Paparella: Volume I: Basic Sciences and Related Principles

Section 2: Physiology

Part 2: Head and Neck

Chapter 14: Physiology of the Lung

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The primary function of the lung is gas exchange. Oxygen from the inspired gas diffuses through the alveolar capillary membrane into the blood, and carbon dioxide and water are eliminated in the expired gas. Some heat loss also is associated with water evaporation. To perform this important function, the lung needs a center to control breathing, a pump (the thorax and respiratory muscles) to suck air from the atmosphere, a conducting system (the upper airway and tracheobronchial tree) to convey fresh air to the gas exchange site (the alveolar capillary membrane, an adequate capillary network, optimal matching between ventilation and perfusion anatomically and temporally, an adequate cardiac output, and a sufficient amount of hemoglobin to carry oxygen to various tissues. If there is a breakdown or disturbance of any of these steps, gas exchange suffers, resulting in alterations of arterial blood gases, respiratory failure, or even death.

In addition to the respiratory function, the lung has many nonrespiratory functions such as acid-base balance by excreting or retaining carbon dioxide, water and heat exchange, metabolic and endocrine functions, defense mechanisms, and many more that remain to be discovered. The purpose of this chapter is to review briefly all these functions and to mention some associated disorders relevant to the otolaryngologic specialty.

Gas Exchange Function

The Conducting System

The conducting system consists of the upper airway (anterior nares, nasal cavity, sinuses, nasopharynx, oropharynx, laryngopharynx, and larynx), the trachea, bronchi, bronchioles, and terminal bronchioles. The physiology of the upper airway has been extensively reviewed (Proctor, 1977, 1986). The respiratory functions of the upper airway are humidification and warming of the inspired air. It was formerly believed that conditioning was completed by the time the inspirate reached the larynx or upper trachea (Ingelstedt, 1956). Now it is recognized that much more of the tracheobronchial system may be involved in the conditioning process. Heat exchange and humidification take place the moment inspired air enters the body. During quiet breathing of ordinary ambient air, conditioning is completed in the upper airways. But when the heat-exchanging capacity of the upper airway is overtaxed by inspiring colder air or by increasing minute volume, incompletely conditioned air may reach peripheral airways. The temperature of central airways then decreases, providing a basis for exercise-induced asthma (McFadden, 1983). Changing from nasal breathing to mouth breathing also shifts the chief site of temperature control and humidification to a more distal location; bypassing the upper airway with an endotracheal tube or tracheostomy cannula moves the site entirely into the trachea and bronchi. The heat and moisture exchanger or

artifical nose has been used satisfactorily to heat and humidify inspired air (Shelly et al, 1986). The felt pad in this device traps moisture and heat from the expired air passing through the endotracheal or tracheostomy tubes and humidifies and heats subsequent inspirate. However, this device can add a substantial amount of resistance to breathing and must be used judiciously in debilitated patients (Ploysongsang et al, 1986). Expiratory braking by reflex glottic narrowing slows expiration (Remmers and Bartlett, 1977). It is believed that this process improves gas mixing and exchange (Knelson et al, 1970). The inspiratory muscle activity during expiration also assists in braking (Shee et al, 1985). The upper airway is also involved in the defense system, which is discussed in detail later.

Heated and humidifed air flows along the tracheobronchial tree to the respiratory terminal units where gas exchange occurs. Normally, the resistance to airflow is relatively small because of the exponential increase in the total cross-sectional area of airways as they divide, hence a marked reduction in resistance (Horsfield, 1986). Most of the resistance of the conducting airways resides in the upper airway and large bronchi (Ferris et al, 1964; Macklem and Mead, 1967; Hogg et al, 1968). There are three major factors affecting airway resistance: lung volume, elastic recoil, and geometry of airways. As lung volume increases, airway resistance decreases and vice versa (Briscoe and DuBois,1958). The elastic recoil properties of the lung affect the caliber of both bronchioles and bronchi by two different mechanisms: first, by providing direct traction on small intrapulmonary airways; second, by being one of the two determinants (alveolar pressure being the other) of intrapleural pressure, which provides the pressure surrounding bronchi and extrapulmonary airways and thereby distends them (Stubbs and Hyatt,1972). Intrapulmonary peribronchial pressure is at least as negative as, and probably slightly more negative than, pleural pressure (Mead et al,1970). Changes in the geometry of normal bronchi depend on both the transmural pressure across their walls and the distensibility of the elements composing the walls. An increase in smooth muscle tone (ie, bronchospasm in asthma) or narrowing of tracheal lumen from stricture after a prolonged and traumatic tracheostomy or intubation increases airway resistance. Tracheal tumors, vocal cord lesions, or paralysis produce the same effect of increased resistance to airflow. Flow rates during forced inspiratory and expiratory maneuvers are reduced proportionally to the increases in resistance. Effects on the flow volume loops of obstruction to airflow at various levels in the tracheobronchial tree, especially in the upper and large airways, can be summarized graphically.

The maximal expiratory flow-volume curve is composed of two parts, the effort-dependent (top 15 to 20 per cent of forced vital capacity) and effort-independent (bottom 80 to 85 per cent of forced vital capacity) portions. The flow in the effort-dependent portion is determined largely by the resistance in the large and upper airways, whereas the flow in the effort independent portion is controlled by the intrinsic mechanical properties of the smaller intrapulmonary airways (Hyatt, 1983). Therefore, a fixed obstruction in the upper airway or trachea or main bronchi has the same effect as adding an external resistance of fixed orifice, causing a marked reduction of flow in the effort-dependent portion on both inspiration and expiration. The midvital capacity expiratory and inspiratory flows decrease equally, hence the ratio is close to unity. In asthma and emphysema, the obstruction to airflow is mainly in the smaller intrapulmonary airways, where flow limitation occurs during expiration but not during inspiration (Hyatt, 1983). As a consequence, the expiratory flow is markedly reduced as compared with the inspiratory flow, resulting in a reduction of the mid-VC ratio to much less than unity. In variable obstruction of the upper airway, trachea, or main bronchi, the

configuration of the flow-volume loop depends on whether the lesion is intrathoracic or extrathoracic. Intrathoracic obstruction is enhanced by the positive pleural pressure during forced expiration, leading to a marked reduction of expiratory flow and mid-VC ratio. Extrathoracic obstruction is worsened by a sudden and marked drop of intra-airway pressure below the atmospheric pressure, which compresses the trachea and reduces maximal inspiratory flow, hence the mid-VC ratio increases to more than unity.

Flow limitation and compression of central airways improve the effectiveness of cough. The increased linear velocity of flow that occurs in compressed airways generates the force necessary to dislodge secretions and particles from the luminal surface. The shearing force generated by coughing alters the viscoelastic properties of sputum, facilitating its removal (King and Macklem, 1977).

Ventilation and Gas Exchange

Even distribution of ventilation as well as evenly distributed perfusion is critical for optimal gas exchange. The ventilation and perfusion matching of unity is considered to be ideal. The evenness of ventilation is determined by three important factors: the resistance and the compliance of lung units, and their product, the time constant. Otis and colleagues (1956) pointed out many years ago that lung units with equal time constants ventilate simultaneously. Units with longer time constants lag behind those with shorter time constants, leading to asynchrony of ventilation and its serious consequences of ventilation perfusion mismatching, ineffective gas exchange, and arterial hypoxemia. A prolongation of the time constant can be caused by an increase in either resistance (such as asthma) or compliance (such as emphysema). When there is an obstruction in an airway leading to a lung unit, that particular unit does not receive fresh air during inspiration while its neighbors do. Its oxygen content is low and carbon dioxide content is high. As a consequence, the gas exchange in this unit is not optimal, leading to arterial hypoxemia and hypercapnia. Furthermore, expired gas that is rich in carbon dioxide and poor in oxygen from neighboring lung units moves into this unit through collateral channels (interalveolar pore of Kohn, bronchiole-alveolar channel of Lambert, interbronchial channel of Martin) during the expiratory phase because of the ventilatory lag of the unit. This has an additional adverse effect on the composition of alveolar gas in that unit with consequently worsened arterial hypoxemia and hypercapnia.

It is believed that inspired gas reaches alveolar ducts by mass flow (sometimes called convection or bulk flow) through the airways, but alveoli are ventilated because of movement of molecules by gaseous diffusion. The completeness of mixing determines whether or not stratified inhomogeneity occurs (Cumming, 1967). Diffusion of molecules within a mixture of gases depends on the physical properties of the gases involved, the distance through which they have to move, and the time available for carrying out the process. The distance for gas-phase diffusion between alveolar ducts and their adjacent alveoli is sufficiently small that in normal subjects breathing at slow resting rates (ie, enough time), stratified inhomogeneity is barely discernible. However, the presence of stratified inhomogeneity can be demonstrated in patients with various forms of lung diseases and in normal subjects by increasing breathing frequency. This stratified inhomogeneity may lead to disturbed gas exchange (Piiper, 1979).

The lungs are contained in the pleural cavities, which have a vertical pleural pressure gradient, being more negative in the upper part than in the lower part of the lung (Agostoni, 1972). As a consequence, the alveoli in the lower part are smaller than those in the upper part, and during tidal breathing, the lower (dependent) lung zone ventilates more than the upper (independent) lung zone (Milic-Emili et al, 1966). The elastic recoil of the lung is composed of the surface force and the tissue force (von Neergaard, 1929). The surface force is generated by the air-fluid interface, which produces surface tension. The surface of alveoli is lined by a thin film of surfactant that reduces the surface tension when the alveolar surface area decreases and increases the surface tension when the alveolar surface area increases (Hildebran et al, 1979). The surfactant is manufactured and secreted by alveolar type II cells. In addition to stabilizing the alveoli, the surfactant also helps to maintain the patency of small airways (Macklem, 1971). The tissue force is believed to be determined by the elastin and collagen fibers (Karlinsky et al, 1976). Loss of tissue force is responsible for the loss of elastic recoil in emphysema. At functional residual capacity (FRC), the inward elastic recoil of the chest wall and the lung is said to be at its equilibrium or resting volume. Inspiration is accomplished by the contraction of inspiratory muscles, which lowers the pleural pressure and inflates the lungs. Expiration is usually passive in nature and results from the elastic recoil of lung and chest wall. Therefore, it requires force or pressure to move the lung from its FRC. Inflating the lung from FRC to total lung capacity (TLC) needs a negative pressure generated by inspiratory muscles. Deflating the lung from FRC to residual volume (RV) needs a positive pressure generated by expiratory muscles. One can easily appreciate that assessment of pulmonary function requires adequate respiratory muscle performance and good cooperation of the patient. It is impossible to interpret lung function tests if the respiratory muscles are weak or the patient does not cooperate.

In order to have an optimal gas exchange, the lung must have a perfusion matched to ventilation at the alveolar capillary membrane level, both temporally and spatially. The perfusion is provided by the pumping action of the right ventricle and the pulmonary circulation. Failure of the right ventricle (such as in chronic obstructive pulmonary disease - COPD) and occlusion of blood flow (such as in pulmonary embolism) can lead to an abnormal gas exchange and consequent hypoxemia. Diseases affecting both ventilation and perfusion (such as congestive heart failure, COPD, asthma) are the most common diseases causing ventilation perfusion inequalities that lead to an abnormal gas exchange and consequent hypoxemia or hypercapnia. Interference with gas diffusion across the alveolar capillary membrane such as in advanced pulmonary edema causes an abnormal gas exchange. Reduction of gas exchange surface in emphysema and interstitial lung diseases also produces inadequate gas exchange. Impairment of gas exchange can be assessed by measurement of the diffusing capacity for carbon monoxide or by analysis of arterial blood gases.

To evaluate the performance of the lung, one performs pulmonary function testing. In general, pulmonary function tests can be classified into four groups: tests to assess ventilatory function, perfusion, gas exchange, and control of breathing. A detailed discussion of all four groups is beyond the scope of this chapter. However, a few clinically and commonly used pulmonary function tests are discussed briefly here.

Spirometric tests have been used in clinical medicine for many years and have stood the test of time to be convenient, practical and informative for clinical purposes. These tests include measurement of lung volumes, an expiratory spirogram, and an evaluation of maximal

voluntary ventilation. The tests are performed on a water-sealed or dry spirometer. The measured lung volumes are vital capacity (VC), inspiratory capacity (IC), expiratory reserve volumes (ERV), inspiratory reserve volume (IRV), RV, tidal volume (TV), FRC and TLC. The lung volumes measure the anatomic dimensions of various compartments of the lung. These lung volumes are reduced in restrictive lung diseases such as idiopathic pulmonary fibrosis, sarcoidosis, and pneumoconioses.

In obstructive lung diseases (emphysema, asthma, bronchitis), the lung volumes can show no change, an increase (increased RV and FRC in emphysema), or a decrease (decreased VC in COPD). The expiratory spirogram is performed by asking the subject to inspire maximally and then breathe out as forcefully and completely as possible. The subject exhales the whole vital capacity forcefully, hence the name forced vital capacity test. From the expiratory spirogram (forced vital capacity tracing), one measures the expiratory volume in 1 second (FEV1), 2 seconds (FEV2), and 3 seconds (FEV3). FEV1, FEV2, and FEV3 assess the degree of airflow obstruction and are reduced in obstructive lung diseases (emphysema, bronchitis, asthma). The FEV1 is the most popular test used in clinical pulmonary function testing because of its simplicity, reproducibility, and sensitivity (Gaensler, 1951).

The maximal voluntary ventilation test (MVV) is performed by having the subject breathe in and out as fast and as much as possible in 12 seconds and the amount of air is measured and multiplied by five to reflect the rate in 1 minute. This amount of air that the patient can breathe in 1 minute is called the maximal voluntary ventilation. The patient's performance on the test varies with his or her age, sex, and body surface area (Kory et al, 1961; Baldwin et al, 1948). This evaluation adds the aspect of stamina to the FEV1 and thus becomes more valuable for preoperative evaluation of a patient's ventilatory ability (Woodruff et al, 1953).

The perfusion of the lung can be evaluated either noninvasively by radioisotopic perfusion scans or invasively by pulmonary angiograms. Clots in the pulmonary circulation are detected by either perfusion defects or filling defects, respectively. Gas exchange is usually assessed by measurement of diffusing capacity using carbon monoxide (CO) as an index gas. A known amount of carbon monoxide, usually 0.3%, in a gas mixture is inhaled and retained in the lung for about 10 seconds. Carbon monoxide is absorbed from the lung into the circulation. The diffusing capacity for carbon monoxide can be computed from the amount of CO that disappeared from the lung (Ogilvie et al, 1957). The diffusing capacity varies directly with the surface area of the alveolar capillary membrane, the amount of hemoglobin, the quantity of blood in the capillary bed, cardiac output, and exercise. It varies inversely with the diffusion distance, the ventilation perfusion mismatch, and aging. Diseases or conditions associated with these factors can alter the diffusing capacity.

Respiratory Muscle and Thorax

The lungs are contained in the thorax. Contraction of respiratory muscles generates sufficient force to enlarge and compress the thoracic cavity, which in turn inflates and deflates the lungs, respectively. There are three groups of respiratory muscles: the diaphragm, the intercostal and accessory muscles, and the abdominal muscles. The diaphragm is a musculotendinous sheet that separates the thoracic cavity from the abdominal cavity and is

the main source of inspiratory muscle force. The diaphragm consists of two distinct muscular components, the costal portion and the crural portion, both of which insert into a central tendon. The costal portion arises anteriorly from the xyphoid process and around the chest wall from the 7th to the 12th ribs. The crural portion arises posteriorly, from the aponeurotic arches on both sides, and from the first to the third lumbar vertebral bodies on the right side, and from the first and second on the left side. The phrenic nerve appears to be the sole motor nerve to the diaphragm; it derives from the third, fourth and fifth cervical nerves. During normal quiet breathing, inspiration depends mainly on contraction of the diaphragm. When the diaphragm contracts, it pushes down on the abdominal contents and displaces the abdominal wall outward. The contracting diaphragm also tends to lift and expand the rib cage but only to the extent that the abdomen resists being displaced and that the intra-abdominal pressure rises (Konno and Mead, 1967; Goldman, 1979; Mead, 1979). It has been shown in dogs that the costal diaphragm expands the lower rib cage by contracting against the abdominal contents (fulcrum effect) and by raising intraabdominal pressure. In contrast, the crural diaphragm, which has no rib attachments, has no expiratory action when abdominal pressure is prevented from increasing (DeTroyer and Kelly, 1982; DeTroyer et al, 1982, 1983 a, b).

Intercostal muscles are external and internal. Both extend between two adjacent ribs. The external intercostal muscles extend from the articulations between the ribs and vertebral bodies to the origin of the costal cartilages. In contrast, the internal intercostal muscles extend from the sternum only to the angles of the ribs. The internal intercostals are subdivided into parasternal and interosseous portions. Both internal and external intercostal muscles receive their motor and sensory innervation from the intercostal nerves, which arise from the first to twelfth thoracic segmental nerves. The scalene and sternomastoid muscles are the only important accessory muscles of inspiration. Classically, it was believed that the external intercostals and the parasternal portion of the internal intercostals are inspiratory muscles, whereas the interosseous portions of the internal intercostals are expiratory muscles (Taylor, 1960). However, DeTroyer and co-workers (1982, 1983a, b) have shown in dogs that at normal resting lung volumes, both groups of intercostal muscles are inspiratory; in contrast, as the lungs are progressively inflated to above approximately half their inspiratory capacity, the action is reversed and both groups become expiratory muscles. The scalene muscles, which elevate or fix the first two ribs, are recruited at approximately the same time during inspiration as the intercostal muscles; thus, they may be used at rest and are active during relatively quiet breathing, hence they should not be considered accessory. In contrast, the sternomastoids, which elevate the sternum, are recruited after about three-quarters of the vital capacity has been inhaled and are utilized only during strenuous breathing (Raper et al, 1966).

Several muscles of the abdominal wall contribute to respiratory movements. Of these, the rectus, external and internal oblique, and transverse abdominal muscles are considered to function strictly during expiration. It is generally believed that, during exercise and other maneuvers that require vigorous breathing, the abdominal muscles are recruited and contribute to active exhalation.

The respiratory muscles are skeletal muscles that have been adapted for the specialized function of breathing. They are the only skeletal muscles on which life depends. They are under both voluntary and involuntary control, and they deal chiefly with elastic and resistive loads. The active force developed is a function of the length of the muscle. In the respiratory

system, as the lungs inflate, the inspiratory muscles shorten and the expiratory muscles lengthen. Therefore, as lung volume increases, maximal inspiratory pressure decreases; whereas maximal expiratory pressure increases and vice versa during exhalation. As might be expected, because of their greater muscle mass, men generate higher maximal pressure than women, and there is some weakening of respiratory muscle strength with increasing age. The force-length characteristics of the isolated dog diaphragm show a maximal active tension at approximately 25 per cent beyond the in situ resting length, a finding that differs from other skeletal muscles in which maximal active tension occurs at approximately in situ resting length. Moreover, the diaphragm still generate appreciable tension at lengths as short as 40 per cent of the in situ resting length; this condition also differs from that found in other skeletal muscles, in which tension becomes zero at 50 to 60 per cent of the in situ resting length (Kim et al, 1976). Another intrinsic mechanical property of skeletal muscle is the relationship between the force generated and the velocity of muscle fiber shortening; the greater the force, the slower the velocity of contraction and vice versa. When maximal inspiratory and expiratory efforts are made through different-sized orifices, to vary resistance to flow, the maximal pressure exerted by the respiratory muscles decreases as the rate of airflow increases (Agostoni and Fenn, 1960; Hyatt and Flath, 1966).

As the O_2 requirements of the diaphragm begin to increase, both blood flow and O_2 extraction increase; however, at high levels of contractile effort and O_2 consumption, extraction tends to plateau and blood flow continues to increase. This dependency on perfusion is unlike that of other skeletal muscles and resembles that of the heart. When cardiac output is low and ventilatory demands are high, the diaphragm has to compete with the other organs for its blood flow and sometimes it does this unsuccessfully. Under these extreme conditions the diaphragm fails and mechanical ventilation may be life saving (Audier et al, 1981). The efficiency of the contracting diaphragm in converting energy to work increases when ventilation is increased but decreases progressively in the presence of increased resistance to inspiratory flow (Rochester and Briscoe, 1978). Approximately one-half of the energy utilized by the working diaphragm comes from carbohydrate metabolism chiefly in the form of lactate utilization, and the remainder is presumably from lipids, chiefly in the form of fatty acids (Rochester and Briscoe, 1978). The canine diaphragm is known to be remarkably resistant to anaerobic metabolism, even when working hard in a hypoxic environment; this reaction is different from other skeletal muscles. Thus, hemodynamic and metabolic attributes of the diaphragm, which more closely resemble those of the heart than other skeletal muscles, endow this key respiratory muscle with extraordinary endurance for high work loads.

The diaphragm is a beautifully designed muscle for the task of breathing for a lifetime. It is, however, not capable of limitless feats of contractile efforts; it can fatigue. The diaphragm and sternocleidomastoid have been found fatigued (Roussos and Macklem, 1977; Moxham et al, 1980). Respiratory muscles are composed chiefly of two types of fibers: type I, slow-twitch, high-oxidation fibers; and type II, fast-twitch, low-oxidation fibers (Lieberman et al, 1973). Type I fibers are more resistant to fatigue than type II fibers. Fatigue has been defined as the inability of a muscle to continue to generate a required force. When applied to the respiratory system, this term means that the respiratory muscles are unable to produce sufficient force to sustain adequate movement of air into and out of the lungs for adequate gas exchange, ie, ventilatory failure. Most causes of respiratory muscle fatigue can be attributed to failure of metabolic regenerative processes in the muscle fiber. Usually, the

failure of these processes can be related to an imbalance between increased demand for energy on the one hand and decreased supply of energy on the other. The factors that govern the energy demands of the respiratory muscles are the work that they need to perform, their strength, and their efficiency in converting energy to work. The factors that determine energy supplies are local energy stores, particularly glycogen; cardiac output; O_2 content of arterial blood; ability to extract and use energy from the blood; and a low blood-substrate concentration. There are several reasons why patients with lung diseases are susceptible to respiratory muscle fatigue. Among the most important are that their muscles are often at a mechanical disadvantage, their O_2 cost of breathing is considerably greater than normal because of extra work required to ventilate abnormal lungs and chest walls, and they may be hypoxic and hypercapnic.

Control of Breathing

The amount of ventilation required for gas exchange to meet the metabolic and non metabolic demands (such as coughing, talking, singing, sneezing) of the body varies considerably during usually daily activities. Remarkably, over this entire range of demands, the arterial blood P_{O2} and P_{CO2} remain constant within narrow limits. This constancy is made possible by a series of control mechanisms that regulate ventilation to meet the metabolic and nonmetabolic demands and roughly in proportion to the associated changes in cardiac output. Basically, the neurologic respiratory control system contains three principal interconnected components: a controller, which is located within the CNS and which initiates signals of its own in addition to integrating information from the sensing units; a group of effectors in the lungs, airways, and muscles of respiration that carry out commands from the controller; and different central and peripheral sensors, which monitor the adequacy of breathing with respect to the particular task being carried out (Pitts, 1946; Berger et al, 1977).

The controllers are the brain stem, which regulates automatic respiration; the cerebral cortex, which affects voluntary breathing; and the integrating neurons in the spinal cord, which process efferent information from both upper and lower respiratory centers in the brain with afferent information from peripheral proprioceptors and send the final signals to the muscles of respiration. Efferent automatic impulses also travel in the vagus nerves from the central nervous system to the airways and lung parenchyma. The medulla appears to be the main headquarters for spontaneous respiration.

There are two bilateral aggregations of respiratory neurons: the dorsal respiratory group (DRG), situated in the ventrolateral portion of the nucleus of the tractus solitarius, which consists chiefly of inspiratory neurons; and the ventral respiratory group (VRG), located with the nucleus ambiguus and nucleus retroambiguus, which contains both inspiratory and expiratory neurons (Cohen, 1981). Axons of the respiratory neurons in the DRG and the VRG project into the spinal cord via bulbospinal pathways. The DRG receives incoming visceral afferent information from the ninth and tenth cranial nerves and serves to process afferent signals into a respiratory motor response. The primary site of automatic respiratory oscillations is in or extremely close to the DRG. Axons from the DRG project to inspiratory spinal motoneurons, principally the phrenic motoneurons. Neurons of the DRG project to the VRG and affect its function but not vice versa. Axons from the VRG, which is driven by the DRG, project either to certain spinal respiratory motoneurons (chiefly intercostal and abdominal) or to the accessory muscles of respiration innervated by the vagus (eg,

sternocleidomastoids).

Neurons with respiratory activity have also been identified in the pons. Pontine respiratory neurons exhibit both inspiratory and expiratory activity, and it is speculated that they serve to smooth the transition from one phase of respiration to the next. The apneustic center in the lower pons act on medullary centers and thus modulate respiratory activity. The pneumotaxic center is believed to act as a fine tuner of the pattern of breathing by influencing the response to afferent stimuli generated during hypoxia, hypercapnia, and lung inflation. The apneustic center seems to contain the normal inspiratory inhibitory mechanisms. When this cutoff switch is faulty, apneusis, or sustained inspiration, results from unrestrained activity of the medullary inspiratory neurons. Voluntary, or behavior-related, control of breathing resides in the cerebral cortex, although the exact sites of activity are not known. Stimulation of some parts of the cortex inhibits respiratory movements, whereas stimulation of other parts increases respiratory frequency. The pathways that conduct signals from the cerebral cortex to the respiratory muscle motoneuron in the spinal cord are distinct from those tracts concerned with automatic respiration. Behavior-related activities involving breathing, such as talking, crying, swallowing, and laughing, cause marked changes in ventilation that may override completely the automatic control, which responds chiefly to chemical stimuli and to changes in lung inflation. For example, during phonation, sensitivity to CO_2 decreases dramatically, and the subject tolerates considerably higher arterial PCO_2 values than when quiet (Bunn and Mead, 1971). Another behavior-related drive to breathing is created by the state of wakefulness, which, in turn, is a reflection of respiratory excitation by the reticular-activating system.

Axons that emerge from the DRG, VRG, cortex, and other supraspinal sites descend in the white matter of the spinal cord, through which central impulses influence the motoneurons that innervate the muscles of respiration. The descending tracts that originate in the cortex and control voluntary breathing are separated from those that originate in the brain stem and subserve involuntary breathing. In support of these experimental observations, patients with neurologic deficits have been described in whom there is preservation of involuntary rhythmic control but loss of voluntary control of breathing (Newsom Davis, 1974) or vice versa (Severinghaus and Mitchell, 1962). It has also been shown that the descending pathways for such nonrhythmic reflexes as cough and hiccup that involve respiratory muscles are distinct from those influencing rhythmic breathing (Newsom Davis and Plum, 1972). The abundant neural traffic in the descending tracts is integrated with local reflex information at the level of the spinal cord, from which the segmental motoneurons that innervate respiratory muscles emerge. The integrative processes at the segmental level are complex and probably different in various respiratory muscles. Inspiratory alpha motoneuron activity is inhibited during expiration and, conversely, expiratory motoneuron activity is inhibited during inspiration. The obvious physiologic benefit of these responses is to prevent reflex contraction of antagonist muscles when agonist muscles are actively contracting.

The main effectors of breathing are the muscles of respiration. Besides controlling the respiratory muscles, central neural mechanisms regulate both the participation in breathing of skeletal muscles in the upper airways and the responses of smooth muscle and mucous glands within the tracheobronchial system. During normal conscious breathing, resistance to airflow through the upper airways decreases slightly during inspiration and increases slightly during expiration. This is due to the action of upper airway muscles and glottis. Neurally mediated

narrowing of the upper airway slows expiratory airflow and contributes, along with antagonistic contraction of the diaphragm during expiration, to the fact that exhalation through the intact larynx is slower than when the larynx is bypassed experimentally and the lungs empty passively (Bartlett and Remmers, 1975). The expiratory "braking" may allow more time for gas mixing and improve gas exchange (Shee et al, 1985).

During sleep, upper airway resistance increases because of loss of upper airway muscle tone and could lead to obstructive sleep apnea, especially in certain obese persons. Preganglionic efferent fibers travel in the vagus nerves from the medulla to aggregates of small ganglia situated in and around extrapulmonary and intrapulmonary airways (Richardson, 1979). Postganglionic fibers travel to smooth muscle and glands located in bronchi. When stimulated, vagal efferent fibers cause smooth muscle contraction and release into the lumen of glandular contents, which may or may not be accompanied by cough. This response is part of an important protective reflex designed to keep the lungs and air passages free of noxious substances. Bronchial smooth muscle contracts during inspiration and relaxes during expiration (Mitchell et al, 1985). Thus, both skeletal and smooth muscle components of the effector system are continuously modulated by neural output from the controller. The actual amount of ventilation at any time depends on the needs of the moment as determined by voluntary and involuntary centers in the controller. The integrated output from supraspinal and spinal pathways is transmitted to the muscles of respiration through the alpha motoneurons that innervate the contractile fibers of a particular muscle.

In a system that must be as responsive as breathing to varying needs for ventilation, it is obviously desirable to have suitable sensors to initiate changes and to monitor whether or not the correction is appropriate. The respiratory system is equipped with both peripheral and central chemoreceptors functioning as sensors. The peripheral chemoreceptors are carotid and aortic bodies. In humans, the ventilatory function of aortic bodies is probably unimportant and will not be discussed further. The carotid bodies are nested in the bifurcation of the common carotid arteries. They are extremely well vascularized and contain two main cell types - type I cells (also called glomus cells, chief cells, and enclosed cells) and type II cells (also called supporting cells, sheath cells, enclosing cells, and sustentacular cells) - that are interspersed among numerous axons and their terminals and abundant blood vessels. Virtually all the nerve endings that are in contact with the glomus cells are axons of afferent sensory nerves that travel in a branch of the carotid sinus nerve and reach the brain in the glossopharyngeal (ninth cranial) nerve (McDonald and Mitchell, 1975). The few terminals on glomus cells that appear to be efferent are from sympathetic fibers that reach the carotid body from the superior cervical ganglion. Ventilatory response to hypoxia in humans is abolished by carotid body resection or denervation. Chemoreceptor activity from the carotid bodies is increased by decreased arterial PO_2, increased arterial PCO_2, or decreased arterial pH. Stimulation of the carotid bodies also caused bradycardia and hypotension, whereas stimulation of the aortic bodies provokes tachycardia and hypertension (Comroe and Mortimer, 1964). The peripheral chemoreceptors are tonically active in normal persons breathing ambient air at sea level, and this activity can be suppressed by breathing high concentrations of O_2. As PO_2 decreases below 500 mm Hg, there is only a slight increase in nerve impulse activity; in contrast, as PO_2 goes below 100 mm Hg, the increase is striking. Below 30 mm Hg, the initial marked increase in impulse activity is not sustained and it gradually declines. Whereas the chemoreceptor response to changing PO_2 is remarkably alinear, the response to changing PCO_2 from 20 to 60 mm Hg and pH from 7.20 to 7.60 is

nearly linear. When two stimuli affect the peripheral chemoreceptors simultaneously, the effects are synergistic. Besides responding to changes in PO_2, PCO_2, and pH, chemoreceptors are provoked by decreases in blood flow such as may occur when systemic blood pressure falls or when sympathetic activity causes vasoconstriction of vessels in the carotid bodies. Today's prevailing evidence suggests that the afferent nerve terminals within the carotid body are the receptors. The glomus cells are dopaminergic inhibitory interneurons that modulate the generation of impulses in the afferent nerve terminals (McDonald, 1980). According to this theory, chemical stimulation of the sensory nerve endings in the carotid bodies generates impulses directed toward the brain stem and also provokes secretion of a neurotransmitter that causes release of dopamine from glomus cells. Dopamine, in turn, modulates chemoreceptor sensitivity.

The results of a variety of neurophysiologic studies have demonstrated three bilateral areas in the medulla that are involved in central chemosensitivity. The best-established of these is the chemosensitive region located by Mitchell and associates (1963) on the ventrolateral medullary surface lateral to the pyramids and medial to the roots of the seventh through tenth cranial nerves. Another chemosensitive area is caudal to the first one, lateral to the pyramids, but medial to the root of the twelfth nerve. A third region, which is not itself chemosensitive, is located between the other two. The importance of this third area can be demonstrated by the nearly complete loss of CO_2-induced ventilatory responses when it is electrocoagulated. This observation has led to the conclusion that afferent fibers from the two chemosensitive regions enter the middle region, from which neurons then project to the respiratory integrating sites elsewhere in the medulla. The central chemoreceptors are stimulated by PCO_2 and H+ and depressed by HCO3 and low PO_2 in the surrounding cerebral (medullary) interstitial fluid. During a steady state, in contrast to acutely changing conditions, cerebral interstitial fluid (H+) is supposedly in equilibrium with cerebrospinal fluid (H+) (Nattie, 1983). This provides the rationale for sampling and analyzing cerebrospinal fluid to find out what is "going on" centrally. It should also be pointed out that the transient ventilatory response to a step change in alveolar CO_2 concentration in humans has a time constant of as high as 89 seconds (Gelfond and Lambertsen, 1973). This means that the central chemoreceptors reach equilibration with arterial blood much more slowly than the peripheral chemoreceptors, which equilibrate virtually instantaneously. Changes in cerebrospinal fluid (H+) and (HCO3-) that occur independent of change in PCO_2 must be accompanied, if not caused, by changes in strong ions, (Cl-), lactate, hydroxybutyrate, and other inorganic and organic anions with high dissociation constants.

The lungs and upper airways are equipped with a multitude of receptors that, when stimulated, have profound effects on breathing. The three main lower airway and pulmonary receptors - the stretch receptors, the irritant receptors, and the C-fibers, including the J receptors - have their afferent pathways in the vagus nerve and their central terminals in the tractus solitarius. As stated, because the DRG is located within the tractus solitarius, there is good reason to believe that the DRG processes incoming afferent information into a respiratory motoneuron response. Stimulation of these receptors can cause bronchodilation, bronchoconstriction, cough, rapid shallow breathing, and mucous secretion. Other cranial nerves as well as the vagus nerve serve as afferent pathways for receptors in the upper airway (Richardson and Peatfield, 1981). When stimulated chemically or mechanically, receptors in the nose send signals by way of the trigeminal and olfactory nerves. Responses to nasal stimulation include sneezing, apnea, and bradycardia. Stimulation of receptors in the

epipharynx causes the sniff or aspiration reflex; afferent fibers from these receptors travel in the glossopharyngeal nerve, which also has its central terminals in the tractus solitarius. There are numerous receptors in the larynx responding to mechanical or chemical stimuli by coughing, slow deep breathing, apnea, bronchoconstriction, and hypertension. There are two main types of muscle receptors in respiratory muscles; the Golgi tendon organs and the muscle spindles. Information from these sensors is integrated at the spinal segmental level and may contribute to agonist-antagonist muscle behavior; however, direct supraspinal control seems to dominate this relationship. It appears that the contribution of inspiratory afferent information from the diaphragm, and possibly from the intercostals as well, to tidal volume regulation is negligible (Duron, 1981). Muscle sensors have been linked to the sensation of dyspnea through research by Campbell (1966).

A variety of tests have been developed to evaluate the control of breathing. In general, each of these measures one or more variables related to the act of breathing, such as minute ventilation, frequency, tidal volume, or developed pressure, under resting conditions and in response to a stimulus to augment ventilation (Lourenço, 1976). When a normal person breathes a low concentration of O_2 in the inspired mixture, it is possible to evaluate the response to hypoxia by measuring corresponding changes in ventilation. The relationship between arterial PO_2 and ventilation is hyperbolic. Ventilatory responses to isocapnic hypoxia vary widely, with nearly a 10-fold variation in normal subjects (Rebuck and Woodley, 1975). Hypoxic sensitivity decreases with increasing age and is characteristically depressed or even absent in long-term residents of high altitudes (Weil et al, 1971). Blunted responses to hypoxia contribute to the pathophysiologic abnormalities of patients with severe chronic obstructive lung disease or massive obesity or after the administration of opiates and other sedative drugs. The ideal test of central chemoreceptor sensitivity is measurement of changes in ventilation that result from a given change in (H+). The standard approach is the use of carbon dioxide response test. Two types are available: the steady-state method, in which the subject breathes air enriched with different concentrations of CO_2, usually 3, 5 and 7 per cent for approximately 10 minutes each before measurements are made; and the rebreathing method, in which the subject breathes from a bag prefilled with 7 to 8 per cent CO_2 and excess O_2 (40 to 93 per cent) while ventilatory volume and end-tidal CO_2 concentration are recorded continuously. The rebreathing method has virtually replaced the steady-state method because it yields similar information and is much easier and faster for the subject to perform. A plot of the relationships between ventilation and end-tidal PCO_2 is obtained, and the CO_2 sensitivity is defined as the slope of the curve. Normal values in healthy adults range from 2 to 5 L/min/mm Hg. The ventilatory response to CO_2 decreases with age, but not as much as the response to hypoxia. Sensitivity to CO_2 is also blunted in certain endurance athletes and can be severely depressed by a variety of sedative, narcotic, or anesthetic agents and in patients with obstructive pulmonary disease.

Breathing is regulated on a moment-to-moment basis, primarily in response to changing metabolic needs. Changes in the control of breathing also occur in normal persons during sleep. The regulatory systems also adjust breathing to minimize the effects of stresses and threaten the O_2, CO_2, and H+ compositions of blood and tissue, such as breathing air with a low PO_2, and respiratory and metabolic acid-base disturbances. During stages 3 and 4 of nonrapid eye movement (nonREM) sleep (slow-wave sleep), the minute ventilation is usually somewhat less than while quietly awake. Accordingly, arterial PCO_2 increases 4.1 to 6. mm Hg, PO_2 decreases 3.5 to 9.4 mm Hg, and pH decreases 0.03 to 0.05 unit (Philipson, 1978a,

b). Breathing during rapid eye movement (REM) sleep is characteristically irregular, with brief periods of apnea lasting up to 15 to 20 seconds or even longer in normal adults and children and 10 seconds in infants. On the average, both ventilation and arterial blood gas values are about the same during REM sleep as during slow-wave sleep (Cherniack, 1984). The ventilatory response to CO_2 and to hypoxia is decreased during slow-wave sleep compared with that during wakefulness and is further decreased during REM sleep (Philipson, 1978a, b; Hedemark and Kronenberg, 1982; Douglas et al, 1982). The reflex stimulation of the muscles that control upper airway patency is diminished during sleep. This, coupled with the gravitational effects of the supine posture usually adopted for sleep, tends to promote upper airway obstruction, a phenomenon of great importance in the pathogenesis of sleep apnea syndrome (Cherniack, 1984).

Acute hypoxia stimulates ventilation when the arterial PO_2 decreases below 60 mm Hg; thereafter, worsening hypoxemia to an arterial PO_2 of about 30 mm Hg evokes a progressively greater increase in ventilation. Below 30 mm Hg, the ventilatory response diminishes. It is generally agreed that the stimulus to increase breathing during acute hypoxia in humans is mediated chiefly by chemoreceptors. Acute hypoxia-induced hyperventilation causes a decrease in PCO_2 and an increase in pH in arterial blood and cerebrospinal fluid, both of which serve to inhibit ventilation. After prolonged hypoxia, the ventilatory response increases further; it was originally postulated that the increase in breathing was caused by a return of blood and cerebrospinal fluid (H+) to normal values by compensatory adjustment in (HCO3-), which removed the inhibitory effects of acutely induced alkalinization in the two compartments. However, Dempsey and co-workers were not able to confirm this postulate (Dempsey et al, 1974). Therefore, the mechanisms that underlie the breathing response during short-term adaptation to hypoxia are unknown. People who have lived for many years at high altitudes and so were exposed to long-term hypoxia lose their ventilatory response to acutely induced hypoxia, and in addition, they ventilate less at rest, during exercise, and when breathing CO_2. The mechanisms by which the ventilatory response to hypoxia are attenuated in highlanders are unknown. There is indirect evidence that chemoreceptor function may be faulty, but other evidence suggests that abnormal suprapontine modulation may be responsible (Dempsey and Forster, 1982). Long-term ventilatory insensitivity to hypoxia is an acquired and not a genetic trait in these people.

Nonrespiratory Function

The lung has many nonrespiratory functions. A few important ones are mentioned briefly here.

Acid-Base Balance

The lung helps maintain acid-base homeostasis of the body by controlling the elimination of carbon dioxide through the bicarbonate buffer system. When there is an acid load from metabolism, the excess hydrogen ions (H+) combine with bicarbonate ions (HCO3) of the buffer system to form carbonic acid (H2CO3), which dissociates to CO_2 and H_2O. The generated CO_2 stimulates ventilation and thus is eliminated by the lung. When there is a base load, the excess bicarbonate ions depress ventilation and elimination of CO_2 by the lung. The retained CO_2 helps to buffer the increased HCO3 and minimizes the rise of pH. The lung itself can be at fault by generating respiratory alkalosis (by hyperventilation). Various lung

diseases, especially obstructive lung diseases (asthma, chronic bronchitis, or emphysema), tend to cause alveolar hypoventilation and CO_2 retention causing respiratory acidosis. The body tries to buffer the increased PCO_2 by generating and retaining HCO3 by the renal mechanism, thus minimizing the drop in pH. Hyperventilation, as in hyperventilation syndrome, pulmonary embolism, and pneumonia, causes a drop in the arterial PCO_2 and produces respiratory alkalosis. To minimize an increase in pH, the kidney excretes HCO3 ions.

Metabolic Functions

Oxygen Utilization and Energy Production

The lung removes O_2 from the inspired air to supply the metabolic needs of itself and the rest of the body. The O_2 consumption of isolated perfused lungs of rabbits has been reported as 39 microL/min.gm dry wt (Koga, 1958) and of dogs at 48 microL/min.gm dry wt (Weber and Visscher, 1969). This O_2 consumption has been calculated to be about 1 per cent of the total O_2 expenditure in resting humans (Fisher, 1976). The quantity of O_2 consumed by the lungs is relatively low compared with that of other organs: heart, 283 to 788 microL/min.gm dry wt; kidney, 259 to 527; thyroid, 421; brain, 200 to 350; liver, 192; intestine, 54; skeletal muscle (resting), 9 to 59 (Weber and Visscher, 1969; Altman and Dittmer, 1968). The lung parenchyma and smaller airways obtain adequate O_2 for their metabolic needs from the inspired air and are not dependent on O_2 supplied through the bloodstream. Thus, whether or not lung tissue death (pulmonary infarction) follows pulmonary arterial occlusion from embolization or other causes probably depends more on the interruption of a supply of substrate, such as glucose, fatty acids, and amino acids, than on an insufficient supply of O_2 (Tierney, 1974).

Surfactant Synthesis

Type II epithelial cells of the lung synthesize surfactant from phospholipids and proteins (King and Clements, 1972). Dipalmitoyl-phosphatidylcholine is a surface-active substance and the principal component of pulmonary surfactant. However, it should be pointed out that more than just dipalmitoyl-phosphatidylcholine is required to produce all of the remarkable surface-active properties exhibited by normal lungs.

Protein and Connective Tissue Synthesis

The lungs contain a large number of diverse proteins (Collins and Crystal, 1976). Some of these proteins, such as the enzymes that participate in energy production, are also found in cells throughout the body, where they subserve general metabolic needs. Other proteins, such as collagen and elastin, are also found in other organs but often in amounts different from those that occur in the lungs. The apoprotein of pulmonary surfactant appears to be unique to the lungs. Although all cells must synthesize proteins to some extent, autoradiographic studies of the lung parenchyma after the intravenous administration of radiolabeled amino acid precursors revealed incorporation chiefly in the cytoplasm of type II epithelial cells (Massaro and Massaro, 1972). Protein synthesis by the lungs is depressed during starvation (Rannels et al, 1979), and this could lead to functional and structural alterations in the lungs. Collagen and elastin are the most abundant proteins in human lungs, and there is more of the former than the latter. These two proteins are synthesized by type

I and II epithelial cells, endothelial cells, mesenchymal cells, blood vessel smooth muscle cells, chondroblasts, and mesothelial cells (Hance and Crystal, 1975).

Endocrine Function

The humoral substances that are believed to be synthesized in the lungs are adrenocorticotropic hormones, arachidonic acid metabolites (prostaglandins, leukotrienes), bombesin-like peptides, calcitonin, histamine, opiate peptides, serotonin, substance P, and vasoactive intestinal peptides. Of these, arachidonic acid metabolites and histamine are the most important one and are discussed in some detail.

The generation of arachidonic acid metabolites is through the action of the enzyme phospholipase A on membrane-bound phospholipids. This is not only the first but the rate-limiting step in the biosynthesis of all arachidonic acid products (Said, 1982). There are two major synthetic pathways through which arachidonic acid is converted to pharmacologically active substances: the cyclo-oxygenase and lipoxygenase pathways. The cyclo-oxygenase pathway generates unstable endoperoxides, from which the primary prostaglandins - PGD2, PGE2, PGF1alpha, PGI2 (prostacyclin), and thromboxane A2 - are derived. The lipoxygenase pathway leads to the formation of 5-hydroperoxyeicosatetraenoic acid (5-HPETE), from which the leukotrienes - LTB4, LTC4, LTD4, and LTE4 - are derived. The major tissue sources of cyclo-oxygenase products are alveolar macrophages, fibroblasts, smooth muscle cells, and type II epithelial cells; endothelial cells are rich sources of prostacyclin, and platelets are active producers of thromboxane A2. The most important cellular sites of lipoxygenase products are mast cells, basophils, and neutrophils. In general, prostaglandins of the D and F series are constrictors, whereas those of the E series are dilators of smooth muscle. PGE2 is, in part, an exception to this generality because, although it is a vasodilator in the fetus and newborn, it is a weak vasoconstrictor in the adult; PGE1 is a potent vasodilator of the pulmonary circulation. Prostaglandins also have profound effects on platelet activity, some enhancing and others inhibiting aggregation. In contrast to the leukotrienes, which also act on pulmonary vascular and airway smooth muscle, prostaglandins neither increase vascular permeability nor promote chemotaxis. Prostaglandins are released from the lungs during anaphylaxis, inflammation, hypoxia, pulmonary edema, and mechanical stimulation (Hyman et al, 1978)>LTC4, LTD4, and LTE4 comprise the mediator originally described as slow-reacting substance of anaphylaxis. Accordingly, these compounds evoke slow, sustained bronchospasm that is greater in peripheral airways than in central airways (Weiss et al, 1982) and may play an important role in bronchial asthma. The same leukotrienes mediate increased vascular permeability in certain tissues, such as guinea pig skin, hamster buccal mucosa, and human skin, but their role in the lung is uncertain. Leukotriene B4 is a potent chemotactic agent and also has endothelial cell adherence activity. In addition to probably playing an important role in the pathogenesis of asthma, the vasoactive, edematogenic, and chemotactic properties of the leukotrienes have made them likely candidates as mediators of the essential components of inflammation.

Histamine is the best known and most thoroughly studied mast cell mediator. It has long been believed to play an important role in IgE-mediated immediate hypersensitivity reactions. Now it appears that other mast cell mediators are as important as or even more important than histamine in accounting for the full spectrum of pulmonary abnormalities encountered in human asthma. The biologic effects of histamine in an intact mammalian lung

include increased airway resistance and constriction of airway smooth muscle (Nadel, 1980). Histamine causes constriction of vascular smooth muscle, particularly in veins, and induces a transient increase in endothelial permeability (Brigham and Owen, 1975). Histamine is one of the leading candidates as the mediator of the pulmonary artery vasoconstrictor response to hypoxia (Fishman, 1980). Recent evidence suggests that leukotrienes may be more important than histamine in the pathogenesis of severe refractory asthma (Weiss et al, 1982; Griffin et al, 1983).

Pulmonary endocrine cells are believed to synthesize several humoral substances. These are Kulchitsky's cells, which are found in the epithelium of airways and also in other organs such as intestines. These cells may be the site of production of adrenocorticotropic hormone or its precursors. These cells have been shown to contain bombesin-like peptides, calcitonin, opiate peptides, and serotonin (Becker and Gazdar, 1984).

Transformation of Biochemical Substances

Gaddum and co-workers (1953) demonstrated first that serotonin was inactivated during perfusion through the lungs. It is now known that many substances such as certain peptides, amines, and steroids are disposed of in the pulmonary circulation. Acetylcholine may be inactivated by the lungs (Eiseman et al, 1964). Continuously infused serotonin is nearly all removed during passage through the pulmonary circulation. Cellular uptake and degradation of serotonin in the pulmonary circulation occur in endothelial cells, especially those within arterioles and capillaries (Strum and Junod, 1972). Approximately 30 per cent of norepinephrine is removed by the pulmonary circulation. In contrast, neither epinephrine nor dopamine is removed by the pulmonary circulation (Gillis and Pitt, 1982). More than 80 per cent of bradykinin is removed during its passage through the lungs of several mammalian species (Said, 1982). Bradykinin is one of the most potent endogenous vasodilator products of the kininogen-kinin system and is believed to play a role in inflammatory responses, hereditary angioneurotic edema, and neonatal circulatory adjustment. Bradykinin is inactivated by angiotensin-converting enzyme, which transforms angiotensin I to angiotensin II. Decapeptide angiotensin I is formed in the bloodstream from an L-globin precursor by the action of the enzyme renin. Angiotensin I is converted to the highly active vasoconstrictor octapeptide angiotensin II, mostly in the lungs and to a small degree in peripheral vascular epithelium. Angiotensin II increases arterial blood pressure and stimulates the release of aldosterone (Longenecker and Huggins, 1977). Between 60 and 90 per cent of the vasoactive prostaglandin E2 and F2alpha are degraded during a single passage through the pulmonary circulation (Hyman et al, 1978). In contrast, thromboxane A2 and prostacyclin are unaffected by the lungs. All four leukotrienes are inactivated by neutrophils, and the three sulfidopeptide leukotrienes (eg, slow-reacting substance of anaphylaxis) are also catabolized by eosinophils (Hardy et al, 1984). In addition, slow-reacting substance of anaphylaxis loses its biologic potency during a single passage through the pulmonary circulation (Piper et al, 1981).

Liquid and Solute Exchange

Normally, there is net outward filtration of liquid from the microvasculature of the lungs, which cannot be measured directly in humans but which is estimated to be 10 to 20 mL/hr in adults (Staub, 1978). Also, a similar amount is removed from the lung through the pulmonary lymphatic circulation to prevent the retention of excessive liquid. Pulmonary

edema nearly always represents an enhancement of the processes favoring liquid filtration, but it can only occur when the rate of filtration exceeds the rate of removal. It is generally believed that liquid and solutes pass from the bloodstream into the interstitial space of the interalveolar septum through interendothelial junctions, which are relatively loose but still restrict the passage of protein-sized, lipid-insoluble molecules; thereafter, liquid is prevented from entering alveolar spaces by the presence of the relatively tighter interepithelial junctions. Once filtered, liquid does not accumulate in the pericapillary interstitial space of the interalveolar septum. Instead, liquid flows into the interstitial spaces surrounding airways and blood vessels where the lymphatic capillaries are located and through which liquid is removed from the lungs. As pulmonary edema occurs, substantial volumes of liquid accumulate in the peribronchovascular spaces, which can be viewed as a large reservoir that must first be filled before liquid overflows into the alveolar space. Although liquid is normally cleared from the distal peribronchovascular space by lymphatic capillaries, when edema accumulates more proximally around large airways and blood vessels, it is removed by the bloodstream, chiefly through the bronchial circulation. When there is endothelial damage, proteins can leak out from capillaries into the interstitial space and also be removed by lymphatics. From animal experimental data, it is estimated that lymphatic removal capacity can increase at least 5- to 10-fold above basal rates. There are two important fundamental processes that cause increased filtration and, hence, pulmonary edema in clinical situations: an increase in net driving pressure (hydrostatic or high pressure, or cardiogenic pulmonary edema) and an increase in microvascular permeability (permeability, normal pressure, or noncardiogenic pulmonary edema).

Defense Mechanisms

Each day, the tracheobronchial and respiratory units are exposed to more than 10,000 liters of ambient air, which contains many infectious microorganisms and hazardous dusts of chemicals. These agents could cause pulmonary or systemic infections, inflammatory lung disorders, and malignancies. Fortunately, the lungs have many mechanisms to protect themselves and the body by effective elimination of the inhaled particles, hence minimizing the serious consequences. There are two principal methods of elimination: the nonspecific (ie, nonimmunologic) defense mechanisms of the respiratory tract and cell-mediated and antibody-mediated (immunologic) defense mechanisms. The nonspecific defense mechanisms consist of clearance, secretions, cellular defenses, and biochemical defenses. Inhaled particles are removed from the air stream by deposition on the mucosal surface. The three physical forces that govern the deposition of particles in the airways and airspaces are inertia, sedimentation, and diffusion (Brain and Volberg, 1979). During inhalation, particles are forced to change their directions repeatedly as they travel through the numerous curves and branches in the nasopharynx and tracheobronchial tree. Once in motion, a particle moves in a straight course due to its inertia and does not change its direction along the tracheobronchial tree. As a result, it will impact and hence be deposited upon the epithelial surface at bifurcations or bends. Because inertial forces increase with air velocity, inertial deposition of particles is greater in the upper than in the lower airways and is enhanced by increased inspiratory flow rates. Impaction is the essential mechanism of deposition of particles greater than 10 microm in the nasopharynx. It also accounts for 19 per cent of the total tracheobronchial deposition of particles as small as 2.0 microm (Hoffman and Billingham, 1975). Sedimentation of inhaled particles is under the influence of gravity and occurs in relatively still air in the peripheral respiratory units. It is the most important mechanism of deposition of particles between 0.2

and 5.0 microm (Newhouse et al, 1976). Deposition by diffusion is important only for particles less than 0.5 microm in the terminal respiratory units, where the mass movement of air is trivial and brownian movement predominates (Newhouse et al, 1976). The particles can be solids, liquids, or dissolved gases. Reflexes can be triggered by chemical stimulation of receptors located in the nose (sneezing, laryngeal closure), larynx (coughing, laryngeal narrowing, hyperpnea, bronchoconstriction), and lung parenchyma (rapid shallow breathing)(Szereda-Przestaszewska and Widdicombe, 1973; Widdicombe and Sterling, 1970; Mills et al, 1969; Nadel et al, 1965). Toxic and water-soluble gases like sulfur dioxide cause injury to the upper airway, whereas less soluble gases like phosgene, nitrogen dioxide, and chlorine produce damage to the tracheobronchial tree and lung parenchyma (Ploysongsang et al, 1982).

The filtering system of the respiratory tract is not perfect, and a certain amount of potentially harmful material is deposited within the airways or airspaces during ordinary daily activities. To guard itself and the rest of the body, the respiratory system has several different nonspecific defense mechanisms, including clearance pathways, secretions with antimicrobial properties, and systems of cells that either impose physical barriers or actively phagocytose particles. Highly water-soluble gases and liquid particles are absorbed at the sites of contact with the epithelial lining of the respiratory tract. Less soluble substances may be either eliminated or absorbed depending on the balance between the clearance mechanisms and the solubility of the substance. The physiologic and pathologic consequences of absorption are determined by how much cellular damage and malfunction result from the biomedical reactions produced by the toxic substance and may vary from mild to lethal. There are two interdigitating clearance systems that serve to remove particles deposited in different locations: clearance from the nasopharynx and tracheobronchial tree is achieved by mucociliary transport, and clearance from the terminal respiratory units is achieved by macrophage transport. The inefficiency of clearance is believed to be crucial to the pathogenesis of the slowly developing pneumoconioses (Hatch and Gross, 1964). Particles deposited in the anterior portion of the nasal cavity can be removed by nose blowing and sneezing (Proctor, 1977). Particles deposited more posteriorly are swept backward over the mucus-lined, ciliated epithelium to the nasopharynx, where they are swallowed. Nasal clearance occurs at an average rate of approximately 6 mm per minute (Proctor, 1977). Removal of particles from the entire system of conducting airways is carried out by mucociliary clearance: a film of mucus is continuously impelled proximally by the beating motion of cilia that cover the surface of the tracheobronchial epithelium. Particles are carried on the mucous film to the oropharynx, where they are swallowed or expectorated. Human ciliated cells have approximately 200 cilia per cell (Rhodin, 1966). In the rat, cilia have been observed to beat at a frequency of 1300 beats/min and to move the overlying mucous film at an average rate of 13.5 mm/min (Dalhamn, 1956). In humans, the speed of the tracheobronchial clearance is almost twice as fast at 21.5 mm/min (Santa Cruz et al, 1974). The clearance is distinctly slowed in the bronchioles (Newhouse et al, 1976). The mucous lining throughout most of the airways is composed of a double hydrosol-gel (sol-gel) layer on the surface of the bronchial epithelium (Yoneda, 1976). The inner layer, in which the cilia beat in a characteristic biphasic stroke (a fast forward flick followed by a slow backward recovery), is the periciliary liquid or sol phase of the transport medium. The outer layer is the viscous or gel phase that serves to protect the sol phase from desiccation. The tip of the beating cilia just strike the innermost portion of the gel covering them, thus facilitating proximal movement of the layer (Camner, 1980). Impaired ciliary motion associated with

ultrastructural defects is now known to predispose a person to multiple respiratory infections and bronchiectasis, and to cause the immotile ciliary syndrome (Mygind et al, 1983).

Particles deposited on the alveolar surface are cleared by macrophage transport (Green et al, 1977). Particles are phagocytosed by alveolar macrophages, which then eliminate the particles either by digesting them or by carrying them along the alveolar surface to the beginning of the mucociliary transport system (La Belle and Brieger, 1960). From there, both the macrophage and its particulate contents are propelled centrally to the oropharynx, where they are swallowed or expectorated. Alternatively, instead of moving along the alveolar surface, the particle-laden macrophage moves through the interstitial space of the interalveolar septum until it enters the lumen of the airspaces at the junctions of respiratory and terminal bronchioles, where it is carried centrally by the mucociliary escalator. Some particles in the peribronchovascular interstitial space enter the lymphatics, by which they are carried to hilar lymph nodes, and sometimes into the bloodstream, through which they may circulate to other organs. It is generally agreed that unless the particle load is heavy and macrophage transport via surface and septal pathways is overwhelmed, little if any of the inhaled material reaches the hilar lymph nodes or the bloodstream. Some of the particles originally deposited in alveoli may be sequestrated in the lung parenchyma by a tissue reaction, as occurs with silica particles, for example.

Secretions that cover the respiratory epithelium contain several antimicrobial substances, such as lysozyme, lactoferrin, and interferon, that serve to destroy or inhibit many bacteria and viruses. The mucous or outer layer is believed to be produced by Clara cells, type II alveolar cells, goblet cells, and bronchial glands (Masson and Heremans, 1973; Litt, 1973; Wanner, 1977). The serous or inner layer of periciliary fluid is probably secreted by the surface epithelial cells (Oliver et al, 1975; nadel et al, 1979; Welsh, 1983). Inflammatory processes, allergic reactions, cystic fibrosis, circulatory failure, and respiratory tract neoplasms all tend to increase the volume and change the character of the secretions from those normally produced. Furthermore, a striking increase or decrease in mucous viscosity affects mucociliary clearance (Barton and Lourenço, 1973), and this is probably one reason why there is such a high incidence of pulmonary infection in patients with these diseases. Alveolar lining fluid contains immunoglobulins G and A and small amounts of complement. Functionally, the fluid is weak in opsonins. Recent data indicate that alveolar surfactant serves as an opsonin and enhances in vitro phagocytosis and intracellular killing of *Staphylococcus aureus* by alveolar macrophages (O'Neill et al, 1984).

Lysozyme, one of the most well-characterized antimicrobial substances found in respiratory tract secretions of humans, attacks muramic acid, a constituent of all bacterial cell walls. It is more effective against gram-positive bacteria than against gram-negative bacteria; the decreased susceptibility of gram-negative organisms is a consequence of the outer, mainly lipoprotein layer of their cell walls, which protects the inner muramic acid-containing portion (Weiser et al, 1969). The combined action of antibody and complement on the outer wall of the gram-negative bacteria exposes the inner layers to the enzymatic action of lysozyme.

Interferon was discovered in 1957 and found to be a potent antiviral substance (Isaacs and Lindenmann, 1957). It has been used to treat viral diseases and malignancies with initially promising results (Cesario, 1983). Interferons are glycoproteins and constitute part of the natural defense system of vertebrate species, from the fishes up to and including humans.

Interferons are extremely potent substances and, in addition to their antiviral effects, have antiproliferative, antitumor, and immunoregulatory actions (Epstein, 1981). Interferon has been found in secretions from the respiratory tract and is known to be produced by alveolar macrophages (Acton and Myrvik, 1966) and sensitized lymphocytes (Epstein et al, 1971).

The complement system is composed of more than 20 component plasma proteins that participate in a sequential, or "cascading", reaction that results in active products that are both cell bound and in the liquid phase. The cell-bound complexes contribute to membrane lysis and cell death and the liquid phase ingredients contribute to the humorally mediated portion of the inflammatory response (Colten et al, 1981; Perez, 1984). Only small amounts of complement components have been found in respiratory tract secretions of normal persons. However, when vascular and epithelial membrane permeability are increased during inflammation, it is possible that complement constituents of plasma have less restrained access to the interstitial tissues, alveolar spaces, and airways. In this manner, they may contribute to the local defenses of the lungs.

In addition to the antimicrobial substances that are naturally present in the secretions lining the respiratory tract, both nonphagocytic and phagocytic cell populations also contribute to the defense of the lungs and the rest of the body. The surface epithelium and basement membrane of the airways and terminal respiratory units impose a physical barrier that guards the interior of the lungs from penetration by infectious agents and toxic substances. There are three types of "professional scavengers" that are constantly on duty in a state of functional readiness. Two types are in the bloodstream (polymorphonuclear leukocytes and monocytes), and one type is in the tissue throughout the body (tissue macrophages, including alveolar macrophages). These cells engulf and kill microorganisms (Stossel, 1974) by using their lysosomal enzymes and toxic oxygen radicals. Alveolar macrophages are common within the liquid film lining the alveolar surface; they are avid phagocytes and are regarded as the chief guardians of the extensive surface of the terminal respiratory unit (Hocking and Golde, 1979). Besides their role as scavengers, pulmonary macrophages have many other important biologic functions, both defensive and nondefensive (Nathan et al, 1980; Cohen, 1979). The defensive functions involve the humoral and cellular pathways of the immune system and many components of the nonimmunologic system. Through the synthesis of chemotactic factors and mediators, the alveolar macrophage also plays an important role in the pathogenesis of inflammation. Finally, pulmonary macrophages participate in a variety of nondefensive functions involving phagocytosis of nonmicrobial particles and the synthesis of arachidonic acid metabolites, platelet activating factors, fibroblast activating factors, enzyme inhibitors, and binding proteins.

The lungs are furnished with biochemical systems to defend against released enzymes and oxidants from inflammatory reactions in neutrophils and macrophages. Among the proteases are elastase and collagenase. Of the protease inhibitors present in human serum, alpha-1-antitrypsin is the most important. Lack of this inhibitor is associated with panlobular emphysema from autodigestion of the lungs by the proteases. To combat the effects of locally generated oxidants (peroxide anion, hydrogen peroxide, hydroxyl radical) the lungs are equipped with several intracellular and extracellular protective mechanisms, including the antioxidant enzyme systems superoxide dismutase, catalase, glutathione peroxidase, nicotinamide-adenine nucleotide phosphate, and cytochrome c reductase, and the oxidant-free radical scavengers alpha-tocopherol and ascorbic acid.

Specific defense (immunologic) mechanisms are latent until activated by natural exposure to foreign antigenic material or by artificial induction (vaccination). Thus, specific defenses are acquired (in contrast to innate nonspecific defenses) and are considered synonymous with immunologic defenses because they involve highly specific stimuli that cause equally specific responses. The immunologic defenses enhance or amplify, both quantitatively and qualitatively, the capacities of nonspecific defense mechanisms (eg, specific opsonizing antibody increases uptake of microorganisms by phagocytes and specifically sensitized T-cells increase intracellular killing of tubercle bacilli by macrophages through release of lymphokines that activate phagocytosis). Lymphoid aggregations in the respiratory tract can participate in immunologic responses, provided a suitable antigenic stimulus reaches them. An antigen is taken up by circulating monocytes or tissue macrophages for presentation to genetically precommitted antigen-reactive lymphocytes. These precursor lymphocytes are then induced to proliferate and differentiate into either sensitized T-cells, sensitized B-cells or (usually) both by a process that is controlled by immuno-regulatory T-cells. The newly sensitized lymphocytes mount effector responses that include synthesis and release of antibodies by fully differentiated B-effector cells or of potent soluble products (lymphokines), and they direct cell-mediated cytotoxicity by completely differentiated T-effector cells.

There are substantial differences among the concentrations of various immunoglobulins at various levels of the respiratory tract (Kaltreider, 1976, 1984). Secretory IgA is the predominant immunoglobulin in samples from the upper respiratory tract, whereas IgG is most abundant in bronchoalveolar lavage liquid. Secretory IgA differs from serum IgA in that the secretory immunoglobulin is a dimer of two IgA molecules linked by a secretory component and a joining chain. Secretory IgA complex has a practical advantage over immunoglobulins of other classes in that it is more resistant to proteolysis. The precise role of secretory IgA in the defense of the lung is not known. Among its possible activities is complement-dependent virus neutralization; when bound with antigen, its activities include agglutination of microorganisms, neutralization of toxins, and reduction of the attachment of bacteria to epithelial surfaces. IgG appears to be an important immunoglobulin in the lower respiratory tract; it produces particle agglutination, bacterial opsonization, complement activation, and toxin neutralization (Kaltreider, 1976). IgM is found in relatively low concentrations in respiratory tract secretions and is also of unknown function. The role of IgE in immediate hypersensitivity reactions that may involve the lung (eg, asthma) is well recognized. But the role of IgE in the defense of healthy lungs remains a mystery.

Relatively little is known about the local expression of cell-mediated immunity in the lungs. From 65 to 80 per cent of recoverable lymphocytes (by bronchoalveolar lavage) from healthy subjects were T-lymphocytes (Hunninghake et al, 1979). These cells can express both cytotoxicity and lymphokine generation. Sensitized cytolytic T-cells appear to contribute to the eradication of viral infection by local containment and lysis of virus-infected cells (Kaltreider, 1984). Lavaged lymphocytes from patients with active pulmonary sarcoidosis spontaneously released macrophage migration inhibitory factor (Crystal et al, 1981) and interleukin-2 (Pinkston et al, 1983), a substance that causes responsive T-cells to proliferate. Macrophages and lymphocytes cannot function effectively without one another. Macrophages process antigens for subsequent presentation to immuno-competent lymphocytes. Macrophages are the key to the induction of an immune reaction. Lymphocyte-macrophage interactions are indispensable to the expression of cell-mediated immunity (Unanue, 1980). This partnership is beneficial because lymphocytes are not equipped to phagocytose and kill microorganisms,

whereas macrophages have these capabilities. Certain lymphokines serve to attract macrophages to a particular site, to keep them at that location, and above all, to activate them to kill organisms more efficiently.