec, at the same time as inspiratory efforts by the diaphragm started.

Both halothane and methoxyflurane when administered by mask, had been shown to stimulate laryngospasm and apnoea in decerebrate cats (see p.54). It was therefore of interest to compare the effects of these 2 volatile agents when they were administered directly into the distal trachea and lungs. The experiment was carried out on 3 cats. In each cat, 6 to 8 per cent halothane, administered through a tracheal cannula, stimulated laryngospasm and an interruption in the regular diaphragmatic rhythm (Fig. 24, Trace 1, facing p.56). 2.9 per cent methoxyflurane, however, stimulated neither laryngospasm nor did it cause any change in the rhythm of the diaphragm when administered to the trachea and lungs (Trace 2), although when administered by mask it did stimulate both

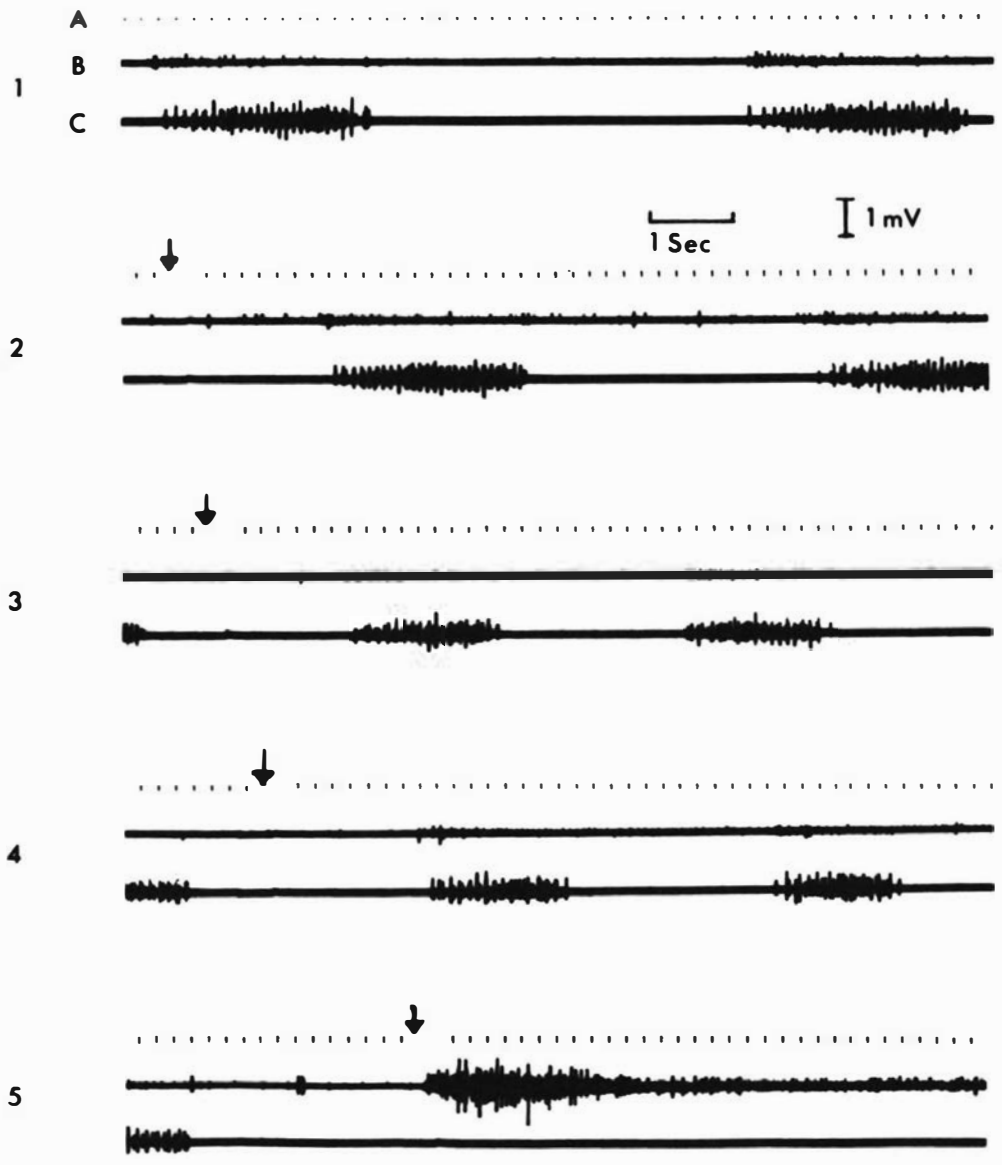
laryngospasm and apnoea (Trace 3). The difference in response to these 2 agents is considered further in the discussion of this chapter (see p.73).

In the work reported up to this point, it has been shown that volatile anaesthetic agents, whether administered as a spray or in vapour form, are capable of stimulating laryngospasm and changes in respiratory rhythm. These reactions may be stimulated by exposure of the intact respiratory tract, or of isolated parts of the tract. The nature and time sequence of these changes differs according to the method and site of administration of the agents. Very early in the series of experiments, it was noted that low concentrations of anaesthetic agents caused increased activity of the cricothyroid muscle and changes in respiratory rate, but did not stimulate laryngospasm or apnoea. These findings suggested that there may be a threshold concentration for stimulation of laryngospasm and apnoea. The experiments described in the next section were carried out to try and determine whether such a threshold exists.

(e) Threshold of stimulation of laryngospasm

Six experiments were carried out in an attempt to determine the lowest concentrations of ether and halothane at which laryngospasm and apnoea were stimulated. The thresholds for stimulation of laryngospasm and apnoea were determined by administering gradually increasing concentrations of halothane and ether. In the first experiment in this group, 2 per cent halothane administered by mask from a "Halox" (British Oxygen Co.) vaporiser stimulated laryngospasm and apnoea in a decerebrate cat. Ether, administered from a standard Boyle ether vaporizer with the lever in the full-on position and the plunger up (10 to 20 per cent), stimulated laryngospasm and apnoea each time it was given by mask. Although, in the same cat,

Fig. 25 **The Effects of Inhalation of Increasing Concentrations of Ether Vapour**

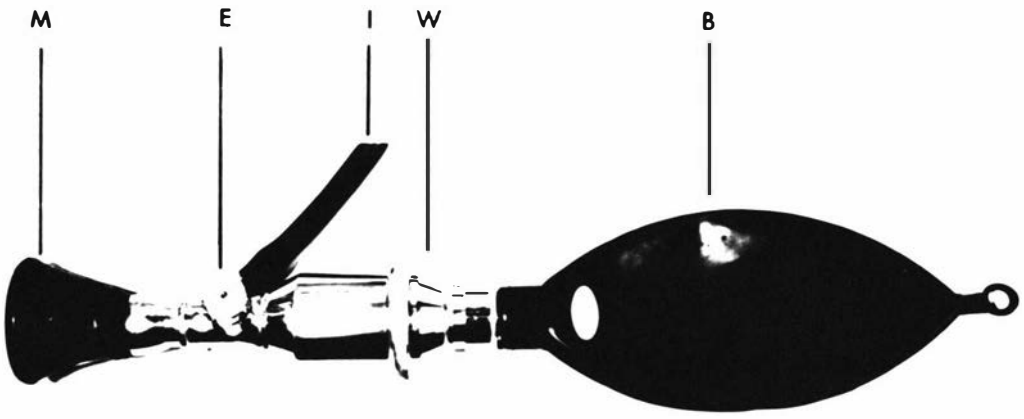


Decerebrate cat 2.0 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration in Traces 2, 3 and 5 and the end in Trace 4).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Quiet respiration, oxygen administered through the mask.
Trace 2: Effects of ether administered through the mask; vaporizer lever at position 1.
Trace 3: Effects of ether administered through the mask; vaporizer lever at position 2.
Trace 4: Effects of ether administered through the mask; vaporizer lever at position 3.
Trace 5: Effects of ether administered through the mask; vaporizer lever at full on.
(Spikes retouched)

apnoea was produced when 2 per cent halothane was inhaled, the concentration had to be raised after the first exposure to induce a cricothyroid discharge characteristic of laryngospasm. In the majority of experiments, halothane was administered from a modified trichloroethylene vaporiser (Hillard, 1957), at a concentration of 6 to 8 per cent, which is considerably higher than the threshold level.

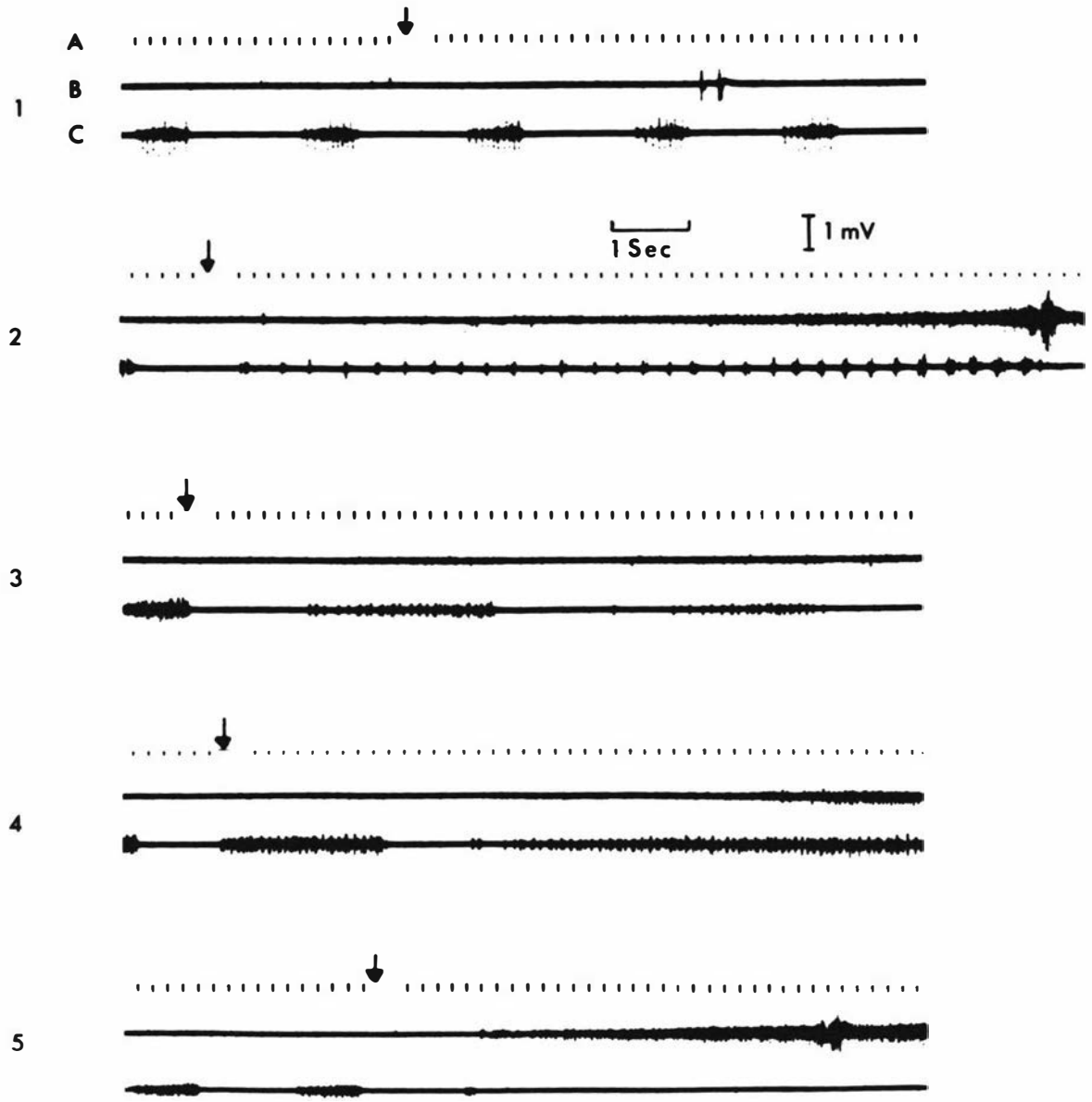
In another experiment ether was administered by mask to the isolated nasopharynx and larynx of a decerebrate cat from a Boyle ether vaporizer with the plunger up. The oxygen flow rate was 4.5 litres per min and ether vapour was passed through the mask for 30 sec at intervals of approximately 30 min. Fig. 25, Trace 1 (facing p.58) shows the activity recorded from the cricothyroid muscle and diaphragm during quiet respiration with oxygen flowing through the mask. There is some cricothyroid activity associated with inspiration. Trace 2 shows the effect of the administration of ether with the vaporizer lever at the first position. There is a very slight decrease in the duration of activity of the diaphragm as compared with the duration during quiet respiration. Three action potential spikes from a motor unit in the cricothyroid previously inactive were recorded during administration of the ether (not shown in this section of the trace). Trace 3 shows the effect of administration of ether with the lever at position 2. There was no change in the records from the cricothyroid or the diaphragm. When ether was administered with the lever at position 3 for 30 sec, a continuous low frequency discharge from the cricothyroid started 1.8 sec after ether administration stopped (Trace 4). This low frequency discharge continued for 18 sec, but there was no change in the respiratory rhythm. With the lever on the vaporiser at the full-on position and the plunger up, administration of ether

Fig. 26 The Waters' System for the Administration of Inhalation Anaesthetics



B Rebreathing bag
I Inlet for fresh gases
W Soda lime canister
E Expiratory valve
M Mask

Fig. 27 The Effects of Inhalation of Increasing Concentrations of Ether Vapour when Ether is Inhaled Continuously



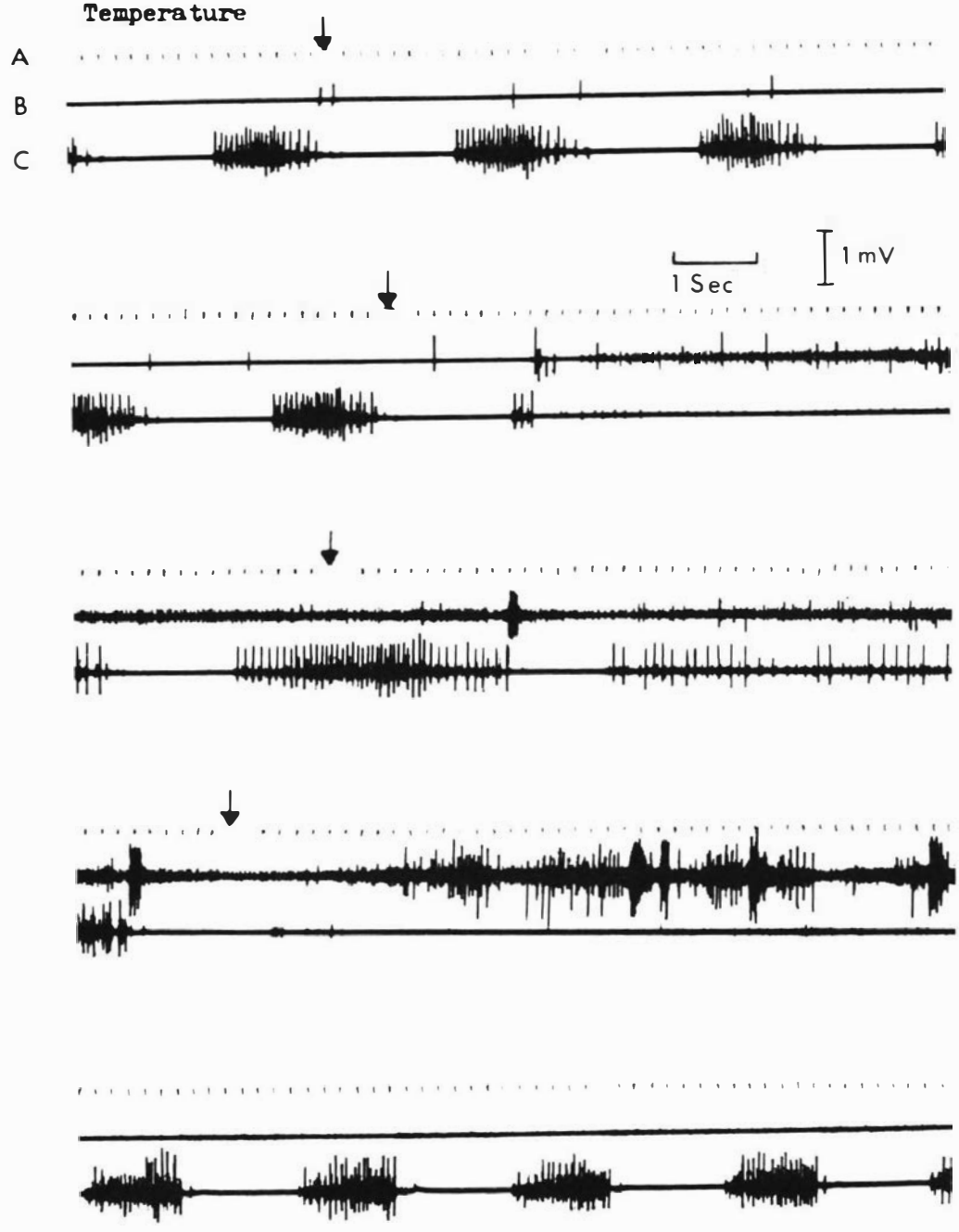
Decerebrate cat 1.8 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate a change in the concentration of ether inhaled).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered with the vaporizer lever at position 1.
Trace 2: Effects of ether administered with the vaporizer lever at position 2.
Trace 3: Effects of ether administered with the vaporizer lever at position 3.
Trace 4: Effects of ether administered with the vaporizer lever at full-on.
Trace 5: Effects of ether administered with the vaporizer lever at full-on, after breathing oxygen by mask for 30 min.

stimulated a high frequency discharge from the cricothyroid muscle within 0.1 sec and apnoea which lasted for 15 sec (Trace 5). The cricothyroid activity was diminishing at the time respiration started again, but persisted as a continuous discharge until after ether administration had stopped.

Since in some experiments it had not been possible to stimulate laryngospasm and apnoea when the interval between exposures to a volatile anaesthetic agent had been short, an experiment was planned in which the concentration of ether vapour inhaled by a decerebrate cat was increased at 15 min intervals. Between recordings, the cat continued to inhale ether vapour at the concentration for which a record had just been obtained. It was thought that in this way the threshold for stimulation of laryngospasm would be raised or the reflex even abolished because the receptors were exposed to ether for a long period, and a deeper plane of anaesthesia was achieved. The concentration was then raised, a further record obtained, and the cat allowed to inhale the new concentration for a further 15 min. The cat breathed oxygen at a flow rate of 4.5 litres per min through a latex rubber mask. No tracheal cannula was inserted. An absorber containing 3 oz of soda-lime was placed between the mask and the rebreathing bag. The expiratory valve in the system allowed excess gas to pass out (Fig. 26, facing p.59). At the start of the experiment the cat's pinna and palpebral reflexes were brisk. The lever on the Boyle ether vaporizer was moved to the first position, with the plunger up (Fig. 27, Trace 1, facing p.59). There was no change in the respiratory rhythm. Four sec after administration of ether had started 2 spikes were recorded on the electromyogram from the cricothyroid. These were not typical of those recorded during laryngospasm and may have been

movement artifacts associated with movement of the larynx during swallowing. The cat continued breathing oxygen and ether through the mask, with the vaporizer lever remaining at the first position. After 15 min the lever was moved to the second position (Trace 2). At this stage the pinna reflex was still brisk, but the palpebral reflex was slightly more sluggish than at the start of the experiment. When the lever was moved to the second position, there was an immediate cessation of regular respiratory rhythm which lasted for 12 sec. During this time a continuous series of action potentials at intervals of 0.25 to 0.5 sec was recorded from the diaphragm. There was a gradual increase in activity of the cricothyroid muscle, starting approximately 3.5 sec after the position of the lever was changed. The cricothyroid activity reached a maximum in frequency and numbers of motor units involved 10.5 sec after alteration of the lever's position, and decreased gradually as normal respiratory rhythm was resumed. The lever remained at position 2 and the cat continued to breathe ether and oxygen through the mask. Fifteen minutes later, the lever was moved to position 3 (Trace 3). At this stage the pinna reflex remained brisk, but the palpebral reflex was sluggish. The duration of diaphragmatic activity increased from 1 to 2 sec, the frequency of the diaphragmatic discharge was decreased and fewer motor units were involved. There was a gradual increase in activity of the cricothyroid muscle, reaching a maximum 10.5 sec after alteration of the lever's position. Increased cricothyroid activity continued for the duration of the record (144 sec). The lever remained at position 3 for 15 min, when it was moved to the full-on position (Trace 4). The pinna reflex was still brisk, but the palpebral reflex was very sluggish. No apnoea was stimulated, but the duration of

Fig. 28 The Effects of Inhalation of Increasing Concentrations of Ether Vapour with the Vaporizer Maintained at a Constant Temperature



Decerebrate cat 2.0 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate a change in the concentration of ether inhaled).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered with the vaporizer lever at position 1.
Trace 2: Effects of ether administered with the vaporizer lever at position 2.
Trace 3: Effects of ether administered with the vaporizer lever at position 3.
Trace 4: Effects of ether administered with the vaporizer lever at full-on.
Trace 5: After administration of ether for 5 min with the lever at full-on.

(Spikes retouched)

activity of the diaphragm was increased from just over 1 sec to 2 sec as the lever was moved to the full-on position and to 6.5 sec after a pause of 1 sec. Increasing cricothyroid activity was observed 7 sec after increasing the ether concentration and this reached its maximum with a burst of activity after 14 sec. Cricothyroid activity gradually subsided and the duration of the diaphragm's activity returned to just over 1 sec during the 98 sec for which recording was continued. After 15 min breathing oxygen and ether with the vaporizer plunger up and the lever in the full-on position, the plunger was pushed down so that oxygen bubbled through the ether. More cricothyroid activity occurred than in Trace 4, but no apnoea was stimulated (not shown in Fig. 27). Palpebral and pinna reflexes could not be elicited at this stage. The cat was then allowed to breathe oxygen through the mask for 30 min. By this time a brisk pinna reflex and sluggish palpebral reflex could be elicited. Administration of ether from the Boyle vaporizer with the plunger up and the lever at the full-on position now stimulated apnoea and laryngospasm (Trace 5).

As ether is vaporized its temperature drops. Two experiments were therefore carried out in which a water bath at a temperature of 28.5°C was placed around the Boyle ether vaporizer. Oxygen was passed through the vaporizer at a flow rate of 8 litres per min. The vaporizer plunger was up and the lever was moved to position 1 at 30 sec (Fig. 28, Trace 1, facing p.61). There was a slight increase in frequency of cricothyroid muscle discharge. After 1 min at position 1, the lever was moved to position 2 (Trace 2). The lever was moved to position 3 after a further minute (Trace 3) and to position 4 (full-on) after another minute (Trace 4). When the vaporizer lever was moved to position 3, the effect of the

increased ether concentration on the diaphragm was to stimulate prolonged inspiratory activity, whereas when the lever was at positions 2 and 4, apnoea occurred and a continuous high frequency discharge was stimulated from the cricothyroid muscle. The lever was then left at position 4. Trace 5 was obtained 5 min after the lever was moved to position 4. There was normal diaphragmatic rhythm at this stage and the spontaneous activity of the cricothyroid was less than at the start of the experiment. Respiration had started again 12.5 sec after moving the lever to position 4, and the high frequency cricothyroid discharge characteristic of laryngospasm had gradually subsided.

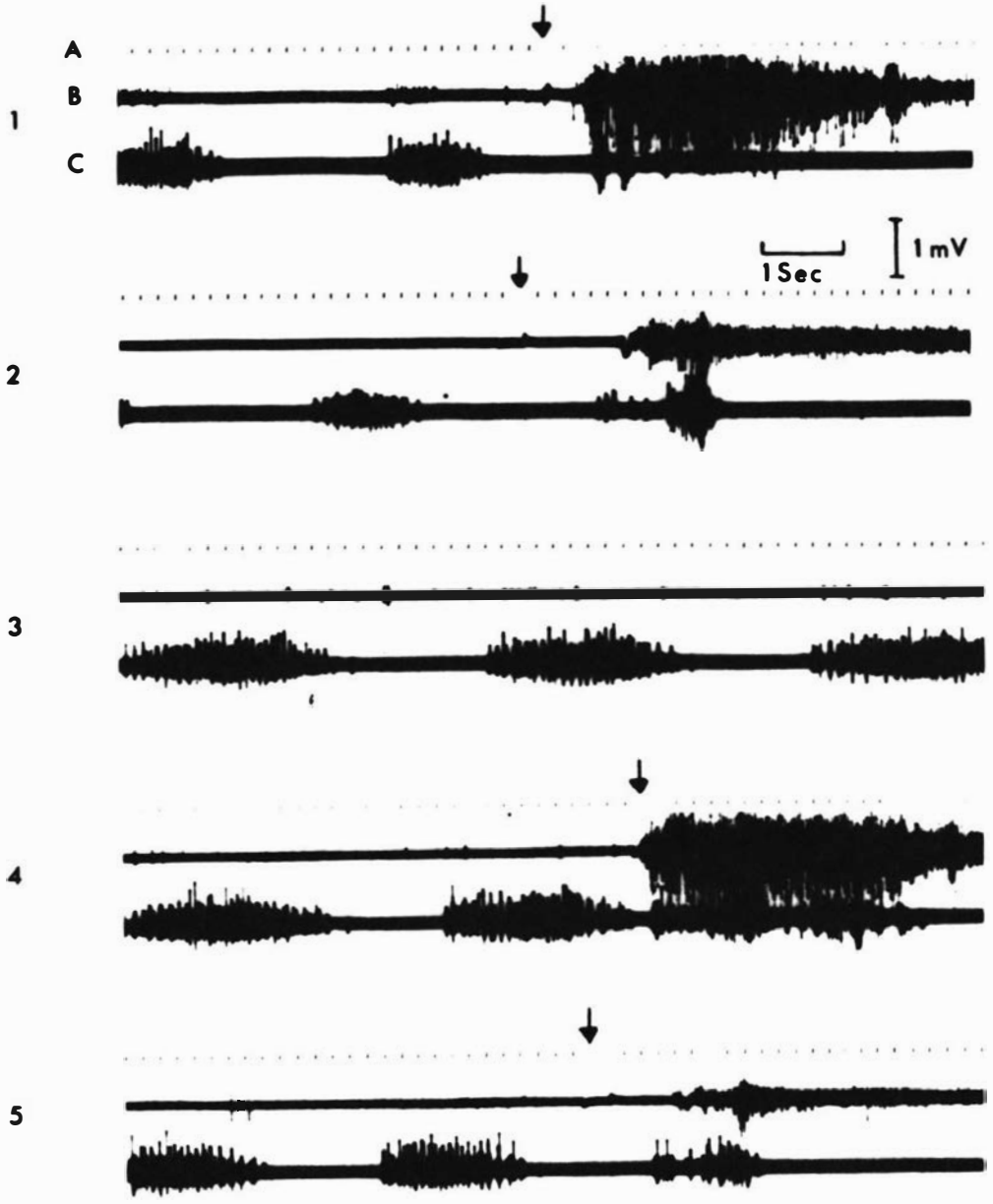
An hour later an experiment was carried out on the same cat in which the lever was placed at position 4 first and then moved down through positions 3, 2 and 1 at 1 min intervals. On this occasion, apnoea and a high frequency cricothyroid discharge were only stimulated with the lever at position 4, apnoea lasted 13.5 sec and cricothyroid activity decreased throughout the experiment. In each of these experiments, the water-bath temperature remained at 28.5°C. Two identical experiments were carried out with the 3 oz Waters' soda-lime canister removed from the system. The results were the same as those recorded with a soda-lime absorber incorporated in the circuit.

Whether or not these experiments provide evidence for the existence of a fixed threshold concentration for the stimulation of apnoea and laryngospasm will be considered in the discussion.

(f) The effects of atropine on the reaction to stimulation of the respiratory tract

The effects of atropine, administered intravenously, on the stimulation of laryngospasm by ether were recorded in 2 decerebrate cats. In the

Fig. 29 The Effects of Atropine on the Stimulation of Laryngospasm by Ether Vapour



Decerebrate cat 3.0 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered by mask.
Trace 2: Effects of ether administered by tracheal cannula.
Trace 3: Quiet respiration after administration of atropine.
Trace 4: Effects of ether administered by mask, 10 min after atropine.
Trace 5: Effects of ether administered by mask, 40 min after atropine.

first preparation, a dose rate of 0.1 mg per kg was given. Atropine at this dose rate, which is commonly used in clinical pre-anaesthetic medication, had no effect on the stimulation of apnoea and laryngospasm when ether was passed through the isolated nasopharynx and larynx.

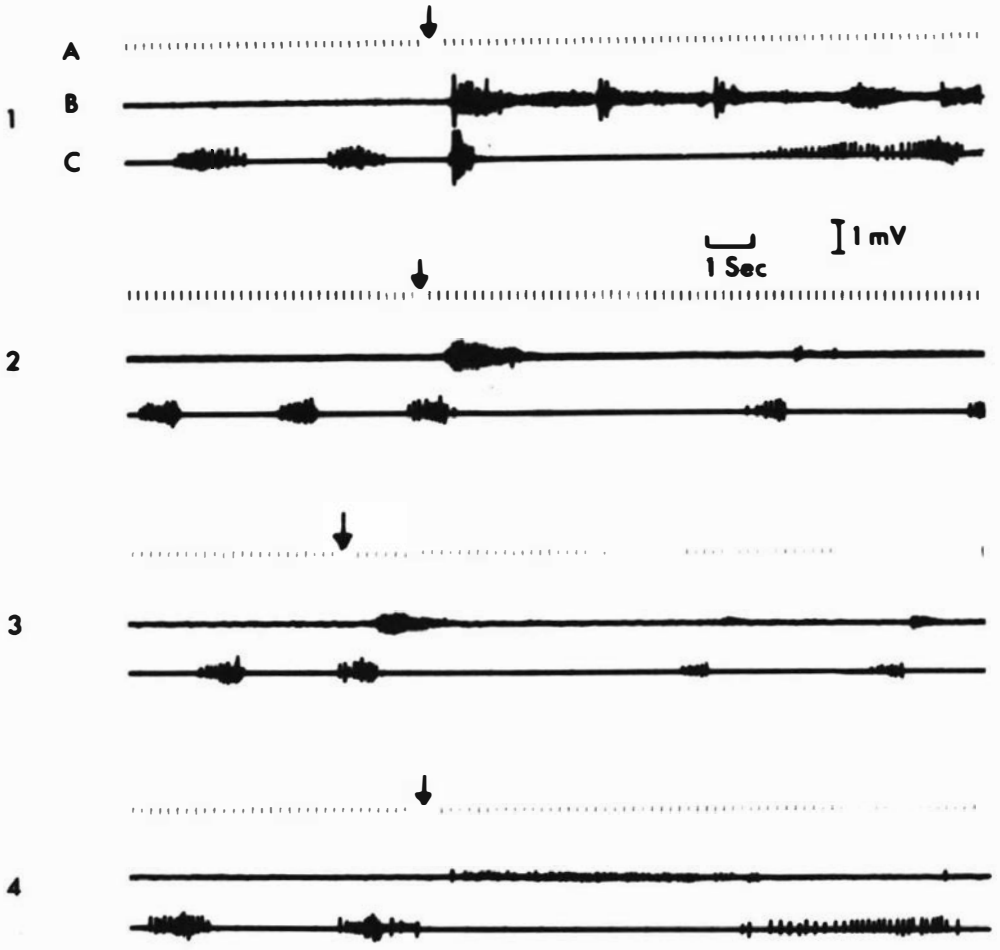
In the second cat a dose of atropine over 30 times that used in clinical anaesthetic practice was administered. Fig. 29, Trace 1 (facing p.63) shows apnoea and cricothyroid spasm stimulated by exposure to ether by mask before the administration of atropine to this second cat. Trace 2 shows the effect when ether is administered through an Ayre's T-piece to the trachea and lungs of the same cat. Laryngospasm is stimulated, accompanied by apnoea which follows an initial inspiratory burst. The effect of the administration of 3.3 mg per kg atropine sulphate in 20 ml of 0.9 per cent saline through a cannula in the femoral vein was to stimulate apnoea for 19 sec, after which the respiratory rate decreased from 22 per min to 18 per min. Ten minutes later the respiratory rate had decreased to 16 per min. The duration of inspiratory activity of the diaphragm increased from 1.5 sec before atropine to 2.5 sec after atropine (Trace 3). Traces 4 and 5 show the effects of the administration of ether by mask and cannula respectively 10 min and 40 min after the atropine had been given. By mask, ether stimulated laryngospasm and an interruption of the regular rhythm of the diaphragm. Ether inhaled into the trachea and lungs stimulated laryngospasm and apnoea. Atropine appeared to have no direct effect on the stimulation of laryngospasm under these conditions.

(g) The effects of local analgesic spraying of the pharynx and anterior larynx on the stimulation of laryngospasm by volatile anaesthetic agents

It was demonstrated in section (a) of this chapter that a lignocaine spray applied to the pharynx and larynx and the lubrication of an endotracheal tube with anethocaine cream abolish or reduce the reaction to mechanical stimulation of the larynx and trachea. In this section, the effects of analgesic sprays were investigated in relation to the inhalation of volatile anaesthetics. In a cat anaesthetized with chloralose, whose respiratory tract was kept intact, spraying with ether stimulated laryngospasm and apnoea. After spraying the pharynx and larynx with 2 per cent lignocaine, no apnoea was stimulated by ether but there were two bursts of action potentials from the cricothyroid muscle 10.5 sec and 14.5 sec after the ether spray. The effects of the lignocaine spray were still found to persist 95 min later. It was similarly demonstrated in decerebrate cats that laryngospasm and apnoea stimulated by the inhalation of ether and halothane could be reduced by spraying the pharynx and anterior larynx with a 2 per cent solution of lignocaine. Reaction to the stimulus was not entirely abolished, however, and the fact that in many cases there was still both an increase in activity of the cricothyroid muscle and some change in the respiratory rhythm suggested that the stimulation of receptors lower down the respiratory tract should be considered.

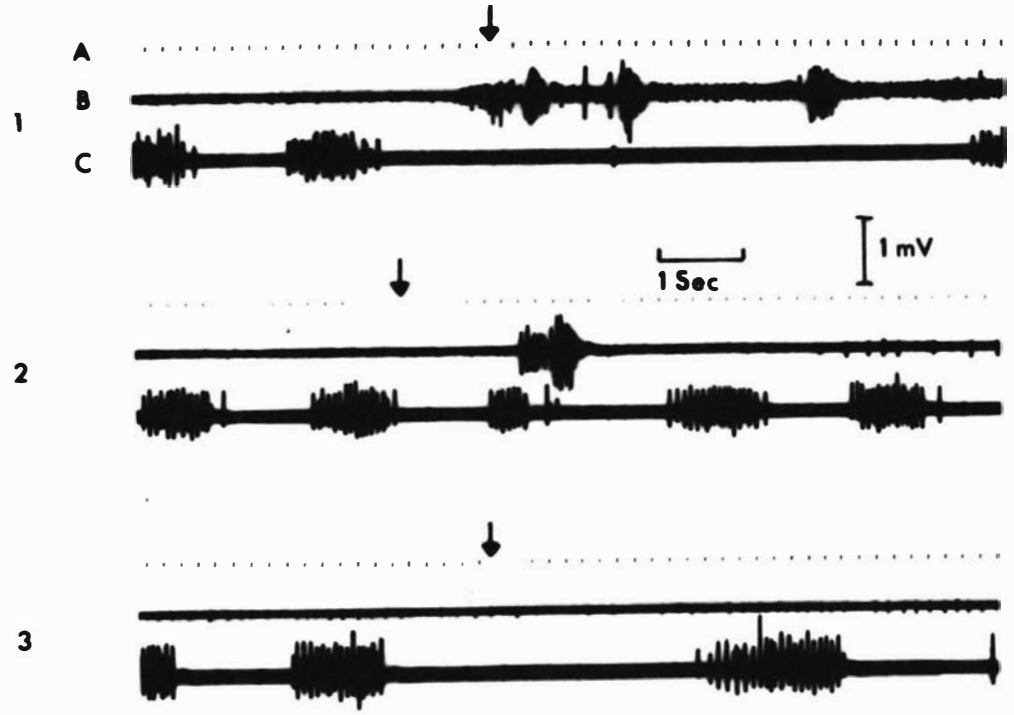
Cats with a tracheal cannula inserted at the laryngo-tracheal junction still showed some increase in activity of the cricothyroid and changes in the respiratory rhythm when exposed to ether either by mask or by cannula. The time between the start of administration of ether and the onset of increased cricothyroid activity ranged between 0.1 and 2.4 sec by mask and

Fig. 30 The Effects of Spraying the Pharynx and Anterior Larynx with Local Analgesic in a Cat with a Tracheal Cannula



Decerebrate cat 1.5 kg. Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered by mask.
Trace 2: Effects of ether administered by tracheal cannula.
Trace 3: Effects of ether administered by tracheal cannula after analgesic spray of pharynx and larynx.
Trace 4: Effects of ether administered by mask after analgesic spray of pharynx and laryux. (Spikes retouched)

Fig. 31 The Effects of Spraying the Pharynx and Anterior Larynx with Local Analgesic in a Cat whose Respiratory Tract is Intact

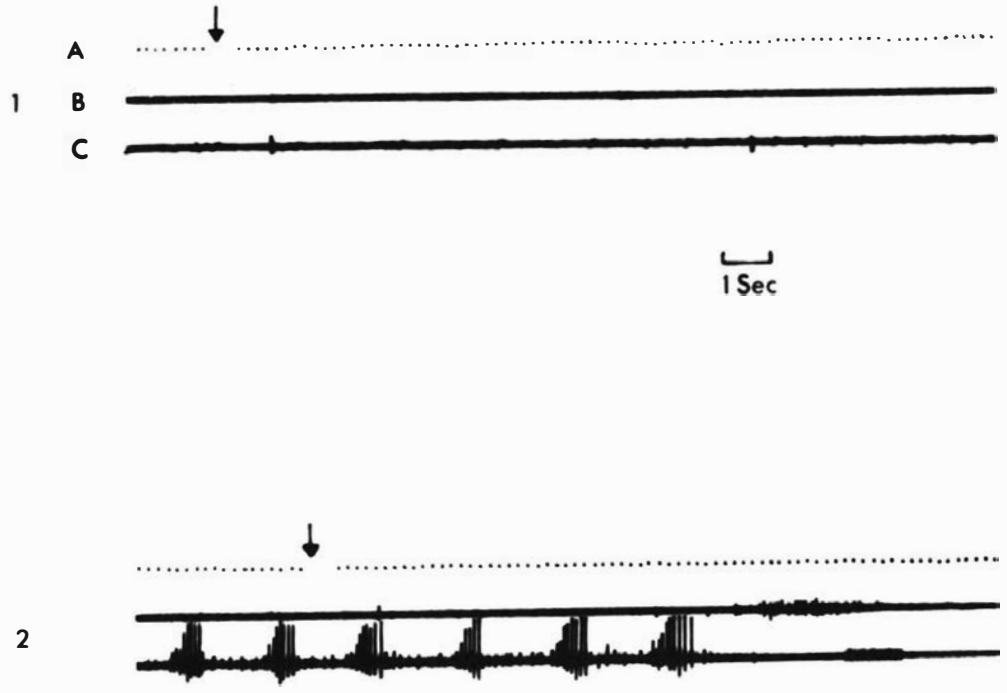


Decerebrate cat 3.4 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of spraying).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of spraying the pharynx and larynx with ether.
Trace 2: Effects of spraying the pharynx and larynx with saline at 37°C.
Trace 3: Effects of spraying the pharynx and larynx with ether after analgesic spray.
(Spikes retouched)

between 0.4 and 7.5 sec by cannula. This is illustrated in traces from a decerebrate cat (Fig. 30, facing p.65). Trace 1 shows the effects of ether administered by mask. There was a high frequency discharge of a large number of motor units from the cricothyroid, and the diaphragm showed apnoea followed by apneusis. Ether administered into the trachea and lungs stimulated a short period of laryngospasm (2 sec) and an increase in the interval between diaphragm activity from 2 to 6.5 sec (Trace 2). The pharynx and anterior larynx were then sprayed with 2 per cent lignocaine. Trace 3 shows the effects of administration of ether to the trachea and lungs after spraying with the local analgesic solution. The record is almost identical in duration of cricothyroid activity and change in respiratory rhythm to that in Trace 2. Administration of ether by mask (Trace 4), however, now produced only a small increase in cricothyroid activity of short duration. There was no initial stimulation of the diaphragm, but there was a period of apnoea followed by apneusis.

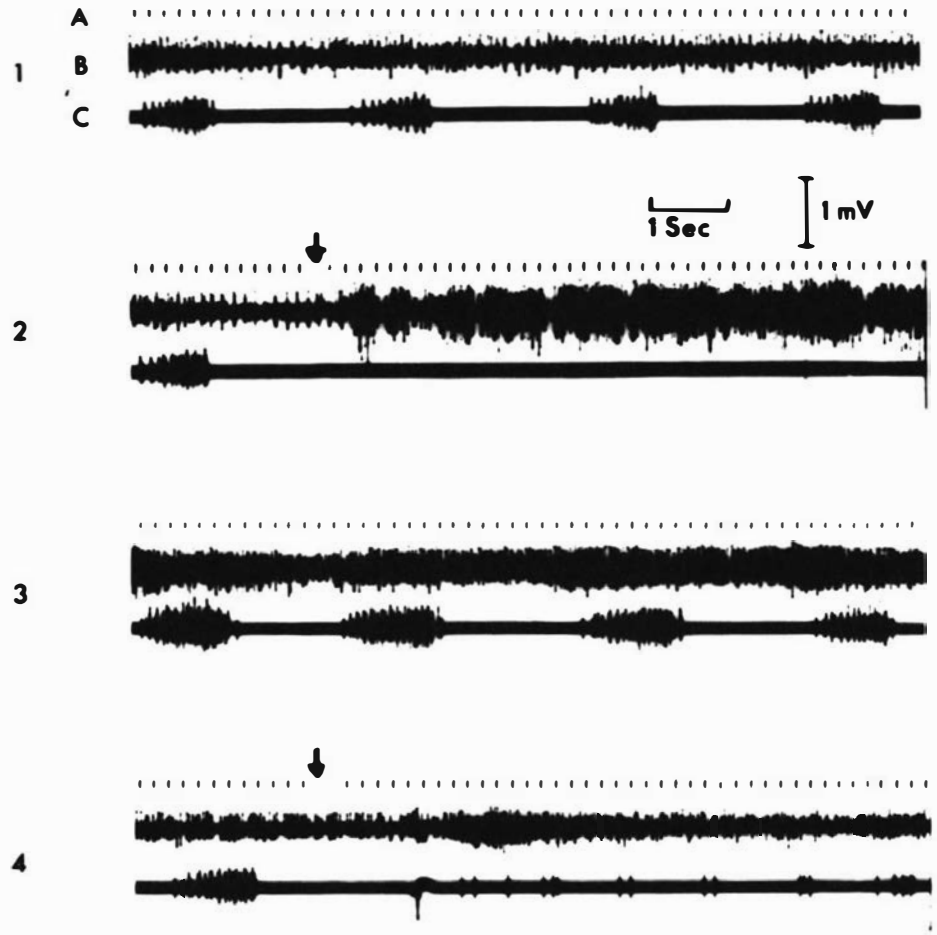
In another decerebrate cat, with no tracheal cannula inserted, the technique of spraying local analgesic solution currently used for intubation of cats in clinical anaesthesia was investigated. In this cat ether spray stimulated laryngospasm and apnoea (Fig. 31, Trace 1, facing p.65) and an 0.9 per cent warm saline spray also stimulated laryngospasm of brief duration and a very minor interruption in the regular respiratory rhythm (Trace 2). After spraying the pharynx and larynx with a 10 per cent lignocaine solution from an aerosol pack, an ether spray stimulated a very slight increase in cricothyroid activity after 4.5 sec. The interval between periods of activity of the diaphragm was increased from 1.5 to 3.75 sec for one respiratory cycle and then returned to normal (Trace 3). In the same cat reaction to mechanical stimulation and

Fig. 32 **Comparison of a Movement Artifact during Artificial Respiration with the emg from the Diaphragm in Spontaneous Respiration**



Decerebrate cat 2.5 kg. Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec.
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: During artificial respiration. Movement artifacts on diaphragm trace.
Trace 2: Spontaneous respiration.
(Spikes retouched)

Fig. 33 The Effect of Suxamethonium on the Stimulation of Laryngospasm, 1.



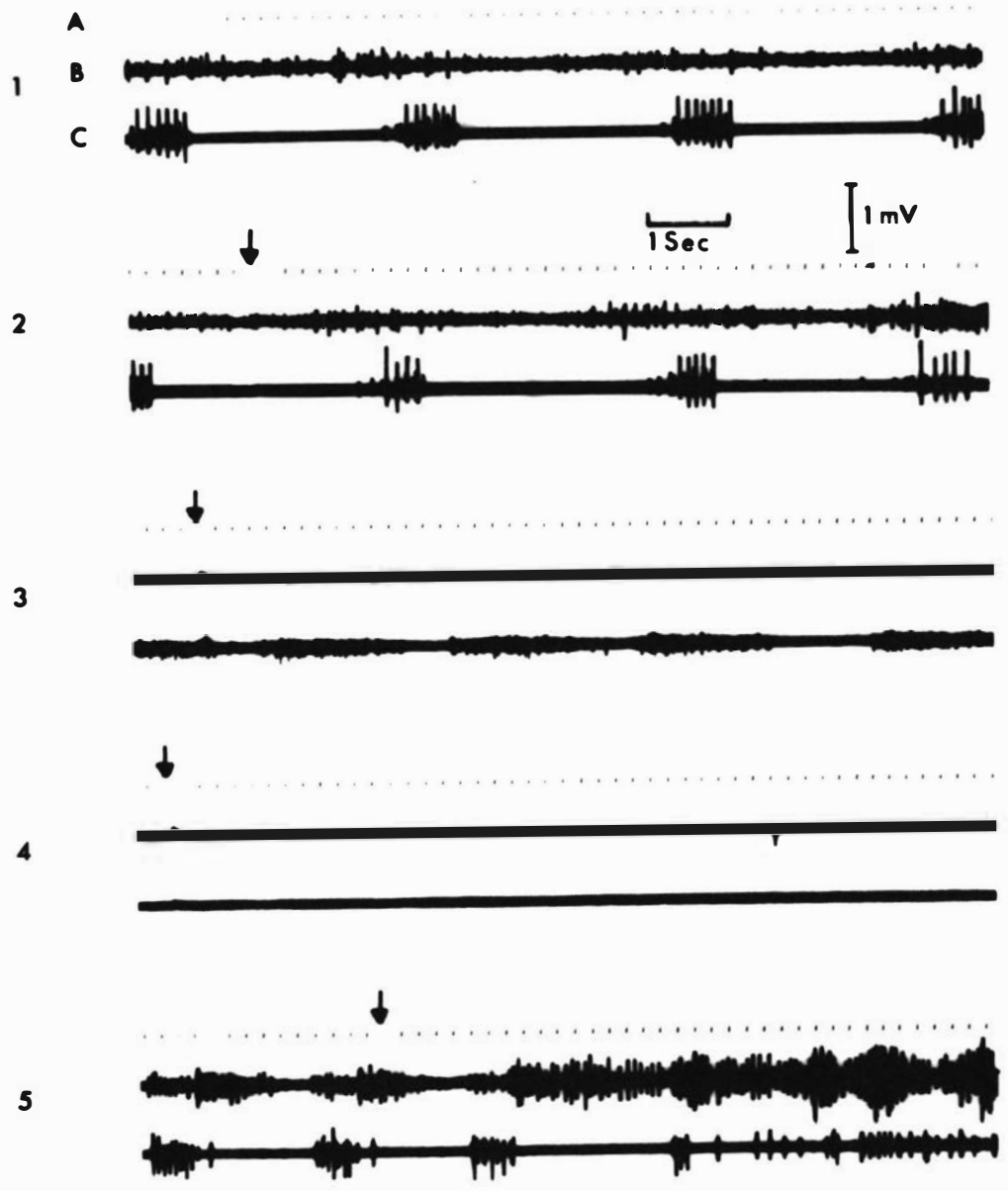
Decerebrate cat 2.7 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Quiet respiration.
Trace 2: Effects of ether administered by mask.
Trace 3: The return of diaphragm activity.
Trace 4: Effects of ether administered by tracheal cannula.

intubation was greatly diminished, as has been described in section (a) of this chapter.

(h) The effect of suxamethonium on the stimulation of laryngospasm and on the activity of the cricothyroid muscle and diaphragm

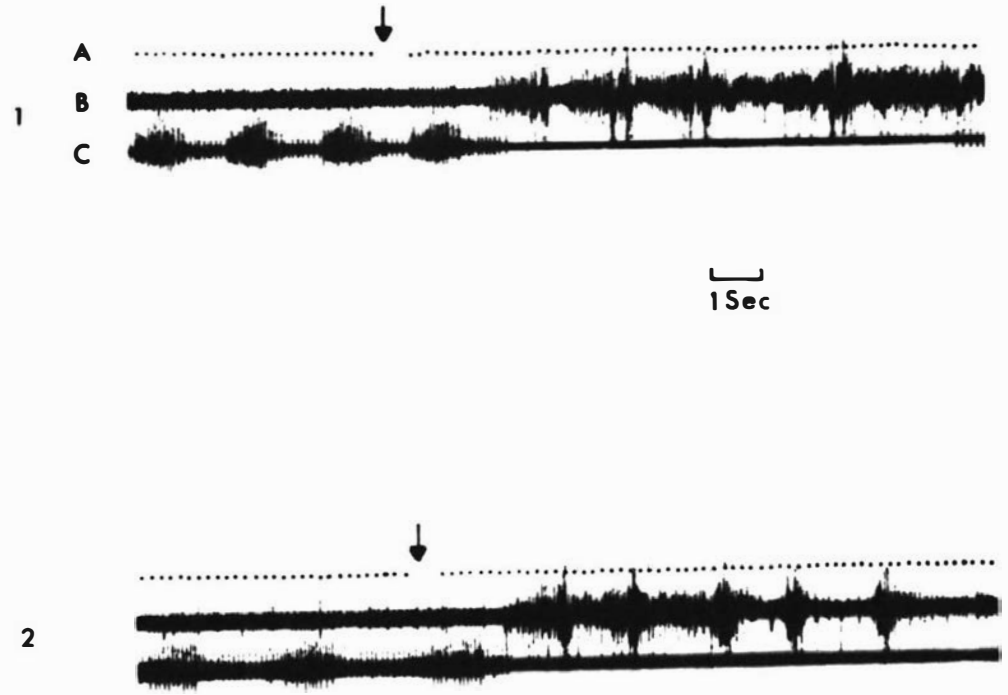
As the cricothyroid muscle and diaphragm are striated muscle structures it was considered of interest to record the effect of suxamethonium (a depolarizing muscle relaxant) on their activity. Suxamethonium (1 mg per kg) was given intravenously to a decerebrate cat which had exhibited laryngospasm when exposed to ether by mask or by tracheal cannula. Apnoea occurred 8 sec after the injection and 0.5 sec later there was a small increase in cricothyroid activity which lasted 3 sec. The cat's lungs were ventilated rhythmically with oxygen by opening and closing the end of the T-piece. Exposure to ether by mask did not stimulate any activity in the cricothyroid muscle, nor was any spontaneous activity recorded. After 25 min, spontaneous respiration started again and exposure to ether by mask now stimulated activity of increased frequency. When the cat's lungs were being ventilated by intermittent positive pressure, there was a slight rhythmical fluctuation in the baseline of the diaphragm trace due to movement of the diaphragmatic needle electrode (Fig. 32, Trace 1, facing p.66). This record was of quite a different nature from that of the diaphragmatic action potentials during spontaneous respiration (Trace 2). Fig. 33 (facing p.66) shows traces obtained from a decerebrate cat with cannulae in the trachea and the femoral vein. The cricothyroid muscle was displaying continuous activity during quiet respiration in this cat (Trace 1). When ether was administered by mask for 10 sec, apnoea and laryngospasm were stimulated within 0.2 sec (Trace 2). Spasm of the

Fig. 34 The Effect of Suxamethonium on the Stimulation of Laryngospasm, 2.



Decerebrate cat 2.7 kg (The same preparation as in Fig. 33).
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration in Traces 3, 4 and 5, and suxamethonium injection in Trace 2).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Quiet respiration.
Trace 2: Administration of 3.0 mg suxamethonium intravenously.
Trace 3: Effects of ether administered by mask.
Trace 4: Effects of ether administered by tracheal cannula.
Trace 5: Effects of ether administered by mask 15 min after suxamethonium.
(Spikes retouched)

Fig. 35 The Effect of Thiopentone on the Stimulation of Laryngospasm



Decerebrate cat 2.5 kg. Decerebration under halothane/ether anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered by mask.
Trace 2: Effects of ether administered by mask after intravenous injection of thiopentone.

cricothyroid muscle continued for 36 sec after the start of regular inspiratory activity of the diaphragm (Trace 3). When ether was administered for 10 sec into the tracheal cannula a much smaller increase in activity was stimulated at the same time as interruption of the regular rhythm of the diaphragm (Trace 4). In the same cat, Fig. 34, Trace 1 (facing p.67) shows activity of the cricothyroid muscle and the diaphragm 20 min after administration of ether by tracheal cannula. Trace 2 shows the effect of the administration of 3 mg suxamethonium intravenously. Increased activity of both the cricothyroid and diaphragm was stimulated 6.5 sec after the depolarising relaxant was given. Activity in the cricothyroid muscle stopped 18 sec after the injection of suxamethonium, whereas the diaphragm remained in a state of apneusis for 30 sec followed by 30 sec of reduced activity, before action potentials from it stopped. The lungs were then ventilated rhythmically by the technique described above. During the period of paralysis of the cricothyroid muscle and the diaphragm, laryngospasm could not be stimulated by the administration of ether by mask or tracheal cannula (Traces 3 and 4). Trace 3 shows that the diaphragm was still exhibiting some rhythmic activity when ether was administered by mask. Fifteen minutes after the suxamethonium had been given, spontaneous respiration started again, and laryngospasm could be stimulated by the administration of ether (Trace 5).

(i) The effect of thiopentone on the stimulation of the respiratory tract by volatile anaesthetic agents

Dundee (1965) stated that there is an apparent increase in the sensitivity of the laryngeal reflexes under light thiopentone narcosis, with an increased incidence of laryngospasm over that observed when inhalation techniques are used. Fig. 35, Trace 1 (facing p.67) shows the

records obtained from the cricothyroid muscle and diaphragm during administration of ether and oxygen by mask. Laryngospasm and apnoea were stimulated. Resting activity was considerable in the cricothyroid and diaphragm in this cat. After 5 mg thiopentone sodium, given intravenously (one tenth the clinical induction dose for a cat of this weight) the respiratory rate slowed from 30 per min to 18 per min and the frequency of the resting discharge from the cricothyroid muscle was lower than it had been before. Administration of ether by mask (Trace 2) still caused laryngospasm and apnoea, but less motor units were involved in the cricothyroid discharge than had been before thiopentone.

2. Discussion of the Experimental Results Reported in Chapter IV

(a) Mechanical stimulation

In experiments described in this thesis, the cat's mouth was held open by a gag while mechanical stimulation of the different areas was carried out. This is one technique adopted for endotracheal intubation in clinical anaesthesia. Another method is to hold the mouth open either with a gag, or by the fingers and the blade of a laryngoscope. Contraction of the dorsal cricoarytenoid muscle (abductor) simultaneously with the adductor group had been observed by Murtagh and Campbell (1954). Semon (1890b) reported that when the adductor and abductor muscles of the larynx were stimulated equally strongly, the overall effect was adduction. Many afferent stimuli causing spasm of the adductor muscle group may cause spasm of the abductor muscles at the same time. When spasm of all the intrinsic muscles of the larynx occurs simultaneously, the end result appears to be laryngeal closure. Reflex protection of the airway takes precedence over rhythmical muscle activity observed during quiet respiration.

There are many references to mechanical stimulation of the respiratory tract and its association with laryngospasm and other protective reflexes in both man and animals (for example: Bucher, 1958; Cole, 1939; Doty and Bosma, 1956; Jackson, 1922; Larsell and Burget, 1924; Murtagh and Campbell, 1954; Ogura and Lam, 1953; Ranson, 1921; and Teitelbaum et al (1936).

In the work reported here, the effects of mechanical stimulation of the pharynx and anterior larynx were essentially the same in decerebrate cats and in cats anaesthetized with chloralose. These were glottal closure, interruptions in respiratory rhythm, and coughing. Movement of the whole larynx cranially occurred during glottal closure. This poses the question as to whether the records obtained were movement artifacts rather than action potentials from the intrinsic laryngeal muscles. Milojevic and Hast (1964), working on the stimulation of laryngeal muscle motor areas in the dog's cerebral cortex, pointed out that gross movement of the larynx and contraction of neck muscles provoked mechanical artifacts which could be confused with action potentials. Records obtained in the present study are similar to those described by Milojevic and Hast (1964) as electromyograms, and quite unlike their examples of movement artifacts.

Movement of the whole larynx cranially when laryngospasm was stimulated mechanically suggests that the reflex may have some similarity to swallowing. Doty and Bosma (1956), investigating the swallowing reflex, showed that in dogs, cats and monkeys, anaesthetized with urethane or ether, a short period of increased activity in the cricothyroid muscle followed a period of inhibition. Swallowing was elicited by tactile stimulation of the pharynx. More recently Storey (1968a) carried out a functional analysis of sensory units innervating the epiglottis and larynx

of cats. His purpose was to find the laryngeal receptors excited by adequate stimuli for the swallowing and coughing reflexes (both protective reflexes of the airway), and to define the characteristics of their discharges. Some preparations were "electrolytically decerebrated" after induction of anaesthesia with thiamylal sodium; others were anaesthetized with chloralose or pentobarbitone sodium. He applied a wide range of mechanical, chemical, and thermal stimuli to the epiglottis and larynx of decerebrate cats to determine the thresholds and most responsive sites for stimulation of swallowing (Storey, 1968b). He concluded that swallowing, initiated from sites innervated by the superior laryngeal nerve, may serve to guard the larynx from saliva and liquid bolus residues, or to clear the larynx of secretions coming up from the trachea and bronchi. Mechanical stimulation of the receptors described by Storey (1968a) during anaesthesia may result in laryngospasm.

A local analgesic spray almost completely eliminated the reaction to mechanical stimulation of the pharynx and anterior larynx and to the passage of a tube into the trachea. This will be discussed more fully later. The observations of Larsell and Burget (1924) and Widdicombe (1954b) that the trachea is more sensitive near the carina than in other regions were confirmed in this study. Confirmation was obtained that there are mechanoreceptors in the pharynx, soft palate, larynx and trachea of cats.

(b) Spraying the pharynx and larynx with anaesthetic agents or saline

Widdicombe (1964a), describing reflexes from the larynx, made the comment: "Receptor discharges on application of irritants seem not to have been described. Presumably the larynx also contains pain endings."

Dirnhuber et al (1965) have described the reaction to two irritant chemical solutions inserted into the larynx, which had been isolated from the trachea by insertion of a tracheal cannula. The preparations used were anaesthetized cats. Sensory fibres in the recurrent laryngeal nerves fired at a higher frequency in response to saline at 5°C than to saline at 32°C. There was also a difference in frequency response to solutions of the two chemicals, one stimulating a response of a higher and the other of a lower frequency than that produced by saline at 5°C. In the experiments reported in section (b) of this chapter, both ether and halothane stimulated discharges from the cricothyroid muscles of greater frequency and duration than those produced by 0.9 per cent saline at 37.0°C and 26.5°C. This could be interpreted as being due to cooling at the mucosa when ether and halothane droplets vaporized, but the fact that in later experiments discharges of similar magnitude were stimulated by ether and halothane vapour makes it unlikely. Spraying with saline at 5°C was not attempted. It appears from the work of Dirnhuber et al (1965) that the receptors in the cat's larynx stimulated by irritant chemicals are those which are cold-sensitive.

An interesting point which came out of the experiments in this section was the possibility of compensatory activity of the dorsal cricoarytenoid muscle after laryngospasm as shown by prolonged activity of this muscle during the inspiratory phase of the cycle after laryngospasm.

(c) Inhalation of anaesthetic agents to the intact respiratory tract

Widdicombe (1964b), commenting on the effects of drugs and chemicals on respiratory reflexes stated: "In minimal doses these may influence one particular group of receptors, but larger doses invariably introduce

further actions. Painstaking experiments may be needed to establish specificity of effect (Dawes and Comroe, 1954). If such experiments are done, a drug may be a valuable tool for studying a reflex." In the work reported in this thesis, reflex laryngospasm was stimulated by the inhalation of volatile anaesthetic agents, and it was in this context that the reflex was being studied. In chapter VI, experiments are reported in which hydrogen cyanide was used as a tool in an attempt to determine the site of some of the receptors involved.

Allen (1929b) reported that the inhalation of strong irritants in man caused depression, slowing, and arrest of thoracic respiration. Mild irritants only reduced the inspiratory phase and produced changes in respiratory rate. In experiments reported in this thesis in which low concentrations of volatile anaesthetics were inhaled, both increases and decreases in respiratory rate were recorded. An anosmic patient in Allen's series responded to inhalation of ether and chloroform, among other substances, but not to wintergreen and xylol, which had produced changes in normal patients. This observation shows that in the upper respiratory tract olfactory receptors are not the only ones involved. In the experiments in this section, similar results were obtained in decerebrate cats, in which the olfactory nerves had no communication with the neuraxis, and in cats anaesthetized with chloralose. This confirmed Allen's observation.

Harrison and Vanik (1963) produced laryngospasm experimentally in anaesthetized cats by stimulating the vocal cords with bursts of ether vapour, but made no attempt to determine the sites of receptors. They were interested in the effect of atropine on laryngeal spasm.

In work reported in this thesis inhalation of ether and halothane to

the intact respiratory tract, at percentages within the ranges used during induction and maintenance of anaesthesia in clinical practice, was capable of stimulating apnoea and laryngospasm. Further experiments were needed to determine the sites of stimulation.

(d) The effects of volatile anaesthetic agents on isolated areas of the respiratory tract

The importance of this section of the experimental work is that it shows quite clearly that areas of the respiratory tract anterior to and including the larynx are not the only ones whose stimulation by anaesthetic vapours may result in laryngospasm and apnoea. This is a very important concept in anaesthetic practice, because it indicates that the presence of an endotracheal tube does not necessarily protect a patient against these undesirable hazards of anaesthesia.

It is interesting that there are apparent variations in the latent periods of ether, halothane, and methoxyflurane. This may be due to differences in solubility in blood of the different agents. Diethyl ether is more soluble than halothane or methoxyflurane. Paintal (1957) reported that the latencies between the start of insufflation and the onset of a discharge from pulmonary deflation receptors were longer after trichloroethylene than after ether. Ether is more soluble in blood than trichloroethylene. Variations in latency must also depend on the condition of the mucous membrane surface, presence of secretions, blood supply and similar factors.

Of even more interest is the failure of 2.9 per cent methoxyflurane administered through a tracheal cannula to the distal trachea and lungs to stimulate laryngospasm or changes in the respiratory rhythm although it

had done so when administered by mask. Six to eight per cent halothane did stimulate the laryngeal reflex when administered by tracheal cannula. This may have been because absorption of methoxyflurane was too slow, because the threshold of the receptors was not reached, or because those receptors sensitive to ether and halothane are not sensitive to methoxyflurane.

The discharge stimulated from the cricothyroid muscle when ether vapour was passed through an isolated tracheal segment was less intense in frequency and of shorter duration than when it was administered by mask to the nasopharynx and larynx, or by cannula to the distal trachea and lungs. This may be explained by Elftman's observation (1943) that in general there are fewer nerve endings distributed along the trachea than in any other part of the respiratory tree. She stated that there were more afferent endings in the region of the tracheal bifurcation and the lung hilus, but added the reservation that the amount of muscle was greater in these regions, therefore there may be no actual difference in the number of endings per unit volume of muscle. Evidence has already been presented, that the trachea is more sensitive to mechanical stimulation in the region of its bifurcation (see section (a), this chapter). Dixon and Brodie (1903), however, stated that sensitivity of the mucous membrane to chemical irritants became less and less the lower down the respiratory tract they investigated. Widdicombe (1954a) stimulated vigorous coughing by exposing the lungs of cats to sulphur dioxide, but found the trachea and bronchi "rather insensitive" to this stimulus. He considered, however, that there are receptors in the trachea and main bronchi which are cough receptors for chemical as well as mechanical stimuli. The two experiments in which laryngospasm was stimulated when ether vapour was passed through

an isolated tracheal segment provide further evidence for the existence of chemoreceptors in that region of the respiratory tract. In both cases the response was of sufficient magnitude to lead one to question Widdicombe's statement that the trachea and bronchi are "rather insensitive" to chemical stimulation.

Comroe (1965b) reported the presence of chemoreceptors in the lung bed and his findings add weight to the experimental evidence presented here. Paintal (1957), discussing pulmonary deflation receptors, stated that insufflation of the lungs with ether, trichloroethylene, or chloroform stimulated and sensitized the deflation receptors. This was followed by a depression or total loss of excitability of the receptors.

Up to this stage in the investigation, the respiratory tract had been exposed to ether or halothane at relatively constant concentrations (10 to 20 per cent and 6 to 8 per cent respectively). The next stage was to ascertain whether there was a threshold for stimulation of laryngospasm and apnoea, and whether prolonged administration of inhalation anaesthetic agents desensitized the receptors involved.

(e) Threshold of stimulation

Adrian (1953) recorded action potentials from the olfactory bulb of the rabbit. He drew the conclusion that for the more volatile substances the threshold concentration needed to produce an olfactory discharge in the rabbit differs little from that needed to evoke sensation in man. Early experiments in the series reported in this thesis established the fact that exposure of the respiratory tract to volatile anaesthetic agents at short intervals produced inconsistent results. This may have been an indication that it was impossible to obtain consistent results. On the

other hand it may have indicated that the receptors were being desensitised, or the whole animal anaesthetised by too frequent exposure to the agents. Paintal (1957), using cats anaesthetized with chloralose, demonstrated that insufflation of the lungs with ether or trichloroethylene was invariably followed by lowered excitability of the deflation receptors. The responses were not always completely abolished, but the duration and intensity of the discharge were reduced. The period of depression varied in different experiments from 2 to 30 minutes and excitability tended to return gradually. Harrison et al (1963) had also shown that the sensitivity of the respiratory tract to stimulation with ether could be depressed by other inhalation agents. Nitrous oxide caused little change in sensitivity, cyclopropane only depressed the response in deep anaesthesia, but halothane and trichloroethylene caused gradually decreasing sensitivity. They confirmed Paintal's observation that there was a tendency for responses to diminish following repeated stimuli at short intervals.

In this study experiments were conducted which demonstrated an approximate threshold for the onset of laryngospasm and apnoea in relation to inhalation of ether and halothane. With the vaporizers used, it was not possible to determine accurately the concentration of vapour at any time in the experiments. At the first exposure to halothane, it was possible to stimulate apnoea and laryngospasm with 2 per cent vapour in oxygen from the "Halox" vaporizer, which is a relatively accurate vaporizer. The concentration had to be raised, however, after the first exposure, confirming the observations on lowered excitability of receptors made by Paintal (1957), and Harrison et al (1963). The experiment in which increasing concentrations of ether vapour were administered for short periods at intervals of 30 min (Fig. 25, facing p.58) showed that cricothyroid

activity increased with increasing ether concentration. When the vaporizer lever was at position 4 (full-on) with the plunger up, laryngospasm and apnoea were stimulated for the first time. The concentration of ether produced with this setting of the vaporizer may be regarded as the threshold concentration for stimulation of laryngospasm and apnoea in this decerebrate cat but it is acknowledged that previous exposure to ether during the experiment may have raised the threshold. In the next experiment (Fig. 27, facing p.59), when the respiratory tract was exposed continuously to ether vapour the response of the cricothyroid muscle to an increase in ether concentration was delayed. The general effect on the activity of the diaphragm was to depress and prolong it, rather than to cause apnoea.

Peters (1954) suggested that bronchospasm may be associated with elevation of the arterial carbon dioxide tension in dogs. Two experiments were carried out in which the ether vaporizer was enclosed in a large water bath at 28.5°C. Absorption of carbon dioxide in one experiment but not in the other had no effect on the results. Although Peters' work showed that an increase in arterial carbon dioxide tension in dogs consistently stimulated bronchospasm, the threshold for stimulation of laryngospasm in the cat was not raised by inserting a carbon dioxide absorber in the anaesthetic system. The increase in inhaled carbon dioxide tension occurring when the soda lime absorber was withdrawn did not potentiate the action of ether vapour in stimulating laryngospasm. No experiments were carried out in which carbon dioxide was added to the inhaled gas mixture. Under temperature compensated conditions (provided by the water bath) apnoea and cricothyroid muscle spasm were stimulated at lever position 2 in both experiments. Under these conditions, it is suggested that the

concentration of ether vapour at that setting provided a threshold for the reflex.

(f) The effects of atropine

Burstein and Rovenstine (1938) suggested that drugs of the atropine group should be administered before using short-acting barbiturates. Their experiments were carried out on cats and were inconclusive, although excessively high doses of atropine were given. Rall, Gilbert and Trump (1945), using decerebrate dogs, reported that in 10 of 11 animals neither vagotomy nor doses of atropine of 10 mg per dog entirely abolished reflex bronchoconstriction. Bronchoconstriction was produced by mechanical stimulation of the nasopharynx, electrical stimulation of the peripheral end of the cut vagus nerve, or injection of drugs such as acetylcholine and histamine. Rosen (1960) stressed that there is no evidence that the laryngeal muscles and their motor nerves differ from other striated muscles and motor nerves in the body. Therefore, atropine should not be expected to relieve laryngeal spasm. He pointed out that the doses of atropine used by Burstein and Rovenstine in cats would be considered poisonous in man. Harrison (1962) reported that atropine, at a dose rate of 1.2 mg per cat in animals anaesthetized with cyclopropane or thiopentone failed to modify responses such as coughing, breath-holding or laryngospasm to the inhalation of cigarette smoke. Subsequently Harrison and Vanik (1963) recorded a slight decrease in severity of laryngeal spasm in cats anaesthetized with cyclopropane which were subjected to bursts of high concentrations of ether vapour. The dose rates of atropine used were 6.6 to 18.2 mg per kg (60 to 180 times the clinical dose rate in cats). They suggested that the antisialogogue action of atropine is the only one likely to have any effect on the incidence and severity of laryngospasm.

In the two cats which were given atropine intravenously, no change was observed in the effects of ether administered by mask or by tracheal cannula, although the second cat received over 30 times the dose rate used in clinical anaesthesia, thus confirming the results of these workers.

(g) The effect of analgesic sprays

In the present study, the fact that abolition or a reduction of the response to mechanical stimulation of the pharynx and larynx occurred after spraying these structures with a local analgesic solution suggests that many of the mechanoreceptors for the laryngeal reflex are situated in these areas. However, in many preparations some laryngeal adductor activity was still stimulated, suggesting the existence of receptors further down the respiratory tract which the local analgesic spray had not reached. Receptors in the nasopharynx similarly would not be blocked by these techniques and this was demonstrated by the fact that when ether was administered through the nasopharynx and larynx after local analgesic spray of the pharynx and anterior larynx there was a small increase in cricothyroid activity and an alteration in diaphragmatic rhythm ending in a period of apneusis (Fig. 30, Trace 4, facing p.65). This was probably due to stimulation of trigeminal receptors in the nasopharynx or receptors in the distal part of the larynx innervated by the recurrent laryngeal nerves. Administration of ether through the tracheal cannula in this cat stimulated effects almost identical with those before the analgesic spray, indicating that depression of the reflex as a whole had not occurred.

When a 10 per cent aerosol spray of lignocaine had been applied to the pharynx and larynx, administration of ether by mask stimulated a very

slight increase in cricothyroid activity after 4 sec (Fig. 31, Trace 3, facing p.65) in a decerebrate cat whose respiratory tract was intact. The normal range of latency for ether stimulation by mask in this study was 0.1 to 2.4 sec. Reaction to mechanical stimulation of the epiglottis and vocal cords at this stage was greatly reduced and endotracheal intubation was achieved with ease. This fact has been applied in clinical anaesthesia in cats with the result that what was at one time regarded as a hazardous and difficult procedure may now be carried out with little danger. Experiments which will be described in the chapter on nerve cutting and stimulation provide a logical basis for the results of the application of local analgesics.

These experiments confirm and amplify earlier work by Larsell and Burget (1924), who described the effects of cocaine on the trachea in the rabbit and dog, and by Teitelbaum et al (1936) who reported that cocaine desensitized the cat's pharyngopalatine mucosa to mechanical stimulation.

Walts and Kassity (1965) used methylene blue to study the spread of a local analgesic solution. They administered the solution through the cricothyroid membrane or between the first and second tracheal rings in conscious men. They found that the degree of spread of the agent was not necessarily related to the site of injection and that extensive spread above the vocal cords could result from both techniques. Their techniques may prove useful for future work in animals, for instance as a method of providing analgesia of the larynx for endotracheal intubation in the pig.

(h) The effects of muscle relaxants

The administration of suxamethonium 2 to 3 mg intravenously immediately after induction of anaesthesia has been used for many years to facilitate

endotracheal intubation in the cat (Hall, 1966b), and is used in human anaesthesia (Evans and Gray, 1965). The duration of action of suxamethonium is longer (usually 10 to 15 min) in the cat than in man (up to 5 min) and therefore it has the disadvantage that a longer period of controlled or assisted respiration is necessary after its use. Bjork and Wahlin (1960) administered suxamethonium iodide in doses of 0.5 to 1.0 mg intravenously to cats anaesthetized with ether and pentobarbitone sodium. They ventilated the cats by means of a pump during apnoea. The diaphragm was exposed surgically and its emg recorded from lacquered needle electrodes. They reported that an apparently normal inspiratory phase which was occasionally prolonged, was generally recorded. This was followed by an extended period of activity equivalent in length to several normal respiratory phases. Martagh and Campbell (1954) gave doses of the order of 5 mg of suxamethonium to several goats of unspecified weights, which were anaesthetized with intraperitoneal pentobarbitone sodium. Respiration stopped within 1 minute, but the action potentials of the intrinsic laryngeal muscles continued. In the animal they used as an illustration, the dose of suxamethonium was a divided one, and they give no record of the amount in each of the two fractions. It is therefore difficult to draw conclusions from their experiment. However, it does provide an indication that the activity of suxamethonium on the intrinsic laryngeal muscles may differ in cats and goats. In the record from the goat, the intrinsic laryngeal muscles are still active although the diaphragm is paralysed. In the two experiments in the cat reported here, paralysis of the diaphragm was accompanied by paralysis of the laryngeal muscles.

In the two experiments in which suxamethonium was administered in

this study it was impossible to stimulate laryngospasm by exposing the cats' respiratory tracts to ether. This result was expected, because the intrinsic muscles of the larynx are striated and they are therefore paralysed by suxamethonium.

(i) The effect of barbiturates

In one experiment in this study, the effect of intravenous thiopentone sodium on the incidence of laryngospasm was recorded. Ether still stimulated laryngospasm after the administration of thiopentone but it was less intense than it had been before the barbiturate was given. This result supports Dundee's suggestion that the supposed stimulation of laryngospasm by barbiturates in man may in fact merely be a failure of depression of laryngeal reflexes (Dundee, 1965). Martagh and Campbell (1954) were also unable to demonstrate any evidence of increased activity of the intrinsic laryngeal muscles in goats in response to thiopentone sodium. Harrison (1962), however, concluded that in man reflex responses to respiratory irritation were more prolonged with thiopentone and cyclopropane than with nitrous oxide alone or halothane with nitrous oxide. The effect of barbiturates on the laryngeal reflex remains to be determined unequivocally, but the evidence appears to point to a failure to suppress the reflex rather than to an active stimulation or sensitisation.

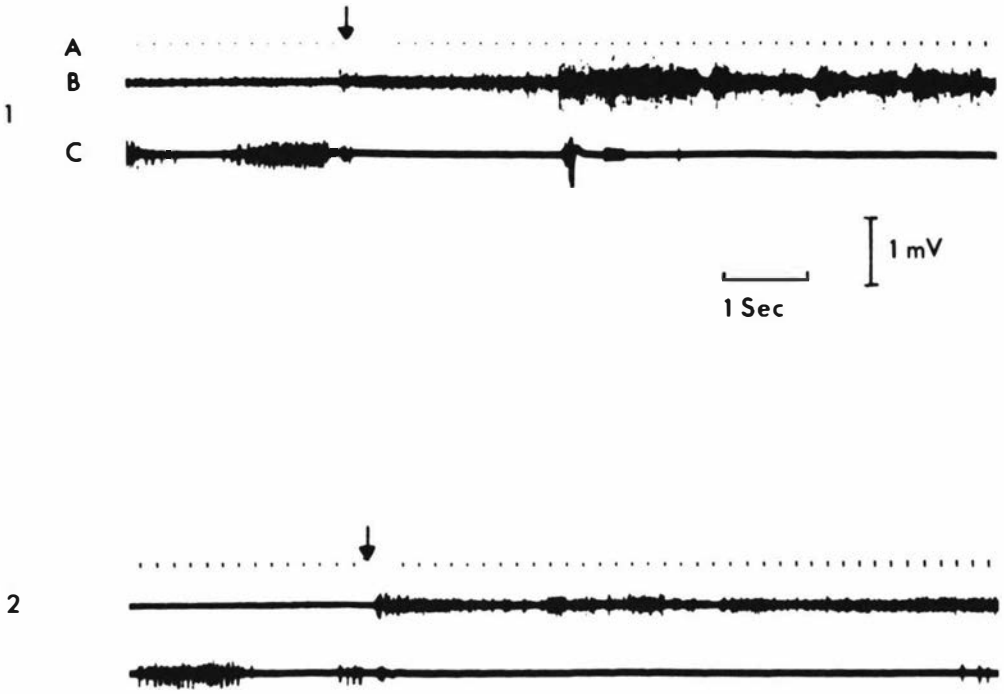
V THE EFFECTS OF CUTTING NERVES WHICH MAY BE INVOLVED IN THE LARYNGEAL REFLEX, AND SOME RESULTS OF THEIR STIMULATION

The literature on laryngeal structure and function considered in chapter II indicated the probable nerve pathways involved in the stimulation of laryngospasm. Hurtagh and Campbell (1954) for example, considered that the afferent pathways involved are those from the surface of the pharynx and larynx (cranial nerves V, IX and X), and (in theory at least) any other afferent nerve since they postulated that the entire central nervous system may act as a connecting pathway between afferent and efferent limbs of the reflex. They considered the efferent pathways to be in the vagus nerve and its branches, the superior laryngeal nerves, and the recurrent laryngeal nerves. They stated that the external branch of the superior laryngeal nerve provides motor innervation to the cricothyroid muscle, and that the recurrent laryngeal nerve has motor branches to the other intrinsic laryngeal muscles.

In chapter IV of this thesis, spraying the pharynx and anterior larynx with a local analgesic solution had been shown to abolish or reduce the effects of exposure of these areas to volatile anaesthetic agents, indicating that receptors in these regions were involved in the reflex, but giving no information as to the afferent nerve pathways.

The experiments reported in chapter IV have shown that receptor sites for laryngospasm are situated not only in the nasopharynx and larynx, but also in the trachea and the lungs. A further series of 46 experiments was now carried out to determine the effects of cutting nerves on the response of the intrinsic laryngeal muscles to the inhalation of anaesthetic agents. In 8 preparations, the effects of electrical stimulation of

Fig. 36 Stimulation of the Nasopharynx and Larynx by Ether after Cutting the Internal Branch of Both Superior Laryngeal Nerves



Decerebrate cat 1.3 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of ether by mask through the nasopharynx and larynx.
Trace 2: Effects of administration of ether by mask after cutting the internal branches of both superior laryngeal nerves.

central and peripheral ends of cut nerves were also recorded.

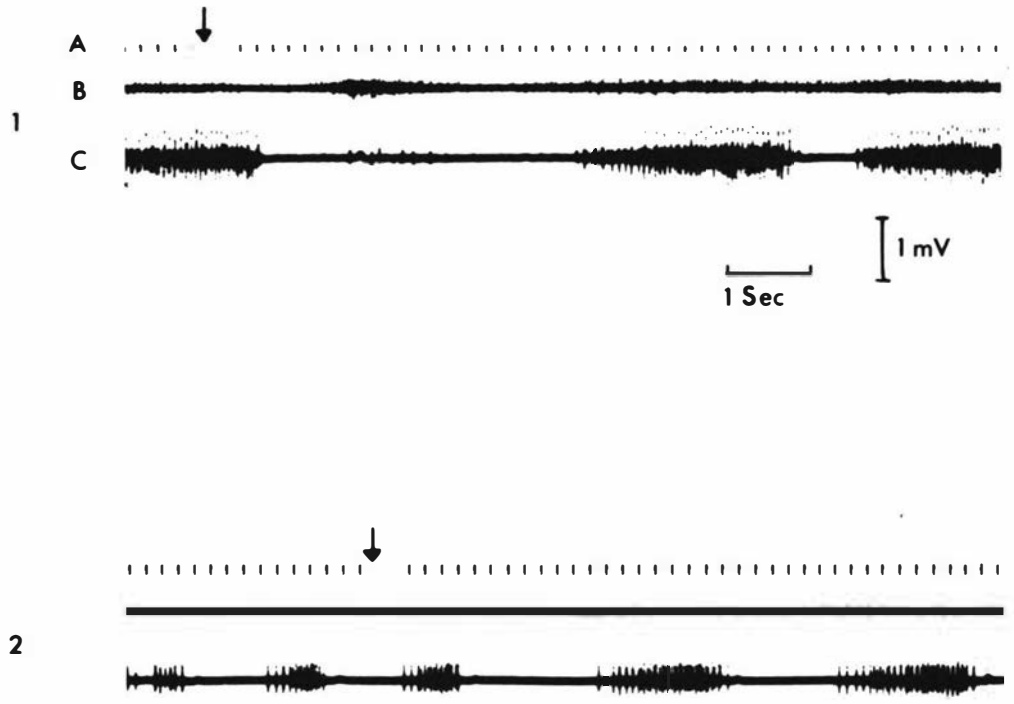
1. Experiments to Record the Effects of Cutting Nerves Which May be Involved in the Laryngeal Reflex and Some Effects of Their Stimulation

(a) The effects of cutting the internal branch of the superior laryngeal nerves

The early experiments on cutting the internal branch of the superior laryngeal nerve were carried out on cats under chloralose anaesthesia, with the respiratory tract intact. In the first experiment of this type, laryngospasm was stimulated 3.5 sec after spraying the pharynx and larynx with ether, and apnoea occurred. The internal branch of the ipsilateral superior laryngeal nerve was then cut. On exposure of the pharynx and larynx to ether spray, laryngospasm occurred 4.5 sec after the start of the spray, but no apnoea occurred. The internal branch of the contralateral superior laryngeal nerve was then cut. On exposure to ether spray there was a very slight increase in cricothyroid discharge, but no apnoea. The cricothyroid activity was not sustained and it was thought at that time that it may have been due to stimulation of receptors lower down the respiratory tract. Stimulation of the intact ipsilateral external branch of the superior laryngeal nerve at the end of the experiment was followed immediately by vigorous contraction of the cricothyroid muscle, showing that there had been no interference with the motor pathway.

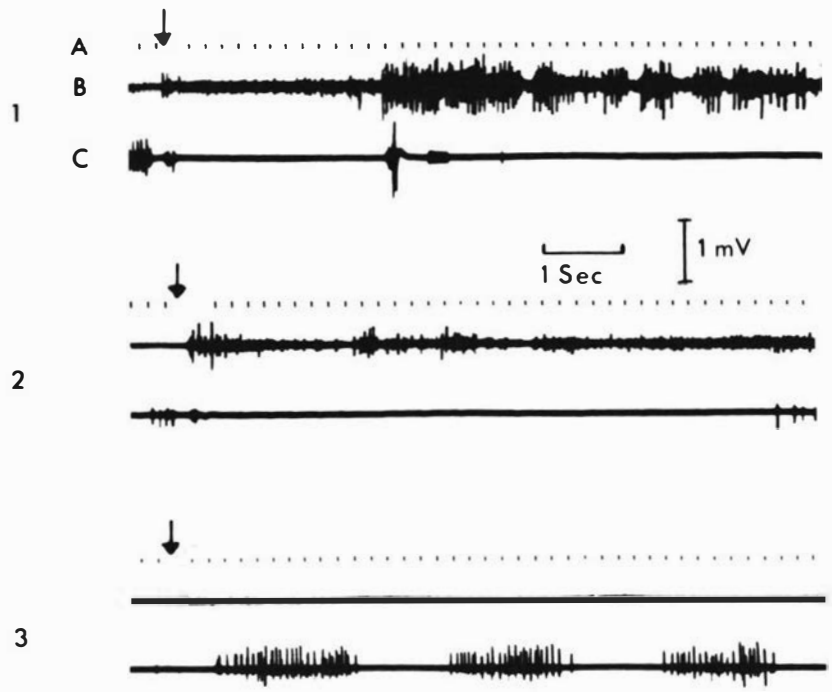
As the investigation continued in decerebrate cats, it was found that even with the nasopharynx and larynx isolated from the rest of the respiratory tract, some response was stimulated when ether was administered by mask after the internal branch of both superior laryngeal nerves had been cut (Fig. 36, Traces 1 and 2, facing p.84). This response could have

Fig. 37 Stimulation of the Nasopharynx and Larynx after Cutting the Recurrent Laryngeal Nerves



Decerebrate cat 2.25 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of ether by mask through the nasopharynx and larynx after cutting the internal branch of the superior laryngeal nerves and the recurrent laryngeal nerves on both sides.
Trace 2: Effects of administration of ether by mask after block of the trigeminal nerves.

Fig. 38 **The Effects of a Perineural Block of the Trigeminal Nerves after Cutting the Internal Branch of both Superior Laryngeal Nerves**



Decerebrate cat 1.3 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of administration of ether by mask through the nasopharynx and larynx.
Trace 2: Effects of administration of ether by mask after cutting the internal branches of both superior laryngeal nerves.
Trace 3: Effects of administration of ether by mask after section of the internal branches of both superior laryngeal nerves and block of both trigeminal nerves.
(Spikes retouched)

been due to stimulation of receptors with afferent pathways in the recurrent laryngeal nerves, or receptors in the nasopharynx with afferent pathways in the maxillary branches of the trigeminal nerves. Branches of the glossopharyngeal nerves may also be involved and their afferent innervation of the carotid bodies is considered in chapter VI.

(b) The effects of cutting the recurrent laryngeal nerves

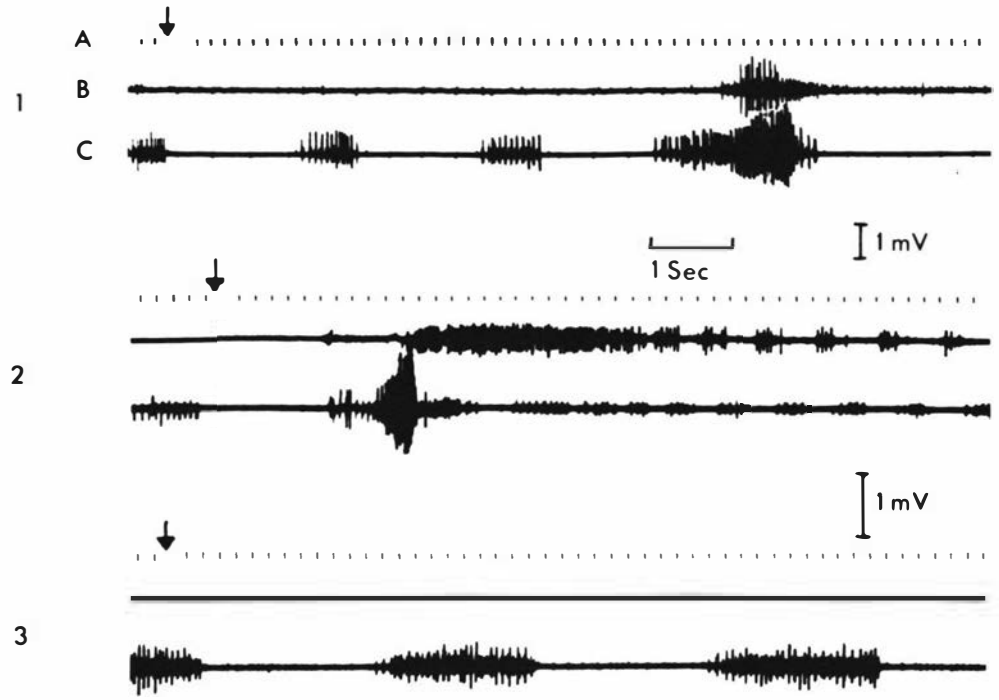
The recurrent laryngeal nerves were cut in 9 experiments during the investigation. This was done in most cases to determine whether they had branches which provided part of the afferent nerve supply to the trachea and lungs and will be considered further in section (d) of this chapter.

When ether was passed through the nasopharynx and larynx after the internal branches of both superior laryngeal nerves had been cut an interruption of diaphragmatic rhythm and laryngospasm were stimulated, as has been described in section (a) of this chapter. If both the recurrent laryngeal nerves were also cut, there was no change in the effect of ether administered by mask (Fig. 37, Trace 1, facing p.85). The injection of lignocaine solution around the trigeminal nerves within the cranial cavity at this stage abolished the stimulation of laryngospasm by ether administered through a mask (Trace 2).

(c) The effects of a perineural block of the trigeminal nerves with local analgesic solution

Laryngospasm, and apnoea or changes in respiratory rhythm were consistently stimulated by passing ether vapour by mask through the isolated nasopharynx and larynx (Fig. 38, Trace 1, facing p. 85). When the internal branch of the superior laryngeal nerve was cut on both sides, the effects

Fig. 39 The Effects of Cutting the Cervical Vagus Nerves



Decerebrate cats 3.0 kg (Trace 1) 1.3 kg (Traces 2 and 3). Decerebration under halothane/ether and halothane anaesthesia.

A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).

B: Electromyogram of cricothyroid muscle.

C: Electromyogram of diaphragm.

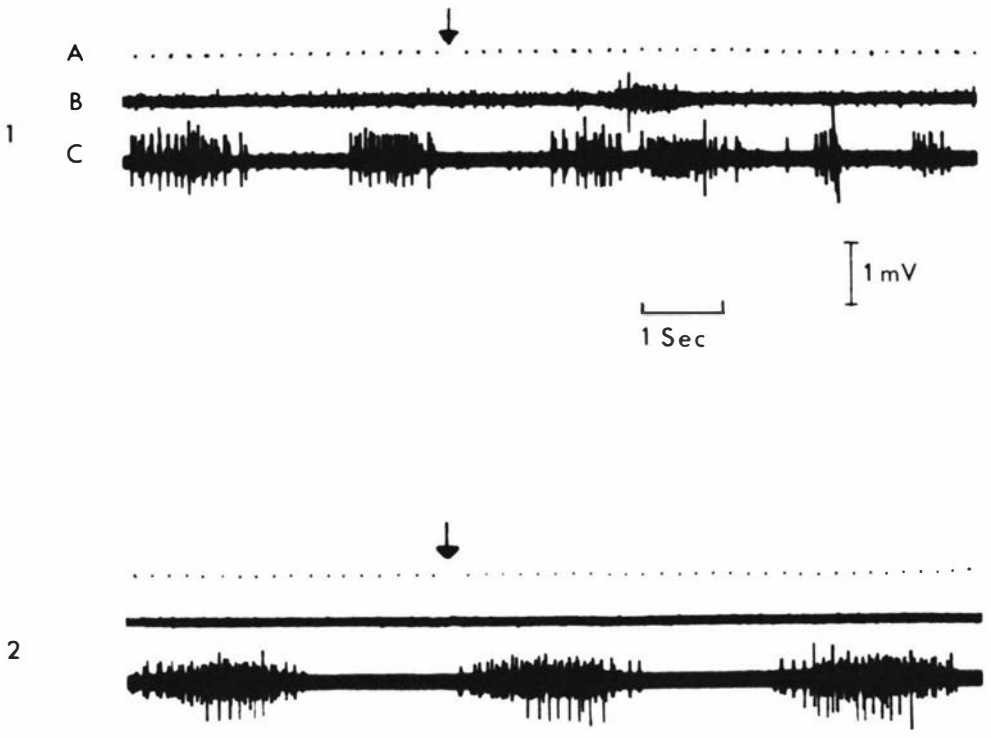
Trace 1: Effects of administration of ether through an isolated segment of trachea.

Trace 2: Effects of administration of ether to trachea and lungs after section of the internal branches of both superior laryngeal nerves and block of both trigeminal nerves.

Trace 3: Effects of administration of ether to trachea and lungs after cutting both vagus nerves at the level of the first tracheal ring.

(Spikes retouched)

Fig. 40 Stimulation of Diaphragmatic Activity when Ether is Inhaled



Decerebrate cat 4.6 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of ether administered to trachea and lungs after section of the internal branches of both superior laryngeal nerves and block of both trigeminal nerves.
Trace 2: As in Trace 1, but after cutting both vagus nerves at the level of the first tracheal ring.
(Spikes retouched)

of ether, administered 30 min later, were reduced, but laryngospasm and apnoea were still stimulated (Trace 2). Perineural block of the trigeminal nerves anterior to the Gasserian ganglion in addition to section of the internal branch of both superior laryngeal nerves abolished the effect of ether on the nasopharynx and larynx (Trace 3).

(d) The effects of cutting the cervical vagus nerves

Ether, administered by tracheal cannula to an isolated segment of trachea when the larynx was by-passed (Fig. 39, Trace 1, facing p.86) or to the distal trachea and lungs when the internal branch of both superior laryngeal nerves had been cut and the trigeminal nerves blocked (Trace 2), still stimulated apnoea and laryngospasm. The evidence therefore indicates that the afferent nerve pathways for laryngospasm initiated in response to receptors in the trachea and lungs are different from those innervating receptors within and anterior to the larynx. The direct pathways from the trachea could be in the recurrent laryngeal or vagus nerves, whereas those from the lungs might be in the vagus nerves. Another possibility is that the cervical sympathetic system may be involved. When both vagus nerves were cut at the level of the first tracheal ring, laryngospasm was not stimulated by inhalation of ether to the distal trachea and lungs in 15 of 19 experiments (Trace 3). In the other 4 experiments there was a delayed effect on respiratory rhythm and stimulation of cricothyroid activity which may have been due to carotid body stimulation (see chapter VI). In one cat after the vagus nerves were cut, inhalation of ether resulted not only in inhibition of cricothyroid muscle activity but also in stimulation of diaphragmatic activity (Fig. 40, Traces 1 and 2, facing p.86). Diaphragmatic activity

was increased both in frequency of action potentials and in the number of motor units involved. These apparent anomalies will be considered in the discussion.

(e) Stimulation of nerves thought to form part of the laryngeal reflex pathways

In 8 cats, electrical stimulation of intact or cut nerves was carried out. This was a minor part of the study for reasons which will be considered in the discussion. Very early in this work, the intact external branch of the superior laryngeal nerve was isolated. Electrical stimulation of the intact external branch of this nerve resulted in contraction of the ipsilateral cricothyroid muscle and an audiosignal from a needle electrode in the muscle. In the same cat, stimulation of the neck muscles produced no contraction of the cricothyroid muscle and no signal from the electrode. In 3 cats, stimulation of the intact recurrent laryngeal nerve resulted in movement of the ipsilateral vocal cord and arytenoid to a position midway between adduction and abduction. The cord stayed in this position for the duration of the stimulus. In another cat stimulation of the intact external branch of the superior laryngeal nerve resulted in almost immediate contraction of the cricothyroid muscle, whereas stimulation of the internal branch produced no similar immediate contraction.

When the internal and external branches of the superior laryngeal nerve were cut in a cat which had shown laryngospasm and apnoea on exposure to ether and halothane, no laryngospasm occurred when ether was inhaled, although the diaphragmatic record became irregular. Electrical stimulation of the central end of the cut internal branch of the superior laryngeal nerve resulted in a discharge of action potentials from the ipsilateral cricothyroid muscle after a pause, thus providing supporting

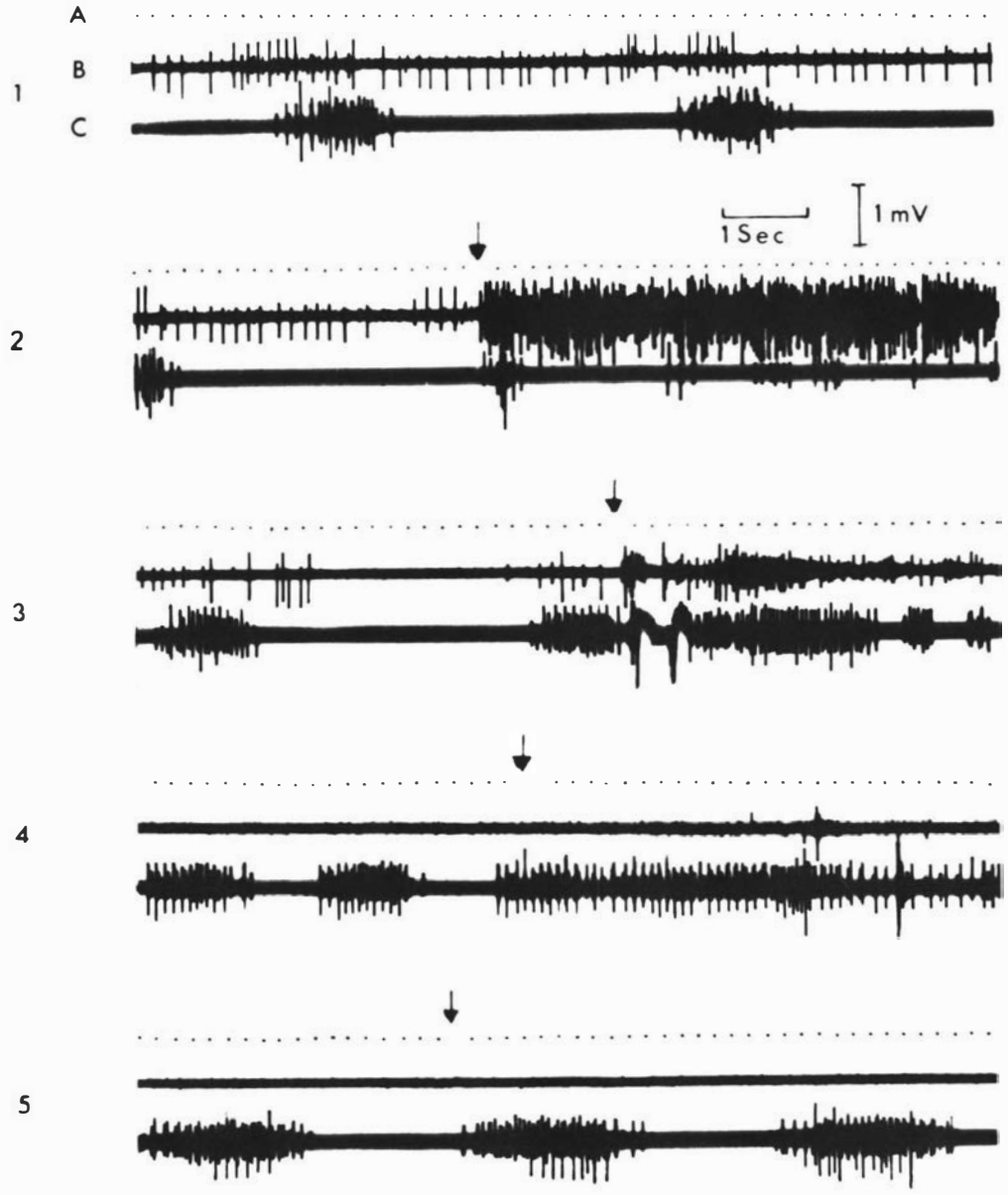
evidence for the role of the internal branch of the superior laryngeal nerve as an afferent limb in the laryngeal reflex. Stimulation of the peripheral cut end of the same nerve resulted in no discharge from either cricothyroid muscle, confirming evidence in the literature that this branch has no motor function to the cricothyroid muscles. This effect was repeated in another cat in which electrical stimulation of the central end of the cut internal branch of the superior laryngeal nerve resulted in the contraction of ipsilateral and contralateral cricothyroid muscles and apnoea.

2. Discussion of the Effects of Cutting or Stimulating Nerves Which May be Involved in the Laryngeal Reflex

Early in the work reported in this thesis, it was demonstrated that cutting the internal branch of the superior laryngeal nerves reduced the effects of inhaling anaesthetic agents. For a considerable time in the study residual effects of exposure of this area to ether (for example see Trace 2, Fig. 36, facing p.84) were considered to be due to stimulation of receptors in the caudal larynx or anterior trachea. They persisted, however, when the vagus nerves were cut at the laryngotracheal junction suggesting that the afferent pathway for the residual effect was neither in the recurrent laryngeal nerves, nor in the vagus nerves caudal to the point at which they were cut.

Allen's work (Allen, 1929a, 1936) and that of Murtagh and Campbell (1954), suggested that the trigeminals may provide a pathway from naso-pharyngeal receptors. When, in experiments described in section (c) of this chapter, the trigeminal nerves were blocked with lignocaine, the effects of exposing the isolated naso-pharynx and larynx to ether

Fig. 41 Stimulation of Diaphragmatic Activity when the Nasopharynx, Larynx, Trachea and Lungs are exposed to Ether Vapour



Decerebrate cat 4.6 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of ether administration in Traces 2, 3, 4, and 5).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Quiet respiration.
Trace 2: Effects of ether administered by mask through the nasopharynx and larynx.
Trace 3: Effects of ether administered to trachea and lungs.
Trace 4: Effects of ether administered by mask after section of the internal branches of both superior laryngeal nerves and procaine block of both trigeminals.
Trace 5: As in Trace 4, but after cutting both vagus nerves at the level of the first tracheal ring.
(Spikes retouched)

were abolished. At first, an attempt was made in decerebrate preparations to cut the trigeminal nerves intracranially anterior to the Gasserian ganglia. It proved difficult to cut the nerves at this site without provoking profuse haemorrhage, which made the preparation unsatisfactory or caused its death. To avoid this complication, attempts were made to cut the nerves using electrocautery. This technique proved no more satisfactory than ligation and cutting, because haemorrhage was equally severe. After these methods had proved unsatisfactory, it was decided to attempt a perineural local analgesic block of the trigeminal nerves within the cranial cavity. The position at which the block was carried out was just anterior to the orbital fissure and round foramen. Because of the vascularity of the dura, haemorrhage still presented such a problem that 3 of the 8 cats in which this technique was used bled profusely during the procedure. Of these 3, 1 died and the other 2 were considered unsuitable for further experimental work. The trigeminal nerves were blocked successfully, as judged by abolition of the laryngeal reflex, in 4 cats in which 2 per cent lignocaine was used and in 1 cat in which 2 per cent procaine was used.

In the 4 cats in which the trigeminal nerves were blocked with lignocaine after cutting the internal branch of the superior laryngeal nerves, stimulation of the naso-pharynx and larynx with ether vapour provoked neither apnoea nor laryngospasm. In the 1 cat in which procaine was used, laryngospasm was inhibited, but instead of inhibition of diaphragmatic activity, stimulation occurred. In this preparation, stimulation of diaphragmatic activity by ether occurred both when it was administered by mask and by tracheal cannula (Fig. 41, facing p.89). Before the vagus nerves were cut, ether evoked intermittent periods of

inspiratory activity of the diaphragm (Trace 2), apneusis (Trace 4), or a combination of these two types of activity (Trace 3). After cutting the vagus nerves, the diaphragmatic activity stimulated was similar to that produced by carotid body stimulation (see chapter VI). It remains to be determined whether in some animals stimulation by inhalation agents causes diaphragmatic spasm rather than paralysis, or whether this was a specific drug effect stimulated by procaine. It is intended that this reaction should be investigated more fully in future work. The results of cutting the internal branch of the superior laryngeal nerves and blocking the trigeminal nerves confirm the reports of the function of these nerves as afferents from the naso-pharynx and larynx (Allen, 1929a, 1936; Faaborg-Andersen, 1957; Gruber, 1917; Jewett, 1964; King and Gregg, 1948; Kirikae et al, 1962; Lam and Ogura, 1952; Lemere, 1932a, 1932b; Murtagh, 1945; Murtagh and Campbell, 1954; Ogura and Lam, 1953; Pressman and Kelemen, 1955; Teitelbaum et al, 1936).

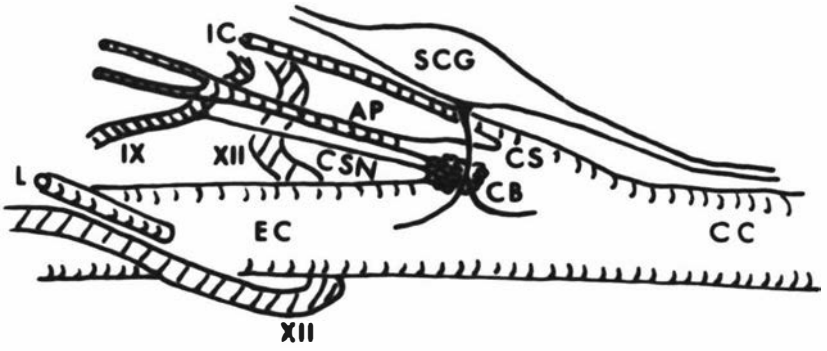
It is well established, from the literature already quoted in chapter II, that afferent nerves from the larynx caudal to the vocal cords innervate chemoreceptors in that area. In the experiment described in section (b) of this chapter, the recurrent laryngeal nerves were not shown to be involved in the laryngeal reflex stimulated from the naso-pharynx and larynx. In this experiment, apnoea and cricothyroid spasm persisted after cutting the internal branch of the superior laryngeal nerves as well as the recurrent laryngeal nerves, but were abolished when the trigeminal nerves were blocked. In other experiments (section (c) of this chapter) the laryngeal effects of ether by mask were abolished by section of the internal branch of the superior laryngeal nerves and the trigeminal nerves without recourse to cutting the recurrent laryngeals.

It thus appears that afferent pathways in the recurrent laryngeal nerves have little part in the effects of the inhalation of volatile anaesthetic agents on afferent receptors in the naso-pharynx and larynx.

A practical problem in experiments in which the recurrent laryngeal nerves were cut was that it resulted in motor paralysis of all the intrinsic muscles of the larynx except the cricothyroid muscle. For this reason, if the recurrent laryngeal nerves or the vagus nerves were cut the procedure was carried out as late as possible in the course of an experiment.

The possibility still remains that the recurrent laryngeal nerves may form part of the afferent pathway for the stimulation of laryngospasm by the action of inhalation anaesthetic agents on an isolated segment of trachea. This was suggested by the experiment illustrated in Fig. 39, Trace 1 (facing p.86). During the course of the experiment, cutting the vagus nerves at the diatal end of the isolated tracheal segment reduced the reaction to ether through the segment (this is not shown in the trace). This interrupted the afferent pathway from the recurrent laryngeal nerves, suggesting that they provided part of the sensory innervation of the trachea. Cutting the vagus nerves at the anterior end of the tracheal segment reduced the reaction to ether passed through it still further. This demonstrated the possible existence of afferent pathways from the trachea to the cervical vagus. When the recurrent laryngeal nerves themselves were cut at the level of the anterior end of the tracheal segment, it was not possible, with certainty, to detect any reaction to ether vapour passed through the segment. Lemere (1932b) had demonstrated clearly in dogs that a ramus anastomoticus existed between the superior and recurrent laryngeal nerves, and that its form varied from a single trunk to a plexus.

Fig. 42 Diagram showing the Innervation of the Carotid Body and Carotid Sinus in the Cat



After Heymans and Neil (1958)

CC	Common carotid artery	CS	Carotid sinus
EC	External carotid artery	L	Lingual artery
AP	Ascending pharyngeal artery	IC	Internal carotid artery
XII	Hypoglossal nerve	IX	Glossopharyngeal nerve
CSN	Sinus nerve	SCG	Superior cervical ganglion
CB	Carotid body		

It is possible that the persistence of reflex stimulation up to this point in the experiment could have been due to afferent impulses in the recurrent laryngeal nerves passing to the vagus through the ramus anastomoticus.

The inhalation of ether vapour into the distal trachea and lungs failed to stimulate laryngospasm and the rhythm of the diaphragm remained regular in most cases when the vagus nerves were cut at the level of the laryngotracheal junction. The latency between the start of ether administration and the onset of increased activity in the cricothyroid muscle was measured in 10 records representative of the series. It was found to range between 0.4 to 7.0 sec when administration was by tracheal cannula. The shorter latencies are consistent with stimulation of receptors in the tracheal mucosa and lungs and an afferent pathway in the vagus nerves. The existence of such a pathway is supported by Comroe's report that chemoreceptors are present in the lung bed (Comroe, 1965a). The longer latencies and the onset of the second phase of biphasic responses (Fig. 23, Trace 2, facing p.56) are consistent with the possibility that chemoreceptors in the aortic arch and carotid body may have been stimulated after ether was absorbed into the bloodstream. Jewett (1964) suggested that there may be a small number of direct nervous connexions between cardiovascular and respiratory organs.

Murtagh and Campbell (1954), in their assessment of possible afferent pathways for the laryngeal reflex, included the glossopharyngeal nerve among possible nerves involved. The sinus nerves from the carotid bodies are branches of the glossopharyngeal nerves (Fig. 42, facing p.92, after Heymans and Neil, 1958). In the next chapter, experiments are described in which an attempt was made to determine whether this pathway

is involved as well as that recognised in the vagus nerves.

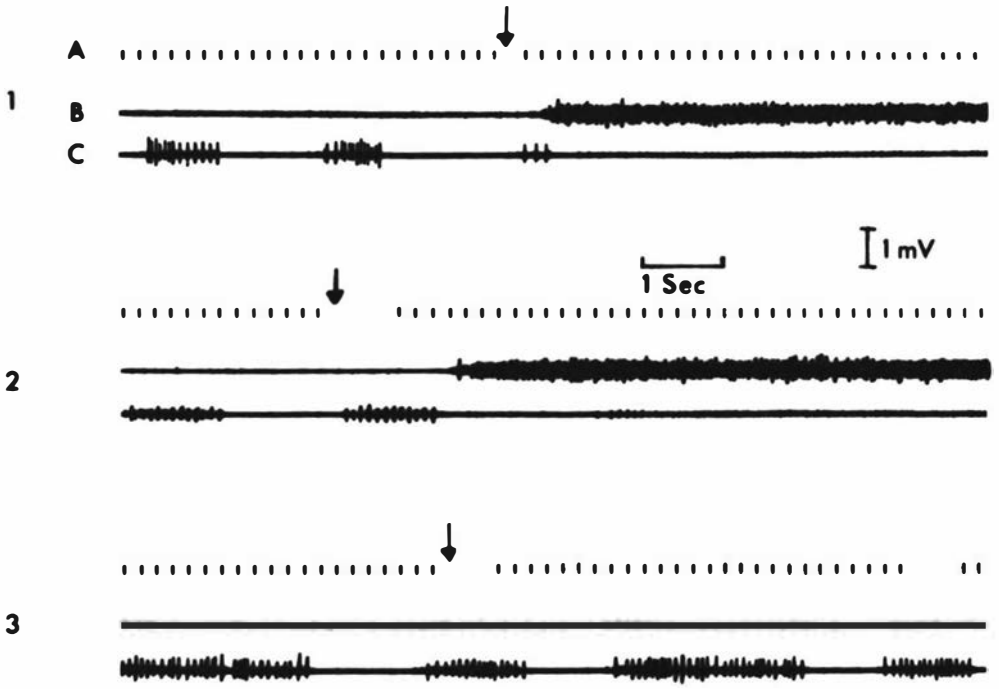
Stimulation of intact and cut nerves in 8 cats confirmed observations of previous workers that the external branch of the superior laryngeal nerve is the sole motor supply to the cricothyroid muscle in the cat, whereas the internal branch provides afferent innervation to part of the larynx. Because the work in this study is mainly concerned with the influence of volatile anaesthetics on the laryngeal reflex, emphasis has been placed on stimulation of receptors in the respiratory tract by these agents, rather than on electrical stimulation of nerves thought to be involved in the reflex. Reflex pathways were defined by recording cessation or modification of the effects of inhalation agents after the nerves considered to form part of the reflex arc had been cut.

VI THE EFFECTS OF INTRAVENOUS INJECTIONS OF A SOLUTION OF ETHER. A COMPARISON WITH THE EFFECTS OF INJECTING A SOLUTION OF HYDROGEN CYANIDE

The experiments described in this chapter were carried out in an attempt to determine more definitely the receptor sites and nerve pathways involved when laryngospasm is stimulated by volatile anaesthetic agents inhaled into the distal trachea and lungs. It was suggested in chapter V that the considerable variations in latencies and the biphasic effects which were found when ether was administered to the distal trachea and lungs may have occurred because stimulation was not only at the tracheal and pulmonary mucosa, but also at some other site or sites after absorption to the bloodstream. When both vagus nerves were cut at the level of the first tracheal ring for example, laryngospasm and respiratory rhythm changes were not stimulated by inhalation of ether in most experiments but there were occasional exceptions (see chapter V, section (d) p.86). Moreover the latency between the start of ether administration by tracheal cannula and the onset of increased activity in the cricothyroid muscle was found to range from 0.4 to 7.0 sec.

That alterations in the composition of the blood in the aorta could cause respiratory reflexes has already been shown (Heymans and Heymans (1927) cited by Lovatt Evans (1949a)). The reflexes, according to these authors, arose from stimulation of the aortic body, and the afferent pathways were in the vagus nerves. More recently Gabel (1961) has described the occurrence of laryngospasm in a horse in which general anaesthesia was being maintained by the infusion of a 5 per cent ether solution. In the experiments reported in this thesis, laryngospasm and apnoea could

Fig. 43 The Effects of Intravenous Injection of Ether and Halothane Solutions



Decerebrate cat 2.8 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate the start of injection in Traces 2 and 3 and the end of injection in Trace 1).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of a 5 per cent halothane solution.
Trace 2: Effects of intravenous injection of a 5 per cent ether solution.
Trace 3: Effects of intravenous injection of 0.9 per cent saline.
(Spikes retouched)

similarly be stimulated in the cat by the intravenous injection of a 5 per cent solution of ether in saline, the injections being made through an indwelling polythene cannula in the femoral vein.

Lovatt Evans (1949b) also recorded experiments in which he showed that a small dose of sodium cyanide, injected into a peripheral vein could be used to measure the circulation time from that vein to the carotid body. When the cyanide reached the carotid body it caused hyperpnoea; after cutting the sinus nerves (afferents from the carotid body) and vagus nerves, the latent period increased. He concluded that the late augmentation of breathing was probably due to the action of carbon dioxide at the medulla.

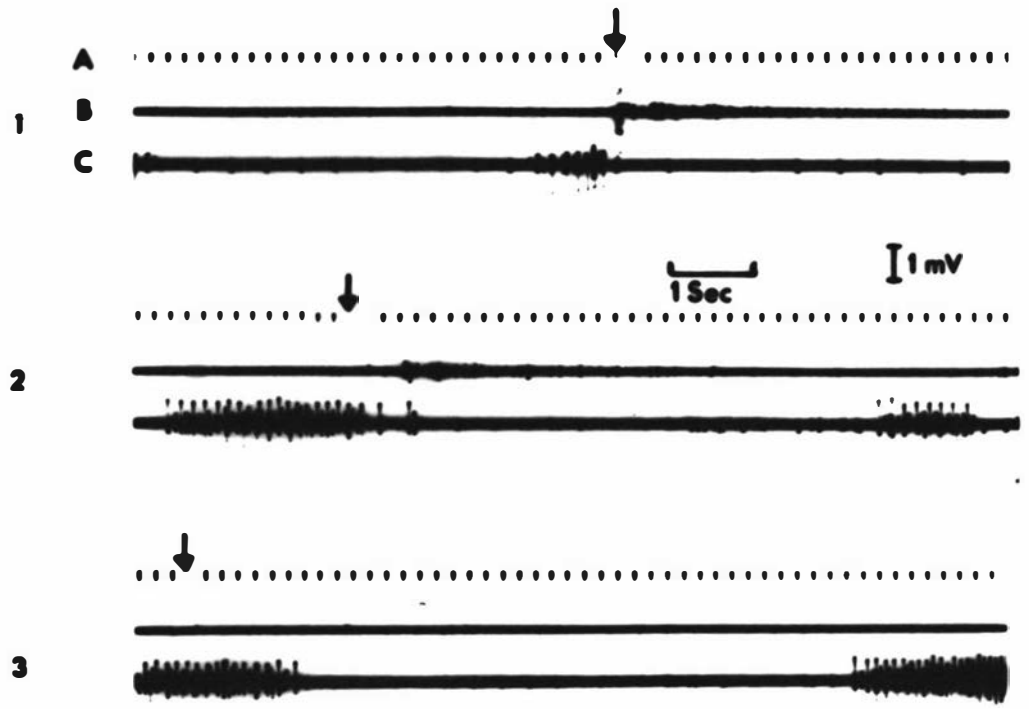
It was considered therefore that a comparison of the effects of injecting solutions of ether and hydrogen cyanide could indicate whether or not the carotid bodies were involved in the laryngeal reflex.

1. Experiments to Record the Effects of the Intravenous Injection of Solutions of Ether and Hydrogen Cyanide

(a) The effects of injecting anaesthetic solutions and saline into the femoral vein

In the first 2 experiments, in which up to 10 ml of a 5 per cent solution of ether in 0.9 per cent saline were injected into the femoral vein, spasm of the cricothyroid muscle and apnoea were not stimulated. In the third experiment an injection of 20 ml 5 per cent ether intravenously stimulated a burst of activity from the cricothyroid muscle and apnoea. Apnoea was followed by a period of apneusis and after this the respiratory rate increased. In the next experiment continuous cricothyroid activity and apnoea were stimulated by a 5 per cent halothane solution as well as by 5 per cent ether (Fig. 43, Traces 1 and 2, facing p.95). A control

Fig. 44 The Effects of Intravenous Injection of Ether and HCN Solutions, 1.



Anaesthetised cat 3.8 kg. Chloralose (65 mg per kg) administered after halothane induction.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate end of injection).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 5 ml 5 per cent ether solution.
Trace 2: Effects of intravenous injection of 5 ml 5 per cent ether solution after section of the internal branches of both superior laryngeal nerves.
Trace 3: Effects of intravenous injection of 1 ml 4 per cent HCN solution.

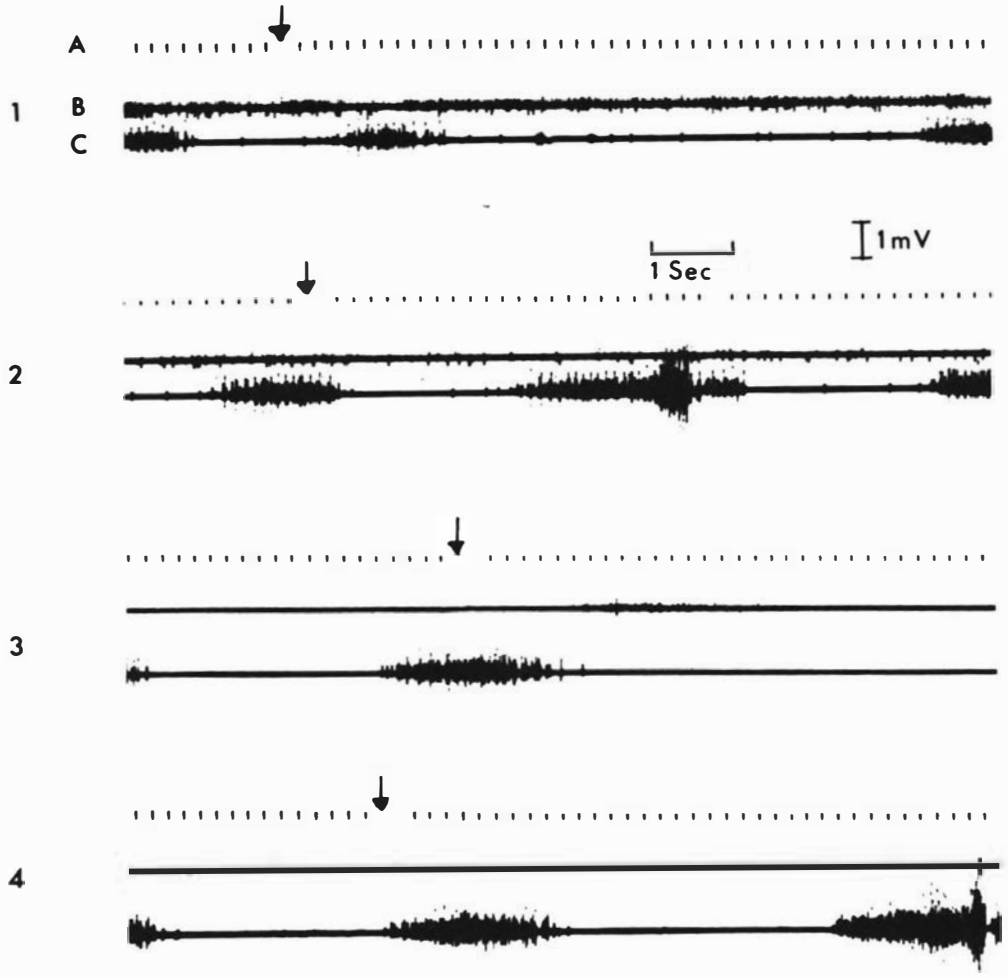
injection of 20 ml of 0.9 per cent saline stimulated no change in the cricothyroid muscle activity or in respiration (Trace 3). The latency between start of injection and effect was much longer in the case of halothane (9.0 sec), than when ether was injected (1.5 sec).

Having demonstrated that intravenous injections of solutions of volatile anaesthetics will stimulate laryngospasm and apnoea, the next step was to attempt to determine where the receptors were located. By cutting various afferent nerves and observing any changes in the effects of the injection of solutions, possible nerve pathways could be determined. In the early experiments in this section the results of cutting nerves were inconsistent. Paintal (1963) states that for a correlation of circulation time with injections of chemicals the important times to record are start of injection and start of discharge. It was decided to compare the effects of injecting 5 per cent ether with those stimulated by injection of hydrogen cyanide solution.

(b) A comparison of the effects of the intravenous injection of solutions of ether and hydrogen cyanide

In a cat under chloralose anaesthesia (65 mg per kg) 5 ml of 5 per cent ether administered intravenously stimulated a burst of cricothyroid muscle action potentials and a short period of apnoea (7.5 sec) which extended beyond that shown on the trace (Fig. 44, Trace 1, facing p.96). In the same cat, after cutting the internal branches of both superior laryngeal nerves, 5 ml of 5 per cent ether given intravenously stimulated some increase in cricothyroid activity and a change in duration of diaphragmatic activity (Trace 2). There was also stimulation of activity of some units in the diaphragm during expiration, which continued for

Fig. 45 The Effects of Intravenous Injection of Ether and HCN Solutions, 2.



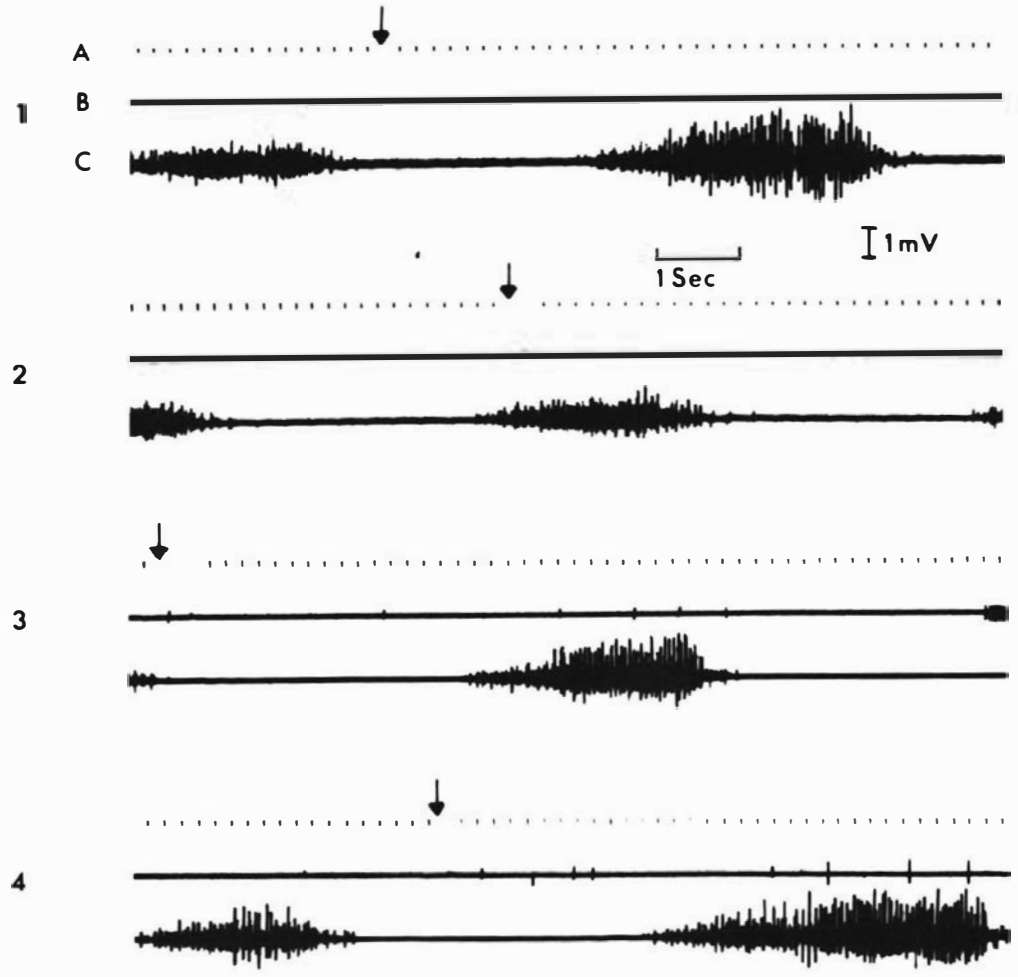
Anaesthetized cat 3.4 kg. Chloralose (65 mg per kg) administered after halothane induction.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate start of injection).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 5 ml 5 per cent ether solution.
Trace 2: Effects of intravenous injection of 1 ml 4 per cent HCN solution.
Trace 3: Effects of intravenous injection of 5 ml 5 per cent ether solution after section of the internal branches of both superior laryngeal nerves.
Trace 4: Effects of intravenous injection of 1 ml 4 per cent HCN solution after section of the internal branches of both superior laryngeal nerves.

8 sec. The start of activity of these units can be seen in Trace 2. 1 ml (40 mg) of HCN solution, administered intravenously and washed in with 1 ml of saline caused diaphragmatic stimulation 6 sec after the end of injection, but no cricothyroid activity was stimulated (Trace 3). The latency for diaphragmatic stimulation by HCN was 6 sec compared with stimulation of the cricothyroid by ether within 0.6 sec of the end of injection. However, the shortening of duration of activity of the diaphragm after ether did not occur until 6 sec after injection. All 20 cats used in this series of injection experiments exhibited increased cricothyroid activity and apnoea or changes in respiratory rhythm when they inhaled ether by mask or tracheal cannula.

Three experiments contributed more information than any of the others towards the location of sites of stimulation outside the respiratory tract itself. It is proposed to describe these in detail:

(1) The cat was anaesthetised with intravenous chloralose (65 mg per kg) after induction with halothane. Ether vapour administered into a tracheal cannula stimulated continuous cricothyroid activity and a break in the rhythm of the diaphragm. 5 ml of a 5 per cent ether solution failed to stimulate increased cricothyroid activity but caused breath-holding for one inspiratory cycle (Fig. 45, Trace 1, facing p.97). 1 ml (40 mg) HCN administered intravenously stimulated an increase in frequency of diaphragm activity and in the number of units involved. The latency was 4.4 sec after completion of the injection and the increase in activity was of the type associated with carotid body stimulation (Trace 2). The internal branches of the superior laryngeal nerves were then cut on both sides. Ether vapour administered to trachea and lungs stimulated a

Fig. 46 The Effects of Intravenous Injection of Ether and HCN Solutions, 3.



Anaesthetized cat 3.4 kg. Chloralose (65 mg per kg) administered after halothane induction (Same animal as in Fig. 45).

A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate start of injection).

B: Electromyogram from cricothyroid muscle.

C: Electromyogram from diaphragm.

Trace 1: Effects of intravenous injection of 5 ml 5 per cent ether solution after section of the internal branches of both superior laryngeal nerves and both vagus nerves.

Trace 2: Effects of intravenous injection of 5 ml 0.9 per cent saline. Nerves cut as in Trace 1.

Trace 3: Effects of intravenous injection of 5 ml 5 per cent ether solution after an attempt to cut both sinus nerves.

Trace 4: Effects of intravenous injection of 1 ml 4 per cent HCN solution after an attempt to cut both sinus nerves.

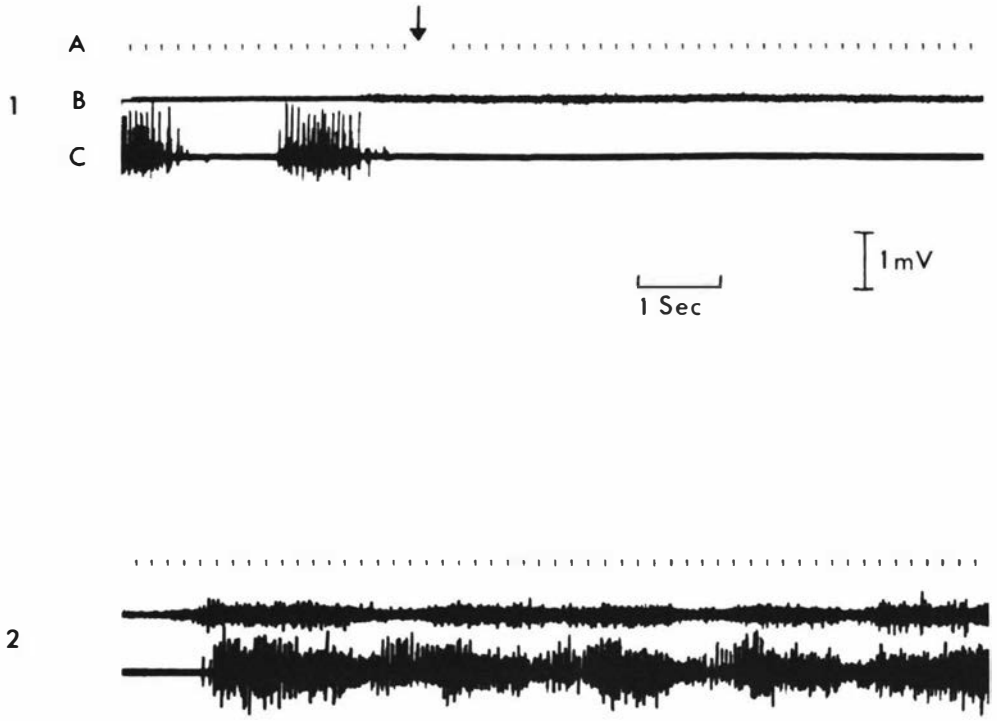
(Spikes retouched)

cricothyroid discharge after a latency of 1 sec. 5 ml 5 per cent ether given intravenously stimulated a burst of activity from the cricothyroid and a short break in the respiratory rhythm 1.5 sec after completion of the injection. Two further administrations of 5 ml 5 per cent ether intravenously at 15 min intervals stimulated a cricothyroid discharge and short apnoea in each case (Trace 3). 5 ml of saline intravenously had no effect on diaphragm or cricothyroid, but 1 ml (40 mg) HCN followed by a 1 ml saline wash-in stimulated an increase in diaphragm activity 6.0 sec after the HCN had been injected, and some action potential spikes from the cricothyroid (Trace 4). Two minutes later there was a considerable increase in cricothyroid activity, lasting 3 min, which was not recorded.

The vagus nerves were then cut at the level of entry of the tracheal cannula. Ether vapour administered into the tracheal cannula now stimulated neither apnoea nor cricothyroid activity. 5 ml of a 5 per cent ether solution given intravenously stimulated no cricothyroid activity, no apnoea, but did stimulate an increase in frequency and number of diaphragmatic motor units 3.0 sec after the start of the injection (Fig. 46, Trace 1, facing p.98) (the same time interval which had occurred between inspirations before the injection). 5 ml of saline intravenously 5 min later stimulated no changes in respiration or cricothyroid activity (Trace 2). Ten minutes later 1 ml (40 mg) HCN given intravenously and washed in with 1 ml saline, stimulated an increase in activity of the diaphragm 2 to 3 sec after the saline wash-in.

An attempt was made to cut the sinus nerves (afferents from the carotid bodies to join the glossopharyngeal nerves) on both sides. 5 ml of 5 per cent ether administered intravenously still stimulated diaphragmatic

Fig. 47 The Effects of Intravenous Injection of Ether and HCN Solutions, 4.

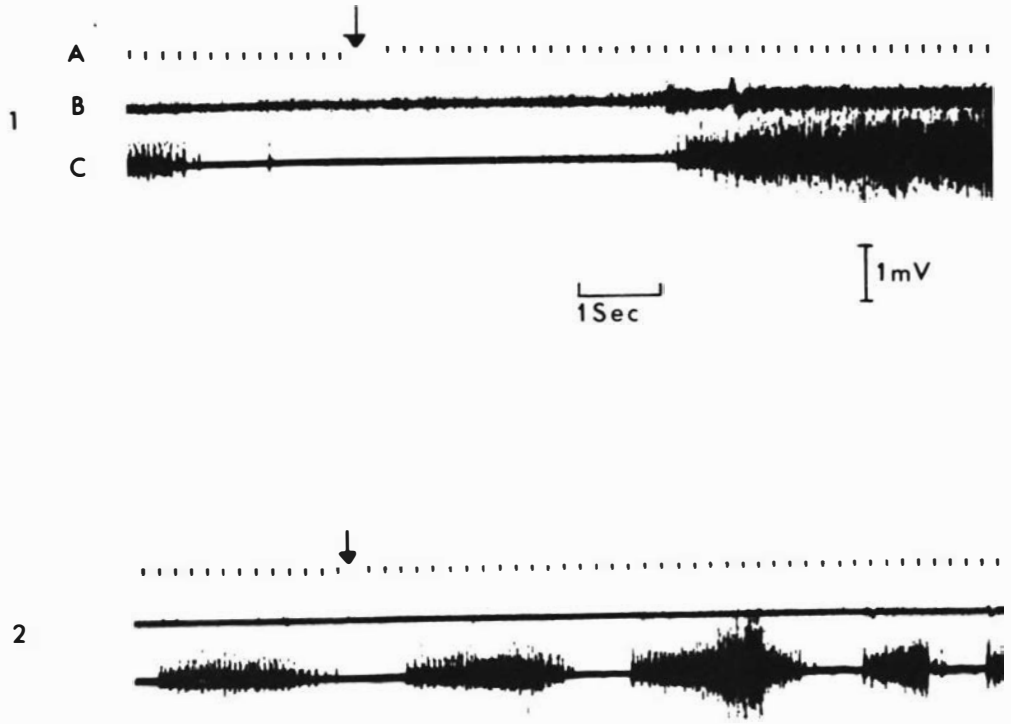


Decerebrate cat 2.5 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruption of the time trace and arrow in Trace 1 indicates end of injection).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 20 ml 5 per cent ether solution.
Trace 2: The same as Trace 1, 8.5 sec after the end of injection.
(Spikes retouched)

activity 4.5 sec after the start of injection (Trace 3). No apnoea was stimulated but there was a slight increase in cricothyroid activity at the same time as the diaphragm was stimulated. Ten seconds after the injection there was a sudden increase in frequency and number of active units in the cricothyroid muscle, the start of which can be seen at the end of Trace 3. This indicates that all the afferent nerves from the carotid bodies had not been cut. Traces 3 and 4 in Fig. 46 suggest the possibility that, after cutting the vagus nerves, both ether and HCN cause stimulation of carotid body chemoreceptors.

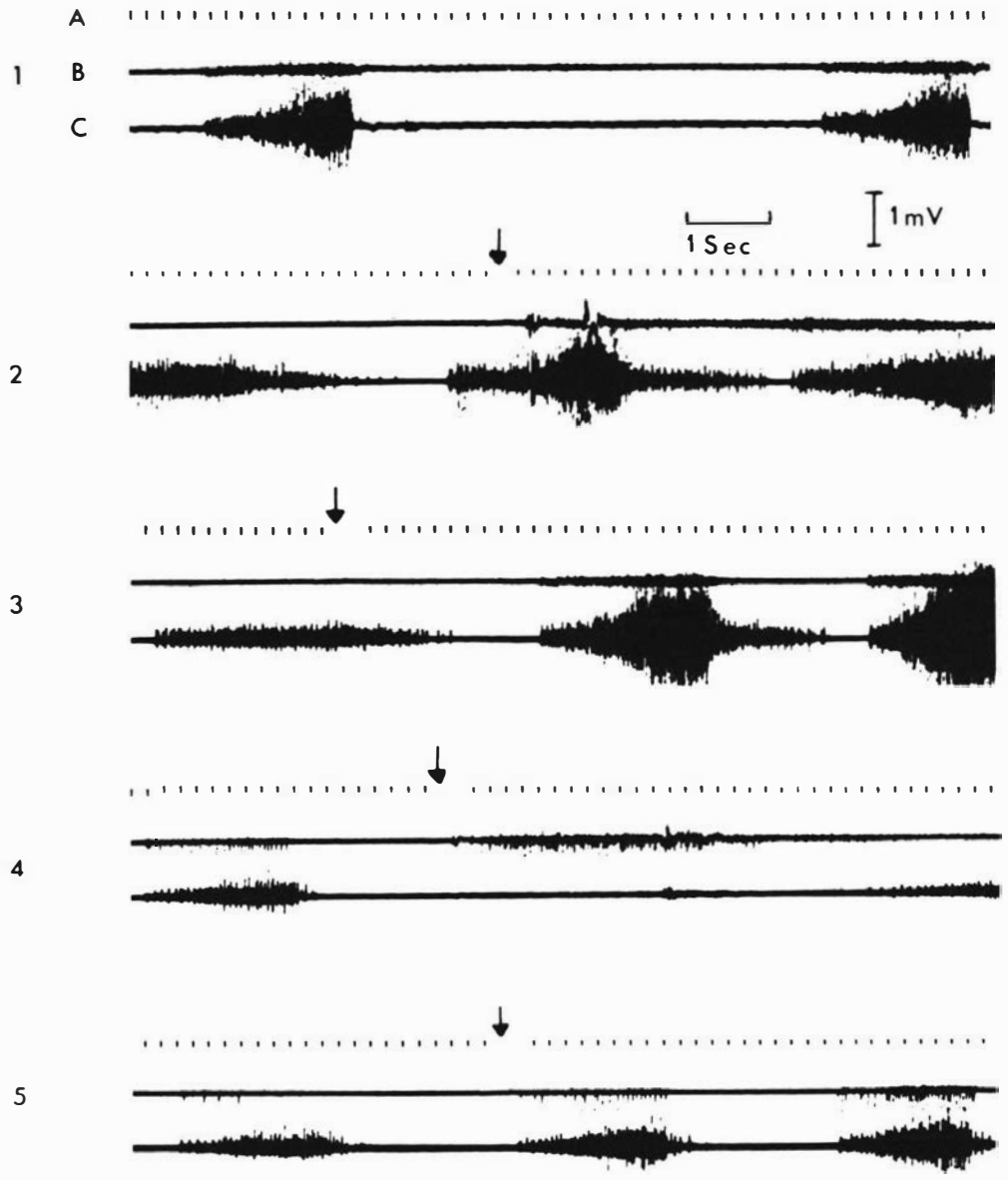
(ii) The cat was decerebrated by intercollicular section under halothane anaesthesia. Ether vapour administered through a tracheal cannula stimulated continuous cricothyroid activity and apnoea. In this experiment all injections were of 20 ml of solution, whereas in some experiments ether and HCN were given in different volumes of solution. 20 ml of a 5 per cent ether solution given intravenously stimulated apnoea and an increase in cricothyroid activity before the end of the injection (Fig. 47, Trace 1, facing p.99). This was followed 9 sec later by a more violent cricothyroid response (Trace 2) as the diaphragm activity started again with a period of apneusis (continuous diaphragmatic activity). 20 ml 0.9 per cent saline given intravenously stimulated no response. 20 ml (40 mg) HCN given intravenously stimulated an increase in frequency and number of units active in the diaphragm which was synchronous with stimulation of a discharge from the cricothyroid. Both these effects were recorded 3 sec after the end of injection. Rhythmic cricothyroid activity persisted in phase with inspiration, gradually diminishing over a period of 18 sec.

Fig. 48 **The Effects of Intravenous Injection of Ether and HCN Solutions, 5.**



Decerebrate cat 2.5 kg. Decerebration under halothane anaesthesia (Same animal as in Fig. 47).
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate end of injections).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 20 ml 5 per cent ether solution after section of the internal branches of both superior laryngeal nerves.
Trace 2: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution. Nerves cut as in Trace 1.

Fig. 49 **The Effects of Intravenous Injection of Ether and HCN Solutions, 6.**



Decerebrate cat 2.5 kg. Decerebration under halothane anaesthesia (Same animal as in Figs. 47 and 48).

A: Time marker 0.2 sec (interruptions of the time trace and arrows in Traces 2, 3, 4, and 5 indicate end of injection).

B: Electromyogram from cricothyroid muscle.

C: Electromyogram from diaphragm.

Trace 1: Quiet respiration after section of both vagus nerves.

Trace 2: Effects of intravenous injection of 20 ml 5 per cent ether solution after section of both vagus nerves.

Trace 3: Effects of intravenous injection of 20 ml 0.2 per cent HCN after section of both vagus nerves.

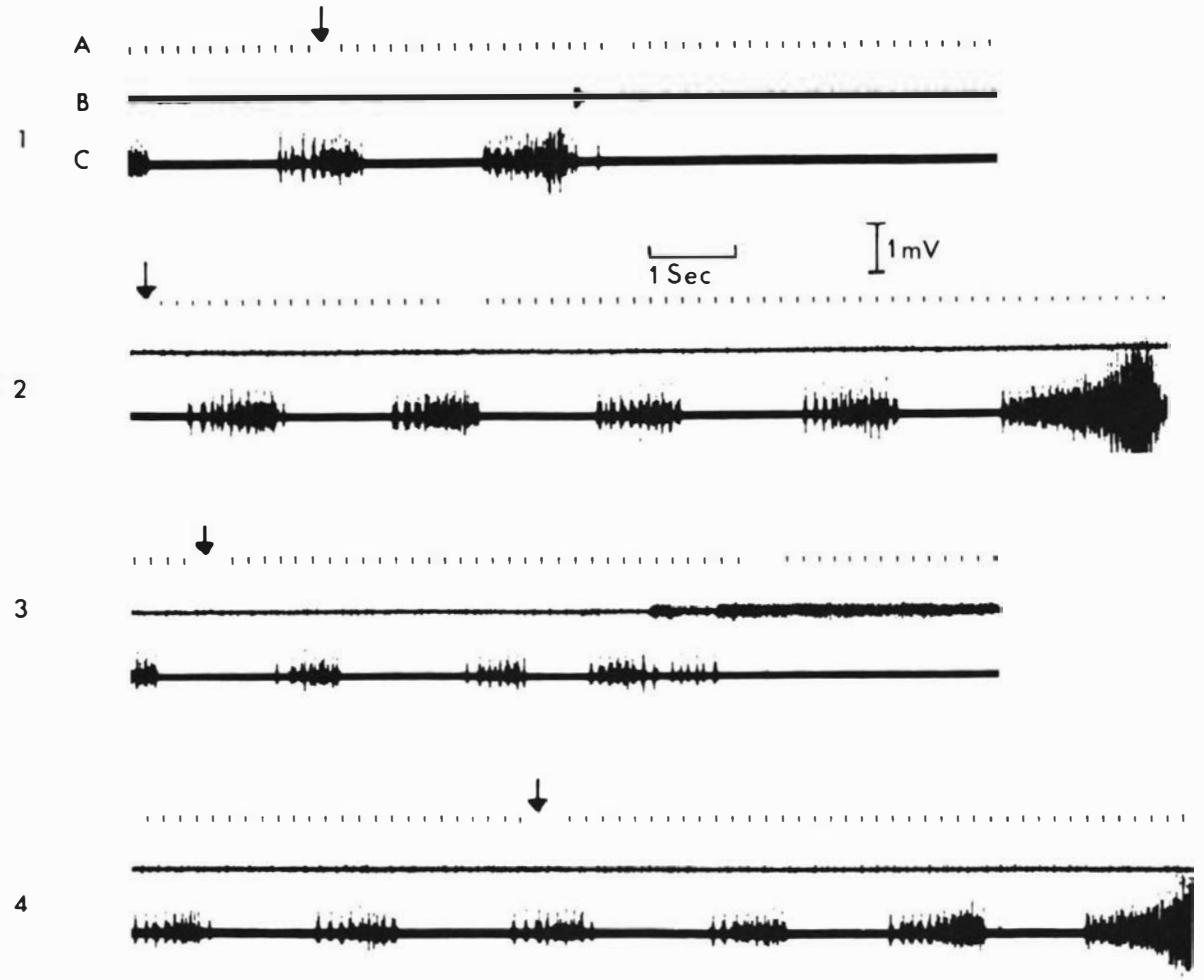
Trace 4: Effects of intravenous injection of 20 ml 5 per cent ether solution after section of both sinus nerves.

Trace 5: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution after section of both sinus nerves.

The internal branches of the superior laryngeal nerves were then cut on both sides. Ether vapour, administered to the trachea and lungs still stimulated apnoea and a cricothyroid discharge. The pattern of response to injection of 20 ml of a 5 per cent solution of ether changed. There was a pause in respiration of 4 sec at the end of injection. After this there was a simultaneous increase in cricothyroid frequency and units and in diaphragmatic activity (Fig. 48, Trace 1, facing p.100). 20 ml (40 mg) HCN given intravenously stimulated an increase in frequency of diaphragm discharge, an increase in respiratory rate and a small cricothyroid discharge 4 sec after the end of the injection (Fig. 48, Trace 2).

Both vagus nerves were then cut. Trace 1, Fig. 49 (facing p.100) shows the pattern of activity of the cricothyroid muscle and diaphragm after the vagus nerves were cut. Note that cricothyroid activity is synchronous with inspiratory activity of the diaphragm. Ether administered by tracheal cannula did not stimulate apnoea. Five seconds after the start of ether administration there was a small response from the cricothyroid. Twenty one seconds after ether administration started, continuous diaphragmatic activity was stimulated for 11 sec and no activity was recorded from the cricothyroid. 20 ml 5 per cent ether given intravenously stimulated no apnoea. A cough and increased cricothyroid activity were stimulated 0.2 sec after the end of the injection and the cricothyroid activity continued for 6 sec (Trace 2), then for a further 3 sec after a 1 sec break in activity. Continuous diaphragmatic activity started 7 sec after the end of the injection and lasted 11 sec, being followed by a period in which there were 1 sec gaps of lessened activity.

Fig. 50 The Effects of Intravenous Injection of Ether and HCN Solutions, 7.



Decerebrate cat 2.1 kg. Decerebration under halothane anaesthesia.
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate start of injection).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 20 ml 5 per cent ether solution.
Trace 2: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution.
Trace 3: Effects of intravenous injection of 20 ml 5 per cent ether solution after section of the internal branches of both superior laryngeal nerves.
Trace 4: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution after section of the internal branches of both superior laryngeal nerves.

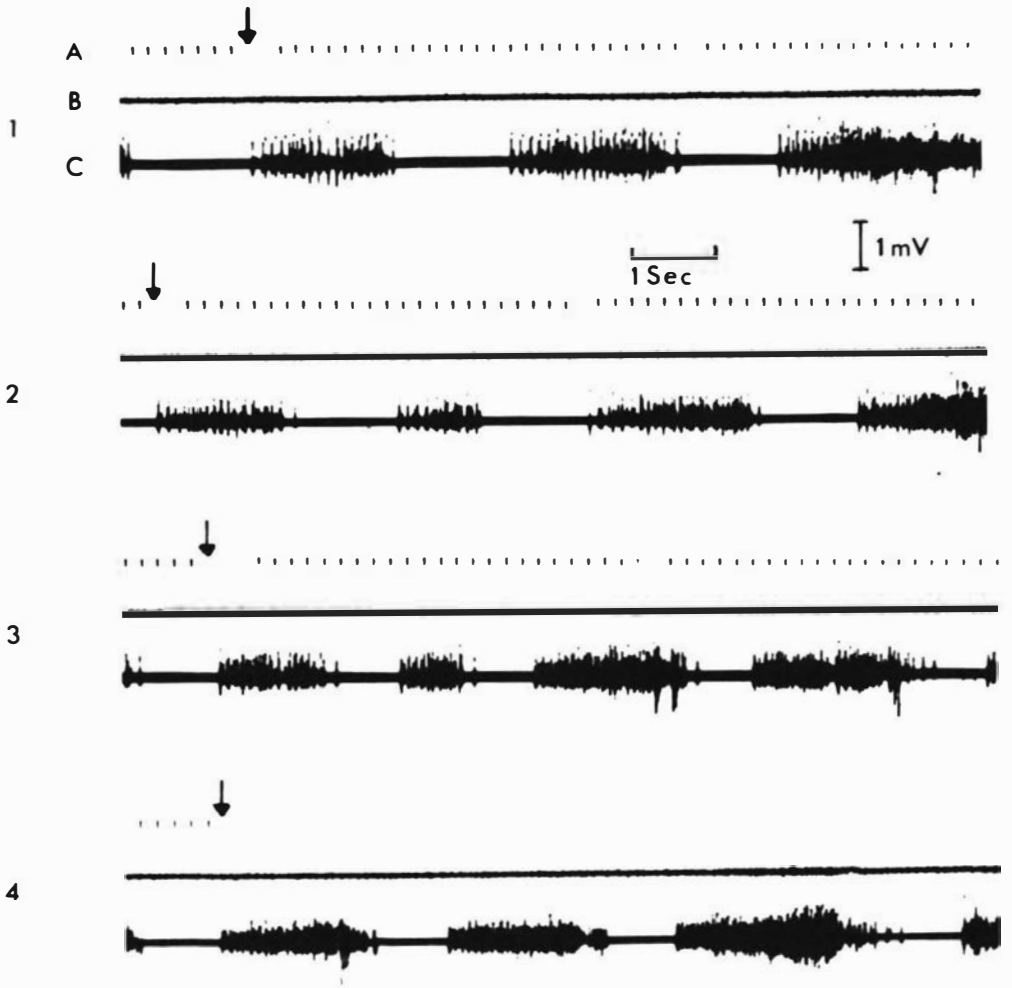
20 ml (40 mg) HCN given intravenously stimulated an increase in frequency and in the number of active diaphragm units 2.5 sec after the end of the injection, which was accompanied by an increase in cricothyroid activity (Trace 3).

The sinus nerves were then cut on both sides. 20 ml of 5 per cent ether intravenously stimulated an increase in frequency of the cricothyroid muscle 0.2 sec after the end of the injection. This increase in frequency was maintained for 7 sec. One period of diaphragmatic inspiratory activity was missed and then activity was resumed with extended duration and a very short pause between bursts of activity (Trace 4). 20 ml saline, given intravenously, stimulated no changes in diaphragm or cricothyroid activity. 20 ml (40 mg) HCN intravenously stimulated an increase in diaphragmatic and cricothyroid activity simultaneously 0.4 sec after the end of the injection (Trace 5). These two injections were completed in approximately the same time, and therefore the latent periods between start of injection and effect may be regarded as virtually equal for ether and HCN solutions.

(iii) The cat was decerebrated by intercollicular section under halothane anaesthesia. Ether vapour administered by a tracheal cannula stimulated cricothyroid spasm and an interruption in the rhythm of the diaphragm. 20 ml of 5 per cent ether given intravenously stimulated apnoea for 10 sec and an increase in cricothyroid activity 3 sec after the start of the injection (Fig. 50, Trace 1, facing p.101). 20 ml (40 mg) HCN given intravenously stimulated increased diaphragmatic activity 11 sec after the start of the injection (Fig. 50, Trace 2).

The internal branches of the superior laryngeal nerves were then cut on both sides. 20 ml of 5 per cent ether given intravenously stimulated

Fig. 51 **The Effects of Intravenous Injection of Ether and HCN Solutions, 8.**



Decerebrate cat 2.1 kg. Decerebration under halothane anaesthesia (Same animal as in Fig. 50).
A: Time marker 0.2 sec (interruptions of the time trace and arrows indicate start of injection in Traces 1, 2, and 3, and the end in Trace 4).
B: Electromyogram from cricothyroid muscle.
C: Electromyogram from diaphragm.
Trace 1: Effects of intravenous injection of 20 ml 5 per cent ether solution after section of both vagus nerves.
Trace 2: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution after section of both vagus nerves.
Trace 3: Effects of intravenous injection of 20 ml 5 per cent ether solution after an attempt to cut both sinus nerves.
Trace 4: Effects of intravenous injection of 20 ml 0.2 per cent HCN solution after an attempt to cut both sinus nerves.

apnoea and an increase in cricothyroid activity 5 sec after the start of the injection (Fig. 50, Trace 3). 20 ml (40 mg) HCN given intravenously stimulated increased activity of the diaphragm 10 sec after the start of the injection (Fig. 50, Trace 4).

Both vagus nerves were then cut. 20 ml of 5 per cent ether solution given intravenously stimulated a burst of diaphragmatic activity 7 sec after the start of the injection (Fig. 51, Trace 1, facing p.102). 20 ml (40 mg) HCN, given intravenously stimulated an increase in the activity of the diaphragm 9 sec after the start of the injection (Fig. 51, Trace 2).

An attempt was made to cut the sinus nerves on both sides. 20 ml of 5 per cent ether intravenously stimulated an increase in the activity of the diaphragm 4 sec after the start of the injection (Fig. 51, Trace 3). 20 ml (40 mg) HCN intravenously stimulated a much smaller increase in diaphragm activity than previously, 11 sec after the start of the injection (Fig. 51, Trace 4).

2. Discussion of the Results of Experiments on the Intravenous Injection of Solutions of Ether and Hydrogen Cyanide

Comroe (1965a) had described chemoreceptors in the lung bed; Widdicombe (1954b) described them in the trachea. In some experiments, ether vapour administered to the trachea and lungs had stimulated effects with latencies longer than those which would be expected if the receptors were in the lungs. Also, in some experiments, cutting the vagus nerves had not inhibited the effects of ether inhalation. In some experiments ether was shown to stimulate diaphragmatic activity. The receptors outside the pulmonary bed may be in the aortic bodies, carotid bodies, or they may be central receptors. Gabel (1961) described the occurrence of

laryngospasm in a horse receiving an ether solution intravenously. Laryngospasm is rarely encountered in the horse, therefore, it was decided to see if the effect could be produced in this way in the cat in which laryngospasm is a common hazard. Then latencies for effects were compared with those after similar injections of HCN with the vagus nerves intact and cut. This will differentiate an effect at the lungs from an effect at the carotid body, and will demonstrate whether ether has an effect at the carotid body after vagotomy.

It was found that although small volumes of 5 per cent ether solution injected intravenously sometimes stimulated cricothyroid spasm and changes in respiratory rhythm, up to 20 ml were required to stimulate this type of activity consistently. Twenty experiments were carried out in which the effects of solutions injected intravenously were studied. In all 20, a 5 per cent ether solution was injected, in 10 cats this was compared with the effects of intravenous HCN, and in 1 preparation the effects of intravenous halothane were recorded.

Cricothyroid spasm and apnoea can be stimulated by the injection of a 5 per cent ether solution intravenously and by a similar injection of 5 per cent halothane. The latency after halothane injection was considerably longer than that following ether, and this may be related to their relative solubility in blood. To discount the possibility that the activity stimulated was merely caused by the introduction of 20 ml of fluid into the circulation, injections of 0.9 per cent saline were given intravenously. They stimulated neither cricothyroid activity nor apnoea.

Paintal's statement (1963), that if a correlation of circulation time with injection of chemicals is sought the important times to record are the

start of the injection and the start of the reaction, was found to be true in the experiments in this section. Results were less consistent when this technique of marking was not followed. In the early experiments, with the vagus nerves intact, however, it was immediately apparent that there was a difference in the effect of intravenous ether compared with that obtained when HCN was injected intravenously. Ether stimulated an increase in cricothyroid activity and apnoea or respiratory rhythm changes, possibly with some other delayed effects; HCN stimulated an increase in diaphragmatic activity identical with that described by Lovatt Evans (1949b) but no cricothyroid activity. In later experiments slight cricothyroid activity was stimulated as well as increased diaphragmatic activity (see Fig. 49, facing p.100). Latency was 0.6 sec for ether compared with 6 sec for HCN, but 5 ml of ether was used compared with 1 ml (40 mg) HCN.

Three experiments in the intravenous series contributed more information than any others. In the first of these ((i) p.97), the results followed the same pattern of activity seen in the earlier experiments, in that in every instance except at the first injection, the results of HCN injection were observed after a significantly longer latent period than the results of the injection of ether. Either the same receptors were stimulated more quickly by ether, or circulation time to the receptors responding to ether was shorter than that to those responding to HCN. This suggested that ether was acting at Comroe's (1965a) "lung-bed receptors" and HCN at the carotid bodies. It is interesting to note that HCN did stimulate some increase in cricothyroid activity after 6 sec in this cat and that there was a considerable increase in cricothyroid activity after 2 min. This may possibly have been an anoxic effect. After cutting

the vagus nerves, intravenous injection of ether produced a similar effect on the diaphragm to that stimulated by an injection of HCN, with a similar latent period. This suggested that ether and HCN were now both stimulating receptors in the carotid bodies. The sinus nerves from the carotid bodies to the glossopharyngeal nerves carry afferent impulses from receptors in the carotid bodies. An attempt to cut the sinus nerves in this experiment failed.

Experiment (ii) (p.99) confirmed that, in the cat with vagus nerves intact, the latent period for stimulation of diaphragm activity by HCN given intravenously was longer than that for stimulation of apnoea and cricothyroid activity by intravenous ether. In this cat (a decerebrate one compared with one under chloralose anaesthesia in experiment (i)) the pattern of response to injection of an ether solution changed after cutting the internal branch of the superior laryngeal nerves on both sides. The latent period for the effects of ether was now the same as for those of HCN. The lung chemoreceptors may have been desensitized by previous exposure to ether vapour, or ether in the blood reaching the larynx was unable to provoke the reflex because the receptors had been denervated by cutting the internal branch of the superior laryngeal nerves. The effects may now have been the result of carotid body or central nervous system stimulation. In this cat, after cutting the vagus nerves, continuous diaphragmatic activity was stimulated by ether vapour after 21 sec and lasted for 11 sec. This was probably a central effect. Intravenous ether solution also stimulated continuous diaphragmatic activity and some cricothyroid activity after cutting the vagus nerves. This contrasted with the results of experiment (i). The effects of an intravenous injection of HCN were unchanged after cutting the vagus nerves.

In this experiment, it appears from the results that all fibres in the sinus nerves were not cut, as stimulation of the diaphragm by intravenous HCN persisted.

In experiment (iii) (a decerebrate cat) the latent periods for an effect after intravenous administration of HCN were again significantly longer than those for a 5 per cent ether solution before the vagus nerves were cut, but very similar (9 sec for HCN, 7 sec for ether) after the vagus nerves had been cut. After an attempt to cut the sinus nerve fibres a 5 per cent ether solution stimulated an increase in diaphragm activity 4 sec after the start of injection, whereas HCN stimulated only a very slight increase in diaphragm activity 11 sec after the start of injection. These may both have been central effects, but the difference in latencies is difficult to explain.

It may be concluded from the experiments in this chapter that ether probably stimulates effects at the carotid bodies and possibly centrally also. These effects are normally obscured by the reaction to stimulation of receptors at other sites, but they have been observed in some experiments as biphasic or "abnormal" reactions.

VII GENERAL SUMMARY AND CONCLUSIONS

The work reported in this thesis has been concerned with the mechanism of laryngospasm during anaesthesia in the cat, with some of the ways in which it may be stimulated, and, most important for the clinician, with methods of preventing it.

One of the problems was to find a way in which a permanent record of the occurrence of laryngospasm could be obtained. Electromyography was used to obtain records of the action potentials from the intrinsic laryngeal muscles. In this way, the sustained activity of the intrinsic laryngeal muscles occurring during laryngospasm could be recorded. This sustained activity, causing closure of the aditus laryngis, is laryngospasm. Most of the recording was done from a needle electrode in the cricothyroid muscle because it was easily accessible, and had been found to be representative of the adductor group of laryngeal muscles in the cat. An electromyogram recorded from a second needle electrode in the diaphragm in most experiments made it possible to determine if any changes in the respiratory cycle were associated with laryngospasm. The technique of electromyography has great potential as a tool in the investigation of anaesthetic problems. Its value for investigation of laryngeal reflexes has been shown in this thesis, as well as in the work of other authors (see p.32, chapter III of this thesis). It is possible that the technique may prove useful in the investigation of "bronchospasm" during anaesthesia, and it has already been used as a technique for assessing the depth of anaesthesia and the degree of muscular relaxation (Nanjo, 1955).

The preparations used in this work were cats, either anaesthetized with chloralose or decerebrated by intercollicular section during halothane

or halothane/ether anaesthesia. Decerebrate preparations were used in 128 experiments, as compared with 24 in which anaesthesia was maintained with chloralose. In neither case was the addition of any anaesthetic drug required to maintain anaesthesia after the experiment had started. No recordings were taken until one hour after the administration of halothane or halothane and ether had stopped. The decerebrate preparations could thus be regarded as having no persisting drug acting during the experiment, whereas in the anaesthetized cats chloralose persisted in the preparation throughout the experiment. The decerebrate preparation has the advantage that there is no persisting pharmacological activity during an experiment, but the neuraxis is transected and reflexes in which that part of the brain anterior to the point of transection is involved may be missed. The forebrain may be involved directly, for example in stimulation of the olfactory receptors, or indirectly there may be modification of reflexes lower down the neuraxis. It is intended, in future work, to explore laryngeal reflex activity in cats with an intact brain without the influence of chloralose.

Laryngospasm and apnoea or changes in respiratory rhythm were induced in the course of these experiments by mechanical stimulation of the pharynx, larynx and trachea as well as by the sudden application of high concentrations of volatile anaesthetics in the form of a vapour or a spray. It was also possible to stimulate laryngospasm by the intravenous injection of solutions of ether or halothane. An endotracheal tube of the type commonly used in clinical anaesthesia was capable of providing sufficient mechanical stimulation when inserted into the unprepared pharynx, larynx or trachea. Mechanical stimulation of the nasopharynx was not attempted - this route is rarely used for endotracheal intubation in animal anaesthesia.

Volatile anaesthetics were applied as a spray to the pharynx and anterior larynx, and in vapour form to the nasopharynx, larynx, trachea and lungs. Laryngospasm was stimulated not only by exposure of the intact respiratory tract to these agents, but also when each part of the tract was exposed in isolation from the rest. Stimulation of receptors in systems other than the respiratory tract is capable of evoking laryngospasm (for example mechanical stimulation of the diaphragm and anterior abdomen, Brewer and Bryant, 1935). This investigation has been confined to direct effects on the respiratory system, or to the effects of drugs after they are absorbed from the respiratory system.

Ether was the anaesthetic agent whose action was studied in most of the experiments, but its effects were compared with those of halothane and methoxyflurane in a small number of cats. In the early experiments in the investigation, the effects of ethyl chloride were also observed. All these volatile anaesthetic agents, when administered in sudden high concentrations, were capable of stimulating laryngospasm and apnoea or changes in respiratory rhythm. The action of methoxyflurane vapour did not conform to the pattern established for ether and halothane. Whereas ether and halothane stimulated laryngospasm whether administered by mask or by tracheal cannula, methoxyflurane was only effective in stimulating the reflex when it was administered by mask. The reason for this difference was not established, although it is suggested that it may be due to the fact that methoxyflurane has a low vapour pressure and is also less soluble than halothane or ether. A series of experiments was carried out to determine whether there was a threshold concentration of ether vapour at which laryngospasm was stimulated. The results indicated that although it may be possible to determine a "concentration threshold"

for an individual animal, it was not possible to establish a threshold applicable to every cat. What was perhaps more important was the confirmation that long exposure to ether or halothane vapour decreased or abolished the ability of successive stimuli to evoke laryngospasm. This may be due to an effect at the receptors themselves, or to the effect of an increased depth of anaesthesia on the central pathways involved.

The influence of other drugs on the incidence of laryngospasm is of considerable importance in clinical anaesthesia. Atropine, particularly, has been recommended by some authors as a drug which will prevent laryngospasm or reduce its incidence during general anaesthesia (Burstein and Rovenstine, 1938; Lamb, 1963a). In this study, atropine was not found to have any "protective effect" against laryngospasm when administered to cats before they were exposed to ether vapour.

Thiopentone sodium solution, administered intravenously at a low dose rate, was not found to increase the sensitivity of the laryngeal reflex. On the contrary, laryngospasm stimulated by ether at this stage was less intense than it had been before the thiopentone was administered. This confirmed the experimental observations of Murtagh and Campbell (1954) in goats, but gave no support to Harrison's (1962) conclusion that reflex responses to respiratory irritation in man were more intense after thiopentone. This may merely be an indication of a species difference in the effect of thiopentone, but it seems more likely that the truth lies in Dundee's suggestion that the supposed sensitization by barbiturates in man is merely a failure to depress the reflex (Dundee, 1965).

Suxamethonium, by causing depolarization of the intrinsic laryngeal muscles, was effective in preventing the stimulation of laryngospasm. The order of muscle group paralysis in the cat followed that described by Hall

(1966c) as being common to all species, in that the diaphragm remained active after paralysis of the intrinsic laryngeal muscles. In the goat, however, Murtagh and Campbell (1954) reported that the cricothyroid muscle remained active after the diaphragm when suxamethonium had been administered. There is a conflict of opinion here which should be investigated in future work.

In clinical anaesthetic practice, laryngospasm, and other forms of obstruction of the airway are hazards which may cause hypoxia or anoxia. Techniques which will reduce or abolish the possibility that laryngospasm may be stimulated during general anaesthesia are worthy of consideration.

Spraying the pharynx and anterior larynx with a local analgesic solution reduced the response of the intrinsic laryngeal muscles to inhalation of ether and by abolishing the effect of mechanical stimulation of these areas facilitated the insertion of an endotrahceal tube. It was shown, however, that stimulation of laryngospasm could still occur after such a spray by stimulation of receptors in sites which the local analgesic had not reached. Lubrication of an endotracheal tube with a local analgesic cream such as amethocaine was capable of lessening or abolishing the reaction to mechanical stimulation of receptors in the tracheal wall.

The work reported in this thesis forms a sound experimental basis for a technique of endotracheal intubation in the cat which has proved consistently safe: anaesthesia is induced with an ultra-short-acting barbiturate intravenously, the pharynx and larynx are sprayed with 20-30 mg lignocaine, and a tube lubricated with an analgesic cream is inserted through the larynx into the trachea. Another method of depressing the laryngeal reflex so that intubation may be accomplished, is to induce a deep plane of anaesthesia before inserting the tube. This is effective,

but often the cat must be taken to a deeper plane of anaesthesia than is desired. A third technique of intubation in the cat is to use suxamethonium, a depolarizing muscle relaxant, to paralyse the intrinsic laryngeal muscles. This gives very good conditions for intubation, but the fact that the diaphragm is also paralysed, means that artificial respiration must be carried out for 10 to 15 min. When this technique is used, a local analgesic spray need not be used. This is of particular value if the protective laryngeal reflex is required to be active immediately after surgery, for instance when oro-nasal surgery has been undertaken.

Clinical anaesthesia in the cat is often maintained by inhalation agents administered by mask. In view of the high incidence of laryngospasm in the cat an argument may be presented for spraying the larynx with a local analgesic solution even when intubation is not contemplated. This appears to be a logical suggestion, except in cases where an active laryngeal reflex is needed as soon as surgery is completed.

In the present study, evidence has been presented for the existence of afferent pathways for the laryngeal reflex in the internal branch of the superior laryngeal nerves, the trigeminal nerves, and the vagus nerves. Although the recurrent laryngeal nerves appear to be relatively unimportant as afferent nerves in this reflex, the two experiments in which ether was passed through an isolated segment of trachea suggest that they may carry fibres from chemoreceptors in the tracheal mucosa. It is possible that afferent stimuli may pass from the recurrent laryngeal nerves through the ramus anastomoticus as suggested by Lemere (1932b) as well as up the vagus nerves (see discussion of the experiments in chapter V, p.91).

A number of unexpected results was recorded when the respiratory tract was exposed to volatile anaesthetic agents. The most important of these were: a biphasic response to stimulation; a delayed response to stimulation; and an increase in inspiratory activity of the diaphragm rather than interruption of rhythm or apnoea. These three results suggested that volatile agents may act not only on receptors within the respiratory tract, but also on receptors at other sites after absorption to the bloodstream. In chapter VI of this thesis, the results of injecting solutions of ether and halothane intravenously are reported. Laryngospasm could be stimulated in this way and it was accompanied by stimulation of diaphragmatic activity as well as apnoea and interruptions of the normal respiratory rhythm. The effects of intravenous ether were compared with those of a solution of HCN given intravenously. After cutting the vagus nerves, both solutions stimulated increased diaphragmatic activity and the latent periods from the time of injection to effect were similar, suggesting that both solutions were stimulating receptors in the carotid bodies in the classical manner described by Lovatt Evans (1949b). If this were the case, the effect should be abolished by cutting the sinus nerves on both sides. It proved technically difficult to cut all the fibres of the sinus nerves, but in one preparation the reaction to injection of HCN was dramatically reduced (see experiment (iii) p.101). There is considerable support, from this work, for the contention that "abnormal" and biphasic responses are due to stimulation of receptors in the carotid bodies.

Conclusions

1. Laryngospasm and changes in respiratory rhythm or apnoea are stimulated when the respiratory tract is exposed to sudden high concentrations of

volatile anaesthetic agents.

2. The sites of stimulation of laryngospasm are not only the nasopharynx and larynx, but also the trachea and lungs.

3. The most important afferent pathways in the reflex are the superior laryngeal nerves, the trigeminal nerves, and the vagus nerves.

4. A knowledge of the mechanisms involved in the stimulation of laryngospasm is of clinical importance and has led to improvements in technique or provided a logical basis for established techniques of controlling this hazard during anaesthesia.

5. The experimental methods developed in this work may prove of great value in the continued investigation of respiratory problems during anaesthesia.

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