

## **Chapter 120: Physiology**

### **Trachea**

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The trachea is one of the most ignored parts of the entire respiratory tract. Very little attention has been devoted to this organ in ordinary textbooks of anatomy and physiology. According to some authors, the trachea belongs to the upper part of the respiratory tract; according to others, it belongs to the lower part. From a physiologic point of view, it seems more adequate to define the space above the rima glottidis as the upper airway and nominate the lower part as the tracheobronchial airway. The trachea is not just a tube connecting the larynx and the lungs. Its shape and function are of great importance from a physiologic and clinical point of view. Its upper fixation to the laryngeal skeleton (at the level of the sixth cervical vertebra) and its attachment to the main bronchia at the bifurcation (at the lower border of the fourth thoracic vertebra) are of special interest. Flexibility is essential to allow adjustment to stresses such as varying depths of ventilation, coughing, and speech. Because both ends are flexible, the wall must be stable enough to maintain a sufficient square area at all levels during extreme ventilatory efforts.

#### **Structure**

The trachea consists of a fibromuscular tube covered by a respiratory epithelium and supported by about 20 hyaline cartilages that physicians often misname tracheal “rings”. It is, however, essential to remember that functionally these “rings” are open posteriorly and are therefore really and functionally tracheal “arches”.

In adults the trachea is about 10 to 12 cm in length. The width varies from 13 to 16 mm in women and from 16 to 20 mm in men. The sagittal diameter is approximately one fourth that of the transverse diameter. The width and especially the length vary greatly, depending on the movements of the head and neck, larynx, and diaphragm. More moderate changes in length and width depend on the phases of ventilation and coughing. During rapid deep inspiration or clinical “inspiratory stridor” (for example, during pathologic snoring), the thoracic part of the trachea widens and the cervical part narrows. Forced expiration results in the opposite pattern. This difference is mainly a result of the different pressure profiles outside the upper and lower parts of the trachea, respectively.

During respiratory distress - especially in young subjects, in whom the rigidity of the tracheal wall is less than that in adults and the ordinary caliber is smaller - a tendency toward tracheal collapse may result in dangerous clinical problems. The inner diameter may be reduced to one tenth of its original size because of lateral compression and invagination of the nonstabilized pars membranacea (Fig. 120-1). This fact is of clinical importance if a tracheotomy has to be done during inspiratory stridor, when a free airway must be maintained preoperatively by use of an intubation tube or a bronchoscope.

## **Fibromuscular tissues**

The ventrolateral part of the trachea is dominated by the cartilage arches, which are connected by fibrous tissues and a small amount of smooth muscle, often spoken of as the “tracheal muscle”. Actually, at least two muscle layers exist. An inner, circular muscle layer can be recognized, as well as an external, longitudinal layer (Fig. 120-2). This construction is similar to that of the esophagus because both organs originate from a common primary duct. However, the tracheal circular muscles do not have full capacity as constrictors. The reduction of the tracheal lumen seems to be a combination of muscular constriction and elongation of the trachea. During widening of the lumen, the elasticity of the compressed cartilages plays a passive, dilating role (Penn et al, 1989). The difference between the smooth muscles of the trachea and those of the esophagus is that the muscles of the trachea react according to an “all-or-none” law, unlike the slow peristaltic, propulsive contractions of the esophagus (Fig. 120-3; Hakansson and Toremalm, 1968). In the dorsal part (pars membranacea) the tracheal wall is exclusively fibromuscular, with the muscle bundles oriented more or less transversely. They insert into the inner perichondrium of the free ends of the cartilages and in doing so, they have the ability to partly act as constrictors (Hakansson et al, 1976).

## **Submucosal tissues**

The submucosa contains a separate small band of smooth muscles that does not seem to play any important mechanical role. Hypothetically, these mucosal muscles take part in emptying the tubuloacinar glands or squeezing the secretions from the goblet cells. This theory, however, has not been verified. The submucosa also consists of tubuloacinar glands, blood vessels, lymphatic spaces, and nerve endings. Because of the varying thickness over and between the cartilages and in the pars membranacea, these networks have different patterns. These differences have been shown for blood vessels by experimental investigations (Nordin and Lindholm, 1977). The results of these investigations are of great clinical importance with respect to the risk of mucosal injuries after excessive cuff pressure from tracheotomy or intubation tubes.

The submucosa of the pars membranacea is thicker and loosely organized. Contraction of the surrounding smooth muscles brings about longitudinal folds, which allow a faster transportation of secretions as compared with that of the anterior and lateral walls, which can be observed easily during tracheoscopy.

## **Neural Regulation**

Although the innervation of the trachea and bronchia has been the subject of several studies, our knowledge concerning the neural regulation of smooth muscle tone, seromucous secretion, and local blood flow in humans is scanty. This is partly because most experimental work is done on different laboratory animals and they are not quite valid for human conditions. Considerable variations exist among species with regard to the types of receptors present on the smooth muscle cells and the innervation of these cells.

The basic innervation of the trachea and the large bronchia consists of a parasympathetic supply from the vagus nerve and a sympathetic supply from the sympathetic trunk. The parasympathetic, preganglionic nerve fibers send their axons to local ganglia in the tracheal wall. The postganglionic sympathetic supply derives from the cervical ganglia and from the second to the fourth thoracic ganglia. Both the parasympathetic postganglionic fibers and the sympathetic fibers seem to innervate smooth muscles, seromucous glands, and blood vessels (Partanen et al, 1982). In addition, the epithelium contains a rich supply of sensory afferents.

The majority of the tracheobronchial afferent fibers are of vagal origin (Widdicombe, 1964). Classically, the sympathetic neurotransmitter is norepinephrine, whereas the cholinergic transmitter is acetylcholine.

The stimulation of cholinergic fibers causes contraction of tracheal smooth muscles and enhances secretion from the seromucous glands via muscarinic receptors (Rasmussen et al, 1990). In several mammals the adrenergic nervous system plays an important role as a dominating inhibitory system. Despite the presence of alpha- and beta-adrenoceptors on human tracheobronchial smooth muscle, the adrenergic fibers have little if any effect in humans. There is, however, evidence of a nonadrenergic nervous control system with an inhibitory effect in primates (Richardson and Beland, 1976). A number of investigations have indicated a possible role for neuropeptides in the control of tracheal smooth muscle tone and glandular secretion. Thus immunocytochemical studies have revealed the occurrence of nerve fibers containing vasoactive intestinal peptide (VIP), substance P, gastrin-releasing peptide (GRP), and neuropeptide Y (NPY) in the tracheal wall of several mammals, including humans (Nilsson et al, 1977; Uddman et al, 1978, 1984a, 1984b). It has been shown that a subpopulation of the tracheal efferents contains substance P and that antidromic stimulation of these fibers induces constriction of tracheal smooth muscle and increases vascular permeability (Lundberg et al, 1983). Substance P also seems to have a protective role in the regulation of the bronchial motoricity (Schreiber et al, 1988).

The tracheal smooth muscles, secretory glands, vessels, and ciliary activity can also be influenced directly by specific stretch receptors (Ogilvie et al, 1989) and by chemical and inflammatory mediators via different types of local receptors, which are mostly found in the posterior wall. Thus histamine, bradykinin, prostaglandin, and so on stimulate sensory nerve endings in the epithelium and also act via vagal reflexes, leading to tracheal constriction. Epinephrine, on the other hand, has a relaxing effect on the smooth muscles.

Inhalation of dust, smoke, and allergens also brings about tracheobronchial constriction. It is shown that leukotriene D<sub>4</sub> potentiates the electromechanical responsiveness of the airway muscles to muscarinic stimulation (Lee and Murlas, 1989).

Neural regulation as a pacemaker for the well-coordinated movements of cilia is complex and has not yet been convincingly demonstrated.

## **Tracheal Epithelium**

The trachea is lined by a pseudostratified columnar ciliated epithelium resting on an elastic lamina propria. The ciliated cells are dominant and are interfoliated by goblet cells. Normally, the epithelial layer also consists of two or three layers of undifferentiated basal cells that may become either goblet or ciliated cells. Brush cells have also been described. These cells may contain a carpet of microvilli with secretory or resorptive properties. In recent years much interest has also been devoted to the small intercellular bridges (tight junctions) between the ciliated cells. These junctions may explain the observation that cilia in the respiratory tract move in an organized and coordinated manner.

### **Ciliated cells**

The cilia of the human trachea are phylogenetically very ancient structures. They measure about 0.5 microm in length and 0.24 microm in diameter. Each cell is provided with about 200 cilia. The cilia have a specific cell-regulating mechanism and an adenosine triphosphate (ATP) reserve that makes it possible for them to work in vitro for more than 48 hours under optimal temperature and humidity conditions in an environment of not less than 5% O<sub>2</sub>. These characteristics make them valuable in different types of experiments for environmental, pharmacologic, and toxicologic studies. Details regarding the architectural, biochemical, and bioelectrical patterns of cilia can be studied elsewhere (Proctor and Andersen, 1982). Only some points of clinical interest regarding their function are reviewed in this chapter.

### **Tracheobronchial fluids**

The trachea secretions are derived from submucosal glands, goblet cells, and passive transudation. Our knowledge in this field is very much based on experimental research from various mammalian species. The secretion layer consists of the periciliary fluid, in which the cilia perform their mechanical activity, and the mucous layer, which more or less rests like a thin film on the top of the cilia during optimal conditions. The biochemistry of mucus has been the subject of extensive research. The chemical composition is rather complex and composed of water, electrolytes, glycoproteins, immunoglobulins, albumin, lipids, enzymes, antienzymes, antibacterials, cell products, and mediators (Widdicombe, 1989). The glycoproteins are of special importance because of their protective functions as well as their biochemical and bioelectrical properties (Knowles et al, 1982).

The two parts of the secretion layer exert a type of braking force against the propulsive force brought about by the whip-like movements of the cilia. It is therefore more correct to speak of the "mucociliary function" than of the "ciliary beat frequency". Further, most of the methods used for in vitro and in vivo studies of cilia are based on observations of light reflex changes or recognition of trapped particles on the wave ridges and troughs of the surface fluids. The frequency of these surface waves is thus an indirect measure of the two combined forces responsible for the transportation of secretions and inhaled foreign particles in the cranial direction. The frequency of these mucous waves is normally about 20 to 25/sec.

## Tracheobronchial clearance

It is well known that a discrepancy exists between the local mucociliary activity and the rate of transportation of mucus. Proctor and Andersen (1982) have found a normal rate variation in healthy individuals of 3 to 24 mm/min in the nose. Such differences have also been found in the trachea. This may be a result of nonlinear transportation, changing respiratory airflow directions, respiratory movements of the tracheal wall, and perhaps partly an effect of gravity. Particles lodged in the mucus can often be seen circulating or whirling around in varying and irregular patterns. It is therefore not easy to reproduce the speed of transportation for experimental purposes, even on the same individuals. Instrumental trauma and local anesthesia are also disturbing factors in human *in vivo* studies. However, total or partial clearance of the trachea from a known amount of inhaled particles may be useful for special purposes.

During normal conditions the total amount of bronchotracheal secretions that have to be expelled through the larynx seems to be very small, that is, approximately 10 mL over 24 hours, according to experiments by Toremalm (1960a). Mechanical irritation of the tracheobronchial wall, such as by instruments or suction tubes, may, however, increase this amount tenfold.

During pathologic conditions (inhaled particles, inflammatory stimuli, or general diseases) the amount and quality of the periciliary fluid and mucus may change and interfere with the drainage and protective purposes of the mucosa (Seybold et al, 1990). Two extreme conditions are illustrated in Fig. 120-4. The cilia work efficiently in an increased amount of periciliary fluid without any effective contact with the mucous layer (Fig. 120-4, A), whereas when the periciliary fluid is decreased and the mucous layer thick and viscous, the cilia are more or less immobilized (Fig. 120-4, B). In both cases the transportation capacity is reduced or momentarily stopped. A transtracheal or external supply of fluids is necessary to overcome these problems.

The composition of the tracheobronchial fluids is of great importance not only for the mucociliary clearance, but also for other defense mechanisms, such as immunologic, proteolytic, and phagocytic activities. In these respects the mucus from goblet cells is different from that produced by the submucosal glands (Sherman et al, 1981).

The two layers of secretions are of special interest from a biochemical point of view. The border between the two fluids can be viewed as a bioelectric membrane - an epithelial lining with changing electrical resistance (Yoneda, 1976). The influx and outflux of ions through the epithelial layer, especially of Cl<sup>-</sup> and Na<sup>+</sup> ions (the "chloride pump"), constitute a regulating mechanism that may also be influenced by cellular mediators such as histamine, as well as by inhaled gases and particles (Middleton, 1983). Further knowledge in this field will expand our understanding of diffusion, absorption, and transudation across the tracheobronchial wall. This in turn may facilitate the search for more effective mucolytic drugs than are now available.

## **Aerodynamic Patterns**

The rima glottidis constitutes the smallest and at the same time the most variable square area of the upper respiratory tract. Airflow patterns may therefore change, especially in the subglottic space, during inspiration and expiration according to the degree of the glottic opening (Fig. 120-5). The air currents in this region during inspiration are always eddying or turbulent in the upper part of the trachea with a transition to a more laminar flow in the distal trachea. Such variations also have an influence on the intratracheal pressure during forced inspiration and expiration. The most extreme positive pressure is built up just before a cough sequence. At the end of a forced expiration against a closed larynx, the pressure may be as high as 200 cm H<sub>2</sub>O. The speed of the airflow in the central beam during coughing has been estimated to be about 250 km/hr, which brings about a suction pump effect with a capacity to evacuate an excess of secretions adherent to the tracheal wall or deeper airways. A narrow laryngeal opening is often complicated by a simultaneous invagination of pars membranacea during forced inspiration, which in some cases may lead to more or less permanent inspiratory stridor.

The airflow patterns of the trachea are much more complicated in clinical cases with varying types of organic stenoses or tracheomalacia.

## **Air-Conditioning Capacity**

One of the most essential functions of the upper respiratory tract is its capacity to heat and moisten the inspired air. Most of this is accomplished in the nasal cavities, but the trachea also takes part in this process during normal mouth breathing, during exercise, and especially during pathologic mouth breathing resulting from nasal obstruction. The aerodynamic shape of the interior of the nose and the nasal mucosa is especially favorable for the nose's function as an active and passive biologic heat-and-moisture exchanger. Even if most of the moisture exchange takes place in the nose, however, this process is not finished until the air has passed the trachea (Ingelstedt, 1956). Here again, the aerodynamic shape of the rima glottidis and the subglottic space is of extraordinary importance because this region constitutes the smallest passage of the extrathoracic respiratory tract. During hyperventilation, especially in cold air, the temperature of the more distal airway progressively falls, and the point at which the inspired air reaches normal body conditions moves deeper into the periphery of the lungs. This in turn may lead to reflexive bronchial constriction, wheezing, and coughing (McFadden et al, 1982).

However, the mucosa of the subglottic space is always exposed to turbulent airflow and therefore is subject to local damage (drying, impingement of airborne particles, colonization and adhesion of bacteria). This may have relevance for the pathophysiology of pseudocroup and related local subglottic diseases. With a blocked nose, bacteria and other particles are prone to accumulate in the subglottic space because of turbulent air streams below the vocal cords during inspiration. Irritation of nerve endings starts the hollow cough, and the inflammatory edema causes the typical inspiratory stridor.

The air-conditioning capacity of the upper respiratory tract is rather flexible, so that individuals exposed to extremely cold, warm, dry, or humid environments are usually able to normalize the temperature and wetness of the inspired air before it enters the lungs.

## **Pathophysiology of Tracheotomy**

Inspiration through a tracheostoma instead of the nose has a negative influence on the mucosa of the lower respiratory tract. This disadvantage of the operation must be recognized so that prophylactic measures can be prepared for.

Tracheotomy reduces the anatomic dead space by about 50% or from 150 to 75 cc in adults. This reduction is in itself one of the indications for tracheotomy in patients with thoracic or pulmonary insufficiency, which often necessitates a permanent tracheostoma.

Tracheostomy also causes an instability of the anterior tracheal wall along three or four cartilage arches, resulting in either a postoperative organic stenosis or tracheomalacia (Fig. 120-6). However, the adult trachea has a diameter of more than 15 mm, which may be reduced to 8 to 10 mm in both directions without any ventilatory problems during normal exercise. Thus the square area at the level of the tracheostoma is always more or less reduced after tracheotomy.

The conditioning of inspired air through a tracheostoma is often insufficient, resulting in dryness of the mucosa and destruction of the ciliated epithelium just below the end of the cannula (Fig. 120-6). Thick secretions accumulate, and crusting appears frequently, together with a local infection. Many prophylactic maneuvers have been used to reduce these negative effects. The most effective one is to use a regenerative heat-and-moisture exchanger with a capacity to recapture at least 70% of the humidity from the expired air to moisten the next portion of inspired air (Toremalm, 1960b). Ordinary room air in hospital rooms very often has a relative humidity below 35%, but the cilia need a humidity of at least 60% for proper function.

These problems are also prevalent in laryngectomees during the initial postoperative period. Later, adaptation takes place. The columnar epithelium in the proximal part of the remaining trachea is changed to a stratified type with no cilia, and a decrease in secretion-producing cells occurs. This type of mucosal lining works partially as an air conditioner, which may be supplemented by a gauze pad worn over the stoma.

Tracheotomy also results in a poor cough capacity. The intrabronchial pressure cannot be built up for effective evacuation of secretions. Compensatory use of auxiliary neck and thoracic muscles is needed, as well as physical therapy exercises.

## **Esophagus**

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The esophagus constitutes a muscular tube designed for the transportation of food and liquids from the mouth to the stomach. It extends from the upper esophageal sphincter (UES) to the lower esophageal sphincter (LES). Physiologic studies on the esophagus have mainly focused on motor functions, although the production of mucus is essential for bolus transport, esophageal clearance, and mucosal protection. Clinically, it is interesting that several esophageal disorders are manifested by an abnormal motility.

## Stages of Swallowing

The process of swallowing can be divided into three stages: oral, pharyngeal, and esophageal. During the *oral stage* the food is tasted, chewed, and mixed with saliva. The oral stage ends with the formation of a food bolus and its transport into the pharynx. This is accomplished by a backward sweeping movement of the tongue pushing the bolus up against the palate and the pharyngopalatal plicae. To prevent misdirection of the bolus, the tongue is kept in its upward position and the back of the tongue is pressed against the pharyngeal wall. At the same time, the nasopharynx is closed off from the mesopharynx by an apposition of the soft palate to the posterior wall of the pharynx (Ekberg and Nylander, 1982). The pharyngeal wall sometimes displays a ridge in the midline caused by the constriction of a portion of the middle pharyngeal constrictor. This ridge, when prominent, is called *Passavant's ridge* and is often seen in patients with cleft palate or velopharyngeal incompetence. The mylohyoid muscles contract, raising the floor of the mouth, the hyoid bone, and the larynx. The epiglottis is tilted downward, and the rima glottidis is closed. Thus three different mechanisms prevent the entry of food into the trachea: the tilting of the epiglottis, the closure of the laryngeal vestibule, and the closure of the rima glottidis (Ekberg, 1982).

Passage of the bolus to the posterior part of the mouth initiates the *pharyngeal stage*. When the bolus is pressed against the pharyngeal wall, it is met by a peristaltic wave that is initiated by the contraction of the superior pharyngeal constrictor muscle. The bolus is then pressed down onto the uppermost side of the epiglottis and along its lateral folds. The cricopharyngeal muscle starts to relax, opening the UES.

The *esophageal stage* involves the transport of the bolus down to the stomach. This transport is made possible by a sequential activation of striated and smooth muscle in a craniocaudal direction, forming a peristaltic wave. During the esophageal stage the tongue returns to its initial resting position in the mouth. The levators and the constrictors of the pharynx relax, the larynx descends, the epiglottis rises, and the UES resumes its resting state of contraction. Remnants from the bolus may often initiate one or more after-swallows, which serve to transport the rest of the bolus down the esophagus.

## Nervous Control of Swallowing

Receptors in the mouth, pharynx, and esophagus convey information via afferent nerve fibers in the fifth, ninth, and tenth cranial nerves (cranial nerves V, IX, and X) to the nucleus tractus solitarius in the floor of the fourth ventricle (Fig. 120-7; Sinclair, 1970). Some neurons in this nucleus project to the dorsal motor nucleus of the vagus nerve, other neurons send their axons to an area in the reticular formation of the medulla. This area has actually been termed the *swallowing center* (Doty et al, 1967). The center serves as a coordinating and distributing center, relaying the afferent impulses in an orderly and timed sequence to the dorsal motor nucleus of the vagus nerve, the nucleus ambiguus, and the hypoglossal nuclei. These nuclei are the somatic motor nuclei of cranial nerves IX, X, and XII. They activate muscles involved in the reflex stages of swallowing. The cortical motor center of the larynx and the pharynx is situated in the lowest part of the precentral gyrus. The axons of some of the cortical cells in this area project to the nucleus ambiguus. Fibers of cranial nerves IX and X merge to form a pharyngeal plexus encircling the constrictor muscles of the pharynx.

The swallowing center can thus be activated by impulses from the cerebral cortex (voluntary swallowing) or from the nucleus solitarii via receptors in the mouth and pharynx (reflex swallowing). In the absence of stimuli from peripheral receptors (for instance, after anesthesia of the throat), swallowing becomes difficult and the coordination between the pharynx and the UES is impaired (Månsson and Sandberg, 1974).

## **Methods for Studying Esophageal Physiology**

### **Radiography**

Bariums swallow studied with conventional fluoroscopy allow a gross evaluation of esophageal morphologic characteristics and transport function. However, the method is inadequate for evaluating rapid events occurring in the pharynx and sphincter areas. The barium contrast generally used is a high-density viscous fluid with little resemblance to the liquids and food normally ingested. Low-density contrast media or semisolid boluses resembling everyday food may be superior for the elucidation of esophageal transport and gastroesophageal reflux (Lindell and Sandmark, 1979). Cineradiography is the method of choice for detailed studies of the mechanisms of pharyngoesophageal transport (Ekberg and Nylander, 1982).

### **Endoscopy**

Endoscopy is used for direct visualization of the interior of the esophagus, particularly the gross morphologic characteristics of the mucosa. The UES is best visualized with a rigid endoscope. This examination requires general anesthesia and will therefore not give information on the UES function. Flexible endoscopy, requiring only topical anesthesia, allows an excellent view of the esophagus and also reveals some information on the motor function of the esophageal body and LES.

### **Manometric studies of motility**

Manometric studies measure intraluminal esophageal pressure induced predominantly by esophageal muscle activity (Fig. 120-8). Generally, a polyethylene tube assembly is used, consisting of three to six thin tubes, each with its distal orifice placed at different levels. The assembly is swallowed until the orifices of the tubes reside in the stomach. Each of the tubes is connected to external pressure transducers. The tube assembly is then slowly withdrawn from the stomach, and the pressures are recorded at various levels of the esophagus. Manometric studies have become increasingly accurate with the access of low-compliance perfusion systems (Ask and Tibbling, 1979), long pressure sensors for measurement of sphincter pressure (Dent, 1976), and intraesophageal microtransducers (Humphries and Castell, 1977; Isberg et al, 1985). Esophageal manometry gives a quantitative record of esophageal motor function. It records events that take place in the resting state when the lumen is empty - a situation impossible to assess radiographically. It allows a quantitative measurement of the contractions, their temporal sequence, strength, and duration. The main drawback of manometry is difficulty in evaluating sphincter function. The esophagus moves with each swallow, and the sphincter consequently also moves relative to the recording device (Isberg et al, 1985).

## **pH determination**

pH determination is a method used for studying acid gastroesophageal reflux. It tests the LES barrier to reflux, as well as esophageal clearance of refluxed acid material. A pH electrode is swallowed and placed 5 cm above the LES. The electrode is connected to a pH meter. A continuous recording of the hydrogen ion concentration in the esophagus reveals when the pH is reduced from the normal level of about 7 to a level below 4, indicating acid gastroesophageal reflux. Short, transient reflux episodes occur normally. Ambulatory, continuous pH determinations for 24 hours may reveal the number of such episodes, their duration, and the total time of acid reflux (Evans, 1987; Johnson and De Meester, 1974). It should be stressed that a pH electrode records only hydrogen ion concentration (that is, acid reflux). The method does not measure the amount of refluxed material, nor does it detect neutral or alkaline reflux that may be potentially hazardous to the mucosa.

## **Acid clearance test**

The capacity of the esophagus to clear itself of potentially hazardous acid material is an important defense mechanism that might be studied with the acid clearance test (Booth et al, 1968). A pH electrode is placed 5 cm above the LES, and a catheter is then placed 10 cm above the electrode. Through the catheter 15 mL of 0.1 M sodium hydrochloride is injected. The number of swallows and the rapidity with which the esophagus raises the pH to 5 after the injection of sodium hydrochloride are documented. A subject with normal acid clearance can raise the pH to 5 in less than 13 swallows of 5 mL of water.

## **Esophageal scintigraphy**

Scintigraphy is an interesting method for studying esophageal transport function, motility, clearance, gastroesophageal reflux, and aspiration (Malmud and Fisher, 1982; van Heukelem, 1985). Boluses can be labeled with different radioisotopes, ingested, and observed during transport. The method allows a quantitative and qualitative study of transit time and of reflux of ingested material, with no time constraint as far as radiation is concerned.

## **Electromyographic studies**

Electromyographic recordings from the esophageal musculature have so far been performed solely for the purpose of research. The electrical activity of the muscles is recorded via electrodes inserted into the esophagus (Car and Roman, 1970; Hellemans et al, 1970). A close relationship exists between electrical activity in the muscle and intraluminal pressure (Monges et al, 1968). Consequently, electrophysiologic measurements may in the future be a precise means of studying motor activity.

## **Upper Esophageal Sphincter**

The function of the UES is to (1) control the passage of food and liquid down the esophagus, (2) prevent reflux of fluid from the esophagus into the hypopharynx and larynx, and (3) prevent passage of air into the esophagus. The UES consists of striated muscle that for all practical purposes may be considered identical with the cricopharyngeus muscle. Electromyographic studies have shown that the sphincter muscle at rest exhibits action

potentials whereby a continuous active resting tone is maintained (Car and Roman, 1970; Vantrappen, 1973). Thus the sphincter is closed at rest and remains closed even when subject to pressure from above or below (Lund, 1965). Manometric studies readily identify the pharyngoesophageal junction as a 2 to 4 cm-long high-pressure zone that is separated from the atmospheric pharyngeal and subatmospheric esophageal pressure. It is difficult to obtain a true value of the normal resting pressure.

The high-pressure zone displays both radial and axial asymmetry, and the highest pressures are recorded in an anteroposterior direction. In addition, the tone varies with respiration (Asoh and Goyal, 1978; Winans, 1972). The resting tone in healthy individuals, using state of the art manometry systems, is reported to range between 50 and 190 mm Hg (Duranceau et al, 1983; Isberg et al, 1985). Simultaneous manometry and cineradiography have shown that the relaxation starts before the bolus reaches the sphincter zone (Sokol et al, 1966). During swallowing the action potentials of the cricopharyngeus muscle cease and the UES relaxes. When the bolus has passed the sphincter, the resting tone is resumed (Car and Roman, 1970; Vantrappen, 1973).

### **Esophageal Body**

The esophageal body consists of an upper portion of striated muscle and a lower portion of smooth muscle. The upper 10% of the human esophagus is composed of striated muscle, the lower 55% to 60% contains primarily smooth muscle, and the middle part contains a mixture of striated and smooth muscle (Meyer and Castell, 1982). The resting pressure of the body of the esophagus varies from -15 mm Hg to +5 mm Hg, reflecting intrapleural pressure (Goyal and Cobb, 1981). The pressure varies inversely with respiration. In the resting state, when the esophagus has not been stimulated by swallowing or distension, the esophageal muscles are silent.

Swallowing initiates a burst of spikes (Vantrappen, 1973). The contractions of the esophageal body can be divided into primary peristaltic waves, secondary peristaltic waves, and tertiary nonperistaltic contractions. *Primary peristalsis*, induced by swallowing, arises in the hypopharynx and involves the opening of the UES. *Secondary peristalsis* arises in the esophagus in response to a localized distension. It promotes transportation of bolus remains after the passage of the initial primary peristaltic wave. Spontaneous secondary peristaltic waves may occur 7 to 10 times/hr and are important for the clearance of refluxed material from the esophagus. *Nonpropulsive tertiary contractions* in response to deglutition may occur in normal subjects (Duranceau et al, 1983).

Manometric studies have shown that the peristaltic force is higher in the distal portion than in more proximal parts (Duranceau et al, 1983; Humphries and Castell, 1977). Further, the force and velocity of the peristaltic waves vary with the character of the bolus. Large boluses give stronger contractions than do small ones (Dodds et al, 1973). Cold water swallows prolong the contraction wave in the distal esophagus, whereas hot water accelerates it (Winship et al, 1970). The esophageal segment, where the gradual transition from striated to smooth muscle occurs, has a lower speed of primary peristalsis than the rest of the esophageal body (Humphries and Castell, 1977). This segment corresponds to the area of the second anatomic narrowing of the esophagus caused by the aortic arch and the left main bronchus. The reduced rate of peristalsis may well be a contributing factor to the frequent

lodging of foreign bodies in this area (Carlborg et al, 1983).

### **Lower Esophageal Sphincter**

The LES is closed at rest and opens in response to swallowing. The function of the LES is to (1) prevent gastric contents from freely regurgitating into the esophagus and (2) allow regurgitation of gastric contents when the intraabdominal pressure is too high (vomiting). Manometric studies identify the LES as a 2 to 4 cm-long high-pressure zone that constitutes a barrier against reflux. The mean resting pressure is about 10 to 30 mm Hg above the intragastric pressure. Several factors may contribute to the sphincter mechanisms (Ingelfinger, 1958). Mechanical factors such as the pinchcock effect of the diaphragm, the phrenoesophageal ligament, and the diaphragmatic crura are probably of little significance. The mucosal rosette, caused by the redundant folds of the gastric mucosa at the junctional zone, may contribute to the sphincter mechanism. However, several studies (for example, Christensen, 1970) claim that the resting LES tone is an intrinsic function of the sphincter muscle itself. Smooth muscle strips taken from the LES region differ from strips taken from adjacent regions in that they seem to be more sensitive to certain pharmacologic agents, and electrical field stimulation induces relaxation, whereas muscle strips from adjacent regions react with contraction (Christensen et al, 1973). The basal tone of the LES is adaptive to various physiologic stimuli. Food indigestion generally increases the tone. Meals with a very high fat content are exceptions to this rule (Nebel and Castell, 1973).

Far from being an abnormal event, gastroesophageal reflux occurs normally (Boesby, 1975; Spencer, 1969). The reflux periods occur predominantly during daytime. The total exposed time is, however, short (less than 1 hour in a 24-hour period; Johnson and De Meester, 1974). The noxious effects of this reflux are prevented by the normal esophageal defense mechanisms. When awake, normal individuals swallow at a rate of approximately once every minute, thereby initiating primary peristaltic waves that clear the esophagus. Such clearance also occurs through spontaneous secondary peristaltic waves. During deep sleep, swallowing ceases and the only mechanism that clears the esophagus is that of the secondary peristaltic waves (Dent et al, 1980).

### **Nervous Control of Esophageal Motility**

The autonomic nervous control of the esophagus is exerted by parasympathetic, sympathetic, and sensory neurons as well as by local neurons. The digestive tract, including the esophagus, is conspicuously rich in local neurons. These neurons form local short intramural nerve reflexes that mainly regulate secretion as well as coordinate the peristaltic activity of the smooth muscle, resulting in propulsion of the contents (Cooke, 1986). Such short reflexes are necessary for direct, immediate, and precise responses to local stimuli. As a communication system they probably form part of a continuous neural network that encompasses the gut from the esophagus down to its most distal parts.

Extrinsic fibers constitute a minority in the population of neuronal elements in the esophagus. They reach the esophagus via the vagal and sympathetic nerves. Fibers, which terminate predominantly in the intramural ganglia, around blood vessels and glands, have their cell bodies located in jugular, nodose, and local microganglia of the vagus, in cervical and thoracic sympathetic ganglia, and also in the brainstem (Cunningham and Sawchenko, 1990).

Sensory afferents reach the esophagus via the vagal nerve. Dendritic nerve endings are thought to act as mechanoreceptors, thermoreceptors, and chemoreceptors, activating intramural reflexes (Christensen, 1984). Intrinsic fibers that represent most of the nervous elements in the esophagus have their cell bodies in intramural ganglia.

Specific histochemical techniques have been developed to identify the individual neuronal populations on the basis of their transmitter content. Based on the results of such techniques intrinsic neurons have been claimed to store acetylcholine and a great number of neuropeptides. The distribution of neuropeptides varies considerably between different species. Some of these peptides exert specific electrophysiologic effects, either excitatory or inhibitory. Other peptides do not display such effects but have been implicated as neuromodulators, modifying neuronal responses to other neurotransmitters. It is not unusual to find peptides coexisting with "classical" neurotransmitters such as acetylcholine or noradrenaline. In addition, two or more peptides may coexist in the same neuron.

In the myenteric and submucosal ganglia of the esophagus, numerous acetylcholinesterase-positive nerve cell bodies can be seen. Immunocytochemistry has revealed that these nerve cell bodies also store peptides. One of the most abundant peptides is vasoactive intestinal peptide (VIP; Uddman et al, 1978). VIP is synthesized from a precursor peptide that also contains peptide histidine isoleucine (PHI). It is therefore not unexpected that VIP and PHI coexist in the same nerve cell bodies. Subpopulations of these neurons contain, in addition, pituitary adenylate cyclase activating peptide (PACAP) and neuropeptide Y (NPY). Nerve fibers containing these peptides can be seen among bundles of smooth muscle, close to seromucous glands and blood vessels. A particularly rich supply of VIP fibers can be seen around the LES (Alumets et al, 1979). VIP and VIP-like peptides may be involved in the control of local glandular secretion and blood flow. Whether VIP is involved in sphincter relaxation and smooth muscle motility is under debate (Daniel et al, 1989; Goyal et al, 1980).

A moderate number of noradrenaline-containing nerve fibers occurs in the intramural ganglia and between smooth muscle bundles, around glands, and close to blood vessels (Baumgarten and Lange, 1969). Some of these nerve fibers also contain NPY. However, the vast majority of the NPY-containing neurons are found in association with ganglia of the myenteric and submucosal plexa.

A sparse supply of substance P (SP)-containing nerve fibers can be seen in the longitudinal and circular smooth muscle as well as in the muscularis mucosae. SP-immunoreactive fibers are also seen in association with blood vessels, submucosal glands, and epithelium (Christensen et al, 1989). There is strong evidence that SP is a transmitter in primary afferent neurons. SP dilates blood vessels and contracts nonvascular smooth muscle, including the LES (Kamikawa and Shimo, 1984; Mukhopadhyay, 1978). There are also indications that SP is involved in the increase of LES pressure as a response to distal esophageal acidification (Reynolds et al, 1984).

Calcitonin gene-related peptide (CGRP) is a peptide that often seems to be collocated with SP. CGRP immunoreactivity has been located to sensory nerves in the mucosa, in smooth muscle bundles and in motor endplates of striated muscle, in intramural ganglia, and around blood vessels. CGRP is a potent vasodilator and may cause relaxation of the LES

(Rattan et al, 1988). CGRP also seems to exert an inhibitory effect on the peristaltic contraction of the esophageal body that follows swallowing or vagal efferent stimulation (Rattan et al, 1988).

### **Hormonal Control of Lower Esophageal Sphincter**

The role of gastrointestinal hormones in regulating the LES pressure has been a subject of much debate. Various hormones, in unphysiologically high concentrations, may influence the sphincter pressure. The physiologic implications of such studies are open to question. Gastrin is traditionally thought to play a role in the regulation of the LES pressure. However, several facts speak against this view. Patients with hypergastrinemia caused by the Zollinger-Ellison syndrome or by vagotomy (McCallum and Walsh, 1979) do not have abnormal LES pressures. Further, the concentration of gastrin needed to raise the LES pressure in normal subjects is much higher than the normally circulating concentration.

Cholecystokinin may induce a dose-dependent relaxation of the cat LES (Behar and Biancani, 1977). However, intravenous injections of cholecystokinin in humans do not seem to affect the sphincter pressure (Sturdevant and Kun, 1974). Motilin has been suggested to increase the LES pressure by an effect on preganglionic cholinergic neurons (Meissner et al, 1976). In contrast, Hellemans et al (1976) have demonstrated that motilin does not have any effect on the human esophagus. Somatostatin has a dual distribution in the gut, occurring both in nerves and in endocrine cells (Hökfelt et al, 1975). So far, somatostatin-containing nerve fibers have not been found in the human esophagus, and pharmacologic studies indicate that this peptide has little effect on the primate LES (Bybee et al, 1979). Thus the current view seems to be that various hormones do not contribute much to the control of the LES.

### **Esophageal Motility in Elderly Persons**

Several studies have indicated that esophageal motor function becomes disorganized with advanced age (Ali Khan et al, 1977; Soergel et al, 1964). Elderly persons often display an incoordination of the UES function, a reduced incidence of peristalsis, and frequent tertiary contractions. In addition, their LES often fails to open, resulting in delayed emptying. The impaired motor function is often associated with pharyngoesophageal dysfunction and esophageal dilation, manifestations named *presbyesophagus* (Zboralske et al, 1964). The cause of these disturbances is unknown. Serial sections of the esophagus from elderly persons have shown a decrease in ganglion cells in the myenteric ganglia as compared with the situation in young persons (Eckhardt and Le Compte, 1978). Conceivably, this partial denervation may contribute to the impaired motor function.

### **Alterations in Esophageal Motility After Laryngectomy**

Dysphagia is a common complaint after partial or total laryngectomy. Studies have shown marked disturbances in the relaxation and coordination of the UES and a reduction of the normal peristaltic wave in these patients (Duranceau et al, 1976). In contrast, the LES remains normal. This dysphagia may be a result of the interruption of muscle fibers in the cricopharyngeus muscle, the section of nerve fibers, and postoperative cicatrix formation.