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Presentation of Pneumonia

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Clinical Presentation

Dyspnea

The sensation of shortness of breath—dyspnea, or breathlessness—characterized by tachypnea and variable degrees of hypoxemia and hypocapnea is a characteristic clinical phenomenon of pneumonia and occurs even in the absence of pleuritic pain or fever. The alveolar hyperventilation reflected by the hypocapnia has been found to persist in patients with lobar pneumonia even after arterial hypoxemia is eliminated with oxygen therapy. A process of elimination can be observed in the long-standing efforts to attribute the sensation of breathlessness to objective criteria. Classic breath-holding studies have shown dyspnea to be alleviated by a rebreathing maneuver or with inspiration of oxygen and carbon dioxide gas mixtures that resulted in no improvement in either arterial hypoxemia or the associated respiratory acidosis. Thus linkage to chemoreceptor activity has been largely unsuccessful.

Almost all of the afferent impulses arising from airway and intrapulmonary receptors are carried in the vagus nerves. Classic studies in dogs have reported that the tachypnea of lobar pneumonia was entirely dependent on intact vagi. Subsequently, stretch receptors of vagal afferents were shown to be of significance but not critical. More recent studies with differential block suggest that the lung receptors that are excited are those innervated by nonmyelinated vagal afferents.¹ These J receptors lie in the interstitial space of the lung at the alveolar level. The inflammatory mediators presumably act to depolarize these chemically sensitive non-myelinated nerve endings. It has been suggested that J-receptor stimulation alone or in conjunction with the stimulation of irritant receptors is responsible for the tachypnea of pneumonia. Others, meanwhile, have suggested the importance of mechanoreceptors in the thoracic wall, including joint receptors, tendon organs, and muscle spindles.

Muscle spindles, especially prominent in the intercostal muscles in contrast to the diaphragm, are found within the special intrafusal fibers that are arranged in parallel with the main, extrafusal muscle fibers. The annulospiral receptor would be stretched (and stimulated) if shortening of the extrafusal fiber was impeded so it did not match the intrafusal muscle fiber shortening; enhancement of afferent impulses would then induce further extrafusal fiber contraction (length servo).² The contractile extrafusal fibers of a muscle receive the integrated output of the respiratory centers through alpha motoneurons, whereas the gamma motoneurons innervate the intrafusal fibers within the muscle spindles (fusiform system). Misalignment between these intra- and extrafusal systems was therefore suggested as a neuroanatomic mechanism of dyspnea.

Finally, the ongoing search was diverted from classic anatomic and physiologic concepts of cause and effect as both neurophysiologists and respiratory physiologists turned to concepts of the systems engineer. This diversion allowed a concept of appropriateness of response as perceived by the "respiratory center," be it volume or rate of gas flow or thoracopulmonary expansion (respiratory psychophysics) that has continuously gained support and remains at the forefront in current models of the pathogenesis of dyspnea. A unifying concept of the mechanism of detection of both resistive and elastic loads proposed a role for several responsible receptors: probably joint receptors and the muscle spindle to detect volume change, and the Golgi tendon organ to detect tension and resulting airflow. The methodology involves parameters of magnitude scaling and threshold discrimination of perceived effort as psychophysical measurement techniques for assessing the magnitude of "length-tension inappropriateness."^{3,4}

The restrictive lung disease of pneumonia is therefore characterized by tachypnea and hyperventilation attributed to inappropriately increased drive with an increased sense of effort from mechanical changes in the lungs and altered afferent length-tension signals. It is further mediated by enhanced pulmonary reflexes from inflammatory changes in the lung parenchyma. There is also a mechanism of adaptation of respiratory control mechanisms to the increased elastic load in order to minimize the work of breathing. It has been suggested that dyspnea is probably not due to respiratory muscle fatigue in pneumonia, though fatigue may increase the intensity of dyspnea.

In conclusion, no specific peripheral site (dyspnea receptor) is uniquely essential for load detection or perception, but integrated afferent pathways and sites of dyspno genesis exist that may include the cerebral cortex and central motor command.⁵ There is now considerable evidence that discharges from intramuscular receptors project to the cerebral cortex. It is also apparent that much of this confusion as to the mechanism of breathlessness arises from the qualitative description of the sensation and the inability to quantitate accurately what in fact may be different sensations.

Cough

Cough is both a diagnostic sign and symptom of most pulmonary diseases and an indicator of the adequacy of an important pulmonary defense mechanism. It has also been the basis for a lucrative and controversial field of pharmacology: the efforts to suppress a sometimes annoying and debilitating symptom when its functional value is either inapparent or insufficient to tolerate its associated discomfort. More than 600 formulations of cough remedies are on sale in the United States, many on an over-the-counter basis; this class of drugs is the fifth most frequently prescribed.⁶

Cough is characterized by a preliminary deep inspiration, facilitated by glottal dilation, that is highly variable in magnitude but generally not exceeding 50% of vital capacity. This phase is followed by a forced expiration against a closed glottis for the initial 0.2–0.3 second. This period of closure is considered functionally to enhance the effectiveness of the cough but is thought to vary in an unknown manner in the presence of disease and in the elderly. The explosive phase of coughing is no less effective if the glottis remains open, however, and patients with tracheostomies can produce an efficient cough provided there is normal respiratory muscle strength.⁷ The intrathoracic and intraabdominal pressures are elevated to 50–100 mm Hg, achieving expiratory flow rates exceeding 6–7 L/second. This step is again facilitated by active glottal participation, in this phase dilation. The air is explosively emitted at speeds up to 12 meters/second, causing vibration of the upper airways and accounting for the sound that accompanies the cough. The sound is influenced by the violence of the oscillations resulting from forces as high as 300 mm Hg and achieving speeds over 200 meters/second; the compliance of the tissues which is influenced by the degree of inflammation and the nature and quantity of secretions.

The stimuli to the respiratory tract that cause coughing also cause reflex bronchoconstriction in the periphery that may last a minute or more. As the glottis opens, intraluminal pressure within the airways rapidly falls; pleural pressure remains high, however, setting the conditions for dynamic compression of central airways, which accounts for most of the volume change in the airways. Thus the efforts of coughing are superimposed on constricted airways, resulting in greater velocity and therefore turbulence of gas flow, loosening particles attached to mucosal surfaces. It also serves to stabilize the airway walls, enhancing the strength of the cough and minimizing dynamic collapse. In the presence of respiratory muscle disease or expiratory muscle weakness, the maximum expiratory flow rate is decreased owing to the reduced dynamic airway compression. The clearance of mucus is then impaired because of the decreased linear velocity of airflow and shearing force, thereby predisposing to atelectasis and pneumonia.

The neural interactions are intricate, with the mediation of axon reflexes along branches of the sensory end-organs that release neuropeptides, such as substance P and other neuropeptokinins. The motor pathway also releases neuropeptides, such as vasoactive intestinal peptide, a smooth muscle relaxant. Thus the bronchomotor response to cough stimuli is a complex balance of constrictor and dilator influences. The observation has been reported that inhaled β -adrenergic drugs may be efficacious in the treatment of cough, but their action may be elaborate, affecting epithelium, mast cells, or airway vascular beds rather than just simply relaxing airway smooth muscle.⁸

The high air velocity necessary to shear mucus from the airway walls can be achieved only down to the sixth or seventh generation of bronchi. Its effectiveness is further dependent on the viscosity and other physical properties of the mucus. The degree of adhesion of the mucus to the airway epithelium is thought to be influenced by both its lipid components and the degree of hydration. Moreover, the underlying periciliary fluid layer may greatly facilitate mobilization. The actual thickness of the mucous layer is also important. It appears essential that an increased amount of mucus (hypersecretion) is present for cough to be an effective clearance mechanism. Cough is not thought to play a role in clearing normal secretions. The lack of detailed information about the significance of the viscoelastic properties of mucus leaves our attempts to facilitate cough and alter the properties of secretions not only empiric but highly speculative.

Involuntary coughing is an entirely vagal phenomenon related to inflammatory or mechanical abnormalities in the upper airways. A variety of chemical and mechanical irritants can cause coughing. Coughing cannot be induced from the smaller airways and alveoli. Teleologically, it can be reasoned that cough at this level would be ineffective because gas could not be made to move fast enough. Although the larynx is observed to be more sensitive to cough stimuli than the tracheobronchial tree, analysis of the cough mechanisms of the latter is simpler because the sensory innervation of the tracheobronchial tree is not as complex as that of the larynx (Table 7.1).

The cough receptors are variously identified as myelinated irritant and nonmyelinated nerve terminals within the bronchial epithelium. The rapidly adapting receptors are concentrated on the walls of the larger airways and are sensitive to topical anesthesia. They have vagal myelinated fibers; and if vagal conduction is blocked, the cough reflex is inhibited. These receptors decrease with age and loss of the cough reflex. The afferent pathways for the cough reflex pass up the vagal nerve fibers to the medulla oblongata, where they relay in or near the nucleus of the tractus solitarius. From here on, where they connect to the brainstem respiratory complex is unknown; but this "cough center" is presumably the site of action of some antitussive drugs such as codeine. The central

TABLE 7.1. Afferent nerves associated with cough reflex.

Sensory nerve characteristics	Location
Myelinated receptors	
Irritant—mechanical, chemical	Mucosal surface of larynx, extra- and intrathoracic airways
Stretch	
Rapidly adapting: intraepithelial—mechanical	Mucosal surface of proximal extra- and intrathoracic tracheobronchial tree
Slowly adapting: smooth muscle—length change	Smooth muscle of proximal extra- and intrathoracic bronchial tree
Nonmyelinated receptor	
C-fiber—chemical	
Bronchial	Mucosal surface of larynx, proximal extra- and intrathoracic airways
Pulmonary (J receptors)	Peripheral airways; also inhibition

nervous system (CNS) control of coughing is characterized by the ability to voluntarily initiate coughing. Thus patients with brainstem damage, although lacking a cough reflex, can still voluntarily induce coughing to clear the upper airways. Hypoxia, if severe enough, can inhibit the cough reflex through a central rather than a peripheral action via the chemoreceptors.

Pulmonary C-fiber receptors, also called J receptors, can inhibit the cough reflex. For nearly all lung conditions associated with coughing (e.g., airway inflammation, responses to allergens, infections) the magnitude of the cough reflex depends on this interaction. Similarly, therapeutic efficacy of various antitussive drugs may also depend on their selective action on the reflexes. Thus a drug that stimulates C fibers might be antitussive.

There are several mechanisms proposed for enhancement of the cough reflex following infection. The most apparent is a result of epithelial denudation, exposing afferent nerve endings and thereby enhancing their accessibility to mechanical or chemical stimuli. The infection itself results in the release of inflammatory mediators, which also may serve to sensitize sensory receptors directly and by enhancing epithelial permeability. A similar mechanism of “up-regulation” due to an increase in bradykinin has been suggested for the cough associated with the administration of angiotensin-converting enzyme inhibitors.⁹ With pneumonia or early pulmonary edema, irritant receptors may be stimulated as airways become distorted by pressure from surrounding fluid-filled alveoli. It has been further suggested that when there is consolidation of a large mass of lung, as with lobar pneumonia, the cough may be due to the nonexpansibility of that part of the lung, with distortion of the trachea and main bronchi triggering cough receptors.

Both mucous glycoprotein and serum transudate are present in normal bronchial secretions, but the concentration of glycoprotein mucus is greater than that of serum transudate. A normal tracheobronchial tree responds to infection by increasing the concentration of both mucus glycoprotein and serum transudate in almost similar amounts. In addition, there is a shift in the type of mucous glycoprotein to a more sialylated and sulfated form. The danger of successful mucolytic treatment, given systemically or by aerosol administration (which perhaps fortunately has not yet been clearly achieved), is that destruction of the viscoelastic properties of mucus would prevent its effective clearance by cough. On the contrary, it may be argued that after finding low viscoelasticity during the assessment of physicochemical properties of mucus agents that promote restructuring or cross-linking would be more appropriate. Under such conditions, a mucospissic agent should then be given to optimize cough efficacy. Moreover, the rheologic characteristics favoring mobilization of mucus by the shearing force of a cough do not appear to be the same as those that enhance mucociliary clearance, further complicating the design and choice of mucolytic agents and expectorants.

Fever

Thermogenesis and Pyrogens

Body temperature is normally rigidly maintained within a narrow range of 97°–99°F, made possible by the existence of elaborate regulatory mechanisms that control an apparatus geared to the efficient containment or dissipation of the heat that results from the body's metabolic and biologic processes. The febrile response of pneumonia, characteristic of infection, is just one of a variety of immunologic, inflammatory, and malignant processes capable of disrupting this homeostatic state. Thus temperature elevation (or depression), though a nonspecific manifestation, has been an enduring clinical prerequisite for the diagnosis of pneumonia.

Pyrogens, exogenous or endogenous, are substances that alter the set-point of the thermoregulatory processes governed by a controller in the region of the rostral preoptic portion of the hypothalamus. Neural influences, however, are not limited to a specific anatomic site. A circadian and other thermal biorhythms exist, as illustrated by body temperature alterations associated with the sleep–wake, menstrual, and activity cycles. The clinical significance of the thermal diurnal rhythm lies in its exaggeration or elimination as a result of infection.

Contemporary thinking is that, except for the continuous fevers of pneumonia or CNS damage, evaluation of the febrile pattern is without value. The classic febrile patterns remain in the medical students' core curriculum, however, along with the associated manifestations of "night sweats" and leukocytosis. The medical students' dilemma of discerning

the meaning and correlation of restrained, quotidian, double quotidian, tertian, quartan, biphasic, intermittent, diurnal reversal, Pel-Ebstein, and Jausch-Herxheimer fevers are best forgotten. In today's hospital environment, these fevers can most likely be attributed to variations in oral, rectal, and axillary, or the unpredictable timing of, temperature-taking. Thus the technical and labor-related problems of clinical thermometry are perhaps most often responsible for typical or atypical patterns of this vital sign.

Chemical pyrogens of endogenous origin, including the cytokines—interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-2 (IL-2), tumor necrosis factor (TNF), interferon—and prostaglandin E_2 (PGE_2), are those best studied; by definition, they are capable of exciting the temperature controller directly. The best known exogenous pyrogen, endotoxin (the lipopolysaccharide complex in the cell wall of gram-negative bacteria), acts on the hypothalamus directly and causes endogenous pyrogen release from leukocytes, phagocytes, and other cells.

The increase in temperature causes an increase in all metabolic reactions (Q_{10} effect) (VO_2 changes about 11% per degree centigrade change in core temperature) and the attainment of a new homeostatic state. With phasic changes in pyrogen concentration as a result of biologic host factors or treatment with antibiotics or antipyretics, the original set-point returns and defervescence occurs as heat loss responses such as sweating are put into play. Approximately 100 ml of water must be evaporated to effect or prevent a 1°C fall or rise in temperature, respectively.

Pyrogenic responses are also mediated by the muramyl dipeptide component of the peptidoglycan layer of the cell wall in gram-positive organisms, which although also present in gram-negative bacteria is not as potent or abundant as their endotoxin; the biologic activity of the endotoxin lies in the lipid A moiety. Cell walls of fungi are also pyrogenic, but fever with viral infections appears to be exclusively a result of their activation of macrophages with subsequent release of inflammatory mediators acting as endogenous pyrogens.¹⁰ Fever, however, is not a measure of pathogenicity, as the toxicity of endotoxin does not depend on the infectivity of the organism. Severe febrile reactions can be associated with pneumonias produced by bacteria of low pathogenicity. Patients with fatal septic syndromes and high fever may have otherwise trivial infections with negative blood cultures.

An awareness is now growing of the potential benefits of fever and fever therapy and the possible detrimental effects of antipyretics. It is argued that if fever was not beneficial it would not have survived through phylogeny, as it is a most metabolically expensive phenomenon, requiring a 20–30% increase in energy consumption for an increase in body temperature of $2^\circ\text{--}3^\circ\text{C}$. Moreover, repeated reference is now made to infected lizards, which as poikilotherms move to a rock to “bask in the sun” in order to elevate their body temperatures, as their survival is

TABLE 7.2. Effects of fever on immunologic responses.

Polymorphonuclear leukocyte function
Motility
Enhanced chemotaxis
Potentiates migration
Depression of emigration
Phagocytosis—increased killing rate
Mononuclear phagocyte function
Proliferation
Increased responsiveness to cytokines
Phagocytosis
Increased killing zone, i.e., in warmer body regions
Cytokine production
Increased induction
Antibody production
Enhances response of B cells, i.e., priming by T-helper cells
Cell-mediated immunity
Increased generation T-helper and T-cytotoxic cells
Enhanced antigen recognition
Increased rate of IL-1, induced IL-2 release
Enhancement of IL-1/IL-2 cascade, i.e., higher rate and duration of secretion
Cytokine activity
Augmentation with blocking of suppressor cell generation
Optimizes complement activation

correlated with “fever.”¹¹ Thus reptiles and humans can regulate their body temperature by behavior as well as by the more classic physiologic thermoregulatory mechanisms. It has been found that fever also is associated with better prognosis in homeotherms such as humans during bacterial infection, whereas hypothermia has been associated with higher mortality.

Fever appears to affect leukocyte function in regard to the containment of bacterial infection (Table 7.2) by accelerating leukocyte responses; that is, it potentiates migration of leukocytes into areas of infection, and after the migration the leukocytes are more likely to remain at the site of inflammation and increase their killing effect (cytotoxicity). Temperature elevation enhances the processes involved in initial antigen recognition, that is, antigen presenting and functional interaction between antigen-presenting B cells (B-APC) and T-helper cells. The specific events that follow, such as the rate of IL-1-induced IL-2 release, has been also found to be temperature-dependent. These complex immunologic consequences of fever may then account for the observed decrease in the severity of acute inflammation such as rhinitis in human subjects treated with local hyperthermia (warm humidified air).¹²

Cardiovascular Effects of Fever

In response to an increase in the set-point of the central thermostat, an apparent decrease in environmental temperature is perceived and the body's primary thermogenic response, shivering (shaking chills), is initiated. Further protective mechanisms designed to protect the core temperature then dominate, most importantly central regulation of the cutaneous circulation. Whereas endogenous pyrogens have both a direct and a central action on the cardiovascular system, it is the sympathetic nervous system, with its high level of tonic activity, that is critical for homeostatic control and the characteristic cutaneous and systemic hemodynamic alterations that distinguish the rising, plateau, and defervescent phases of fever.

Acute Phase

Tonic sympathetic activity raising cutaneous vascular resistance normally limits skin perfusion to 5–10% of the cardiac output. In concert with the increase in heat production (shivering, Q_{10} effect), heat loss is diminished by further elevation of the cutaneous vascular resistance and the consequent curtailment of flow. The surface area functionally available for heat loss is thus diminished as a result of precapillary arteriolar and venoconstriction, diverting blood flow from superficial to more central vascular beds. This situation is similar to the circulatory adaptations with congestive heart failure, which in part are accountable for the associated low grade temperature elevations observed. Thus although the rigor serves as an immediate thermogenic mechanism, unlike the vascular alterations it is not essential for the elevation of temperature.¹³ Furthermore, along with the withdrawal of vagal tone, the sympathetic discharge results in tachycardia and systemic vasoconstriction. However, the sympathetically mediated vasoconstrictor reflex to dependency is actively maintained. The net effect on flow is variable, serving to achieve the primary goal of maintaining the mean arterial pressure for organ perfusion.

Plateau Phase

As heat production attains its increased level, the thermoregulatory neurons allow the sympathetic tone to return to baseline levels, and cutaneous blood flow resumes its prefebrile levels. Heart rate may remain elevated as a result of a direct effect of elevated blood temperature on the sinoatrial node. Total peripheral vascular resistance (TPR) characteristically falls, and there is an increase in cardiac output in response to this decline in TPR and the residual elevation in sympathetic activity. The TPR falls as a result of the potent synergistic vasodilator actions of endogenous pyrogens, which are both direct and indirect through stimulation of the synthesis of prostanoid vasodilators. The action of IL-1 and TNF to diminish vascular smooth muscle responsiveness to catechols

further explains the refractoriness to pressor agents. The hepatic blood flow in particular increases and is associated with an outpouring of cytokines produced by its Kupffer cells.

The peripheral cardiovascular action of the endogenous pyrogens in part explains the dissociation of fever and hemodynamic profiles. With lobar pneumonia, the pulse rate and core temperature are initially highly correlated, but the first sign of deterioration is a progressive rise in heart rate not accounted for by a rise in temperature, which may even be falling. Relative bradycardia, however, has long been thought to characterize enteric fevers. The decreased left ventricular afterload resulting from the reduced TPR is not as readily available to the right ventricle above and beyond the normal high compliance of the pulmonary vascular bed. Therefore it is in patients with preexisting right ventricular dysfunction and its associated pulmonary circulatory adaptation that sudden overt right ventricular failure might develop during fever.

Recovery

The link between sudomotor stimulation and cutaneous vasodilation is maximal during this phase, and the skin is converted to an arteriovenous fistula, with achievable flow rates as high as 50–70% of the cardiac output. The skin has a highly capacious vascular bed that can accommodate flows as high as 7–8 L/minute. The mean arterial pressure declines further, and thermal homeostasis takes precedence over the nonthermoregulatory reflexes necessary for maintenance of driving pressure. When blood flow is redistributed to the skin's compliant vascular bed, the venous capacity in other regions must be accordingly reduced if cardiac filling pressure is to be maintained; thus it appears that central thermoreceptors, through the sympathetic nervous system, trigger visceral vasoconstriction.¹⁴ Ventricular performance returns to normal with decreased ventricular work and a return of both contractility and compliance to basal levels.

With pneumonia there is further complex interaction between thermoregulation and infection, as hypoxia elicits hypothermia. Teleologically, this adaptive response to decreased oxygen demand should promote survival and be beneficial for oxygen-sensitive organs such as the heart and brain. The heat loss observed in hypoxia is due to peripheral vasodilation. Furthermore, a normal thermogenic response to reduced temperature is depressed, as the set-point of the preoptic thermoregulatory neurons is altered. Arginine vasopressin has been suggested as the mediator responsible for this adaptation.¹⁵ The apparent benefits of hypothermia in response to hypoxia are (1) a shift of the oxygen dissociation curve to the left, enhancing oxygen loading in the lung with increased oxygen affinity of the hemoglobin molecule; (2) decreased metabolic rate (Q_{10} effect); and (3) avoiding cardiac and pulmonary work that results from increasing flow and ventilation and the costly energy expenditures in response to

hypoxic stimulation. Thus with pneumonia a complex integration of defense mechanisms to stress are operative, utilizing thermoregulatory control. A delicate balance is struck between immunologic imperatives, oxygen supply, and oxygen demand to minimize organ dysfunction and maximize survival.

Leukocyte Count

The classic reaction to bacterial pneumonia is mobilization of the marginated leukocytes as well as stimulation of the bone marrow. This response has been attributed to cytokine action, concurrent with alteration of thermoregulation, with a resultant leukocytosis greater than $15,000/\text{mm}^3$. Part of the definition of “atypical pneumonia” is failure of the leukocyte (WBC) count to exceed this value, which represents the upper limits of normal (95% confidence limit). The biorhythm for the WBC count is similar to that for body temperature, which can account for a variation in the WBC count of as much as 100% and in the differential count of 30%.

Physiologic leukocytosis under conditions of noninfectious stress is a well known phenomenon most readily reproduced in the laboratory by mental stress or exercise and in the emergency room by seizure activity.¹⁶ The WBC count of spectators and “bench-warmers” of a football game remains normal despite their excitement, whereas that of the players increases almost 300% (Fig. 7.1). This increase occurs despite the fact that the ball is in play only 8 minutes of the 60-minute game, and it

FIGURE 7.1. White blood cell (WBC) count increase in players following a football game. (Data from Edwards and Wood¹⁶)

persists over the 2 hours of actual playing time. The duration and intensity of playing time correlates with the WBC count. The differential count shows an increase in the polymorphonuclear neutrophilic cells (PMNs) and a decrease in the percentage of lymphocytes, which also appears to be a function of the duration and intensity of the effort. The onset and recovery may range from minutes to hours and are characterized by the absence of band forms (no “shift to the left”). Thus there is no apparent output from the bone marrow, which serves to differentiate this “stress” or “demargination” response from that of an infectious stimulus. Nutritional factors, alcohol intake, and age have been associated with an impaired WBC response; and with pneumonia a “delayed” leukocytosis may be observed during recovery.

The leukocyte count resulting from viral infections in inoculated human volunteers who became ill tended to result in WBC counts greater than $10,000/\text{mm}^3$, associated with an initial increase in neutrophils followed by a rise in lymphocytes after an initial fall.¹⁷ These responses appeared to be a function of the severity of the illness. Moreover, the results did not appear specific for a particular virus. It was also concluded that leukocytosis of $10,000$ – $13,000/\text{mm}^3$ at the onset of illness occurs commonly enough with viral respiratory disease that the WBC count is not useful for differentiating bacterial from viral respiratory infections. It was suggested, however, that subsequent leukopenia favors a viral etiologic agent and leukocytosis a bacterial etiologic agent.¹⁷ As previously noted for thermoregulation, leukocytosis is similarly a manifestation of the invasion or of activation of host macrophages that stimulates endogenous pyrogen release. In addition, cell death and subsequent tissue necrosis also result in pyrogen release and leukocyte mobilization.

An assessment of the WBC count and differential therefore does not have the commonly implied benefit of allowing differentiation between bacterial and nonbacterial disease. Using a WBC count threshold value of $15,000/\text{mm}^3$ for bacterial disease and less than $15,000/\text{mm}^3$ for nonbacterial disease, a study in children demonstrated 53% false positivity, 22% false negativity, and only 49% sensitivity.¹⁸ The differential count fared even less well primarily because of an increased number of band forms with nonbacterial disease. Others have concluded that, statistically, an observed change in a patient's serial WBC differential is much more likely to be due to technical factors than to disease and can account for more than 75% of the total variance encountered.¹⁹ It appears that frequent repeat differential counts are not only an unnecessary expense but an almost worthless indulgence.

Physical Examination—Auscultation

The production of sound at the surface of the chest wall generated within lung parenchyma and airways is a complex process. Efforts at exploring the scientific basis of auscultation have utilized recorders and computer-

ized digital analyzers; although failing to displace the stethoscope, these methods have clearly indicated the poor correlation between noninvasiveness and specificity or sensitivity. A representative investigation into the agreement by observers on the presence or absence of physical signs has shown that interobserver repeatability of respiratory physical signs falls midway between chance and total agreement.²⁰ Similar studies of history taking have also shown considerable interobserver and intraobserver error for symptoms of cough, sputum production, and chest pain.

When the lung between the trachea and the point of auscultation is airless, the higher frequencies, including the formants of vowels, are transmitted, and speech becomes intelligible (the clarity of e.g., say the number ninety-nine). This process is known as *bronchophony*. A study of the frequency analysis of voice sound recorded from the chest wall of pneumonia patients and normal subjects has explained the e to a change over an area of consolidation that should allow the higher frequencies through.²¹ It was found that even though higher frequencies were transmitted by consolidated lung (1000 Hz rather than 400 Hz) the higher frequencies of the sound e (2000–3500 Hz) did not pass, so the sound becomes an a; hence the apparent paradox of bronchophony was clarified.²¹

Breath sounds are produced in the turbulent zone of the respiratory tract from the mouth to the segmental bronchi. Normal lung parenchyma acts as an acoustic filter that attenuates and selectively filters breath sounds, normally allowing penetration of only low-frequency sounds, and their passage to the surface of the chest wall. As a result of consolidation, sounds produced in the large airways are much less altered, thus producing bronchial breathing, during which the higher frequencies are better preserved. The sounds heard on auscultation are probably generated at the level of the trachea. The low frequencies fall below the threshold of audibility early during expiration, but the high frequencies are audible throughout expiration as well as inspiration. Because the whisper lacks the low frequencies selectively transmitted through the normal chest, it is inaudible over air-containing lung. The high-pitched components of the noise of turbulence and the formants of vowels are, however, transmitted through airless lung, so whispered speech (*whispering pectoriloquy*) becomes intelligible.²² It occurs under the same conditions as bronchial breathing and bronchophony and completes the triad of auscultatory signs of consolidation.

Crackles are produced by the sudden equalization of gas pressure and snapping open of air passages. It has been demonstrated that, at low lung volumes, dependent airways close.²³ Atelectasis is a direct consequence of such ventilation below closing capacity, and its occurrence is enhanced by prolonged shallow breathing such as occurs with pneumonia. The resulting decrease in compliance, or increased elastic recoil of the lung, leads to an increase in transpulmonary pressure. Crackles are then

generated with the reopening of the distal atelectatic lung units as they are ventilated at end-inspiration. The more crackles, the greater the number of collapsed peripheral lung units.²³

Pleural disease may also produce crackling, which at times is indistinguishable from that produced by parenchymal disease. A pleural crackle (*rub*) is produced by sudden jerky movements of the pleural surface momentarily delayed by friction.²⁴ The individual components of the crackling are produced by a sudden release of tangential tension in a superficial portion of the lung momentarily arrested in its sliding movements by a frictional force between the visceral and parietal pleura. These sounds may be expiratory as well as inspiratory, which serves to distinguish them from pulmonary crepitations. Fluid in the pleural space increases the acoustic barrier, and the breath sounds become fainter or inaudible over the chest, even in the presence of underlying consolidation. At the upper margin of a pleural effusion the thin layer of fluid still permits transmission of higher sound frequencies, giving the breath sounds a nasal quality termed *egophony*.²² The bubbling sounds heard in the presence of copious secretions are presumably formed by bubbling of air through liquids, which repeatedly form a thin film that breaks explosively. In patients with pneumonia, as with other conditions such as pulmonary edema, this bubbling occurs in the proximal airways, not at the alveolar level. The "inspiratory squawk" combines a crackle followed by a brief wheezing sound. Such sounds have been reported in patients with hypersensitivity pneumonitis. The sounds result from sudden opening of airways of differing sizes.

The value of auscultation, though limited, has been greatly enhanced by standardization of nomenclature corrupted by the passage of time, differences in translation, and qualitative descriptions.²⁵ Efforts to relate lung sounds to physiologic or pathophysiologic events rather than to anatomic changes has also enhanced their value.²² Correct diagnostic testing is ensured by both a careful history and competent physical examination. Repeated studies have shown that pleural rub, decreased percussion note, and reduced breath sounds have physician agreement well in excess of chance, whereas signs such as whispering pectoriloquy and tactile vocal fremitus show agreement that is only a little better than chance.²⁶ Moreover, a comparison of diagnoses based on clinical findings with true diagnoses showed that 28% of diagnoses by physicians were incorrect.²⁶ It was further shown that the more often physicians differed from their peers regarding the presence or absence of signs, the more likely they were to make an incorrect diagnosis. Finally, although such variability appears unacceptable for diagnostic and therapeutic decisions, it has been pointed out that it is about the same as that found with clinical data collection in general, including interpretations of chest roentgenograms, and that it is with good reason that physicians rarely use single observations for clinical decision making.²⁷

Pleuritic Chest Pain

Sharp, stabbing, localized pain related to inspiratory effort has been a classic sign of pneumonia commonly termed *pleurisy*. The visceral pleura does not have pain fibers, which has greatly clarified the mechanism of pleuritic chest pain and focused attention on the parietal pleura, which has abundant pain fibers. Several theories of the origin of pleuritic chest pain have been proposed.²⁸ The oldest and favorite of clinicians attributes the pain to friction produced by the opposition and movement of the two roughened, inflamed pleural surfaces. It has always been somewhat bothersome that pain is often present without, and independent of, the presence of a pleural friction rub. In fact, pain may be at its peak with a breathhold at the maximum inspiratory position only to be alleviated with an expiratory maneuver. Others have attributed the pain to contraction of hyperalgesic intercostal muscles. The pain has also been attributed to the traction of tissues immediately underlying the parietal pleura also served by the distribution of the intercostal nerves. Autopsy studies have failed to shown consistent evidence of pleuritis that would account for the pleurisy in fatal cases of lobar pneumonia.

Most observers have concluded that pain is initiated as the chest expands and exerts tension on the sensitive, edematous (if not inflamed) parietal pleura. With inspiration, the increasing tension brings the pain to its peak, and it subsides with expiration. Thus the tendency of the pain to be greatest in the lower thorax is attributed to the partitioning of the tidal breath and greater tension on the parietal pleura in this area. Such a mechanism is supported by the persistence of pain in the presence of an ipsilateral pleural effusion in patients with pneumonia or as reported after a therapeutic pneumothorax in patients with tuberculosis.

The lower chest, including the outer segment of the diaphragmatic pleura, is innervated by the lower six intercostal nerves, which also supply the abdominal wall. Pleuritic pain may therefore be referred to the abdomen. It is a surgeon's nightmare to have performed an exploratory laparotomy when the diagnosis is actually pneumonia. The central portion of the diaphragm is innervated by the phrenic nerve, which enters the spinal cord through the third, fourth, and fifth dorsal roots. Such pain may be referred homolaterally to the neck and tip of the shoulder (Capps' area).

It must be stressed that not all chest pain seemingly related to inspiration is pleuritic in origin. Pain in the chest wall that is musculoskeletal in origin must be differentiated. Classically, cough may result in an athlete's muscle strain or tear of an intercostal or "accessory" muscle of respiration because of the force involved—even a fracture of the bony or cartilagenous portion of a rib. Such coughing does not have to be violent; it may be only a minor, subtle episode in a mechanically predisposing position. The pain may be indistinguishable from one that is pleuritic in

origin, timing, intensity, or quality. Its origin from chest wall structures is suggested by localized tenderness to direct palpation. Furthermore, on the basis of autopsy studies, roentgenograms show only about half the rib fractures that actually exist.

The mechanisms of pain production have been reviewed elsewhere.²⁹ The initiation of pain is the result of tissue injury with subsequent release of inflammatory mediators, including kinins, prostaglandins, and potassium, which stimulate pain receptors.²⁹ According to the specificity theory, the pain impulses are transmitted by fine myelinated and unmyelinated fibers contained in peripheral nerves. The intensity of reverberation in central circuits determine pain intensity; or as also proposed, the intensity of peripheral receptor excitation beyond some critical threshold level is determinant of pain intensity. Yet another thesis of "gate control" suggests a critical ratio between the inhibitory effects of fast-transmitting myelinated versus the enhancing effects of slow-transmitting unmyelinated fibers. Inflammatory mediators favor stimulation of the receptors of unmyelinated fibers. The neurotransmitters acting as synapses to enhance impulse conduction are unknown, but evidence has pointed to substance P. This neuropeptide is concentrated in pain-mediating neural cell bodies and terminals. This unadecapeptide has also been suggested as a chemical mediator of airway hyperreactivity associated with asthma. It may be responsible for pain, along with other, yet unspecified polypeptides, by influencing differentially the activity of myelinated and unmyelinated pain fibers.

In summary, because there are essentially no pain fibers in the lung parenchyma or visceral pleura the pain associated with pneumonia must be attributed to other structures. Its exacerbation by inspiration, coughing, limb movement, and postural changes tends to cause unilateral splinting and tachypnea with small tidal breaths influencing the movement of the chest wall. The altered partitioning of the tidal breath may contribute to the sensation of dyspnea, the appearance of atelectasis, and the auscultatory findings of crackles; it may also have a significant adverse effect on lung clearance mechanisms and gas exchange. Analgesics are indicated for these reasons and for symptomatic relief.

Radiologic Studies

The routine posteroanterior and lateral radiographs of the chest remain the initial studies for the radiologic diagnosis of pneumonia. Although a chest radiograph may be normal during early pneumonia, it is uncommon. Radiographic findings indicate definite or probable pneumonia in 2.6–28.0% of adults seen in various emergency rooms for acute respiratory illness. Several modern imaging modalities have been applied to the diagnosis and assessment of pneumonia. Among the radiologic armamen-

tarium shown to have a real or potentially significant clinical role in chest diseases are computed tomography, nuclear medicine (nucleology), ultrasonography, magnetic resonance imaging, and digital radiography. In particular, stratagems have been developed utilizing these techniques in the intensive care unit patient.

Chest Radiography

The pneumonias, by convention, have been divided into three types: lobar pneumonia, bronchopneumonia, and interstitial pneumonia. This division was based on postmortem findings and adapted to radiographic description. It is not surprising therefore that the descriptive utility frequently seems forced and artifactual, usually adding little specificity to the diagnosis. All pneumonias, regardless of etiology, present a spectrum of radiographic features resulting in a considerable overlap for specific bacterial infections and even making the differential diagnosis of viral from bacterial pneumonia inaccurate strictly on the basis of their radiographic appearance.³⁰ Despite this problem, continued efforts are made to relate specific pathogens to radiographic characteristics of focal and diffuse processes. With *Legionella* pneumonia, for example, a study of 14 fatal cases found no lobar predilection, whereas others have reported a predilection for the lower lobes.³⁰

Organisms causing atypical pneumonia are by definition more likely to cause bilateral interstitial infiltrates without pleural effusions. However, pleural effusions are reported in 24–63% of cases of *Legionella*.³¹ Radiographic features, similar to the “characteristic” clinical presentations for “atypical” pneumonia, are just as unreliable for distinguishing it from “typical” bacterial pneumonia, and this syndrome classification is falling into disuse. Upper lobe pneumonia has the same differential diagnosis as that for lower lobe pneumonia. Although pyogenic and *Mycoplasma* pneumonias occur more often in the lower lobes, their occurrence in the upper zone is still common enough that radiographic specificity is lost. Involvement of the upper lobes alone is uncommon with either staphylococcal or gram-negative infections. The most common diffuse pneumonias are those caused by viral agents; and in immunocompromised hosts with acquired immunodeficiency syndrome (AIDS), *Pneumocystis* is the first consideration. Confluence of patchy airspace infiltrates is seen with both *Pneumocystis* and influenzal pneumonia and, moreover, may be localized to a single lobe with segmental consolidation.

The relative sparing of the lung periphery seen in cardiac or noncardiac pictures of acute pulmonary edema is nonspecific. It has been suggested that the increased compliance of the lung “cortex” enhances lymphatic resorption, thus diminishing peripheral (relative to central) edema and giving rise to the “bat’s wing” and “butterfly” patterns. This inability to differentiate cardiac from noncardiac pulmonary edema is especially

apparent on supine portable films of patients with severe pulmonary edema.

Rounded pneumonia and possibly a related entity, round atelectasis, are frequently confused with tumor and are appreciated only after a response to bronchodilator therapy and antibiotics.³² The causative agents are usually undefined, but an infectious process is thought to initiate a predominantly alveolar inflammation and exudation. The infiltrate spreads from a small peripheral alveolar locus centrifugally through the interalveolar channels (pores of Kohn and channels of Lambert), accounting for its initial nonsegmental distribution and spherical shape.

Once the diagnosis of pneumonia is established, chest roentgenograms are best used to follow the course of the pneumonia over the following days to weeks for either normal resolution or complications. There is poor correlation between the severity of the abnormalities seen radiographically and the prognosis. Resolution is highly variable but tends to be delayed with *Legionella pneumonia*.³¹ Dehydration, often suggested to mask underlying pneumonia in the elderly, is associated with rapid progression of opacities with "early hydration." Both animal and clinical studies³³ have confirmed that the more appropriate term of this therapeutic if not diagnostic endeavor should be "early drowning."

Chest films are routinely obtained for the evaluation of fever in neutropenic patients, but their usefulness has been questioned and only recently clarified.³⁴ In such a population the chest film is abnormal in 22% of patients. However, 17% of patients had abnormalities in the absence of clinical findings of pneumonia, and the test resulted in changes in therapy in 61% of the episodes of persistent or recurrent fever, of which 40% resulted in clinical improvement. Moreover, there was no evidence that neutropenic patients, as similarly suggested for dehydrated patients, were "unable to mount" an infiltrate with lung infection.³⁴

Computed Tomography

Computed tomography (CT) scans have been suggested for management of patients with pneumonia when the conventional roentgenogram fails to clarify the presence, location, extent, or nature of the infection. The apparent clinical benefit of distinguishing airspace from interstitial disease radiologically is often lost on further pathologic analysis. There are no CT findings characteristic of a specific bacterial infection. It may be useful, though, in a patient whose chest film has not yet become abnormal. CT has been most frequently suggested for the early detection of *Pneumocystis* pneumonia in AIDS patients. Also it is used to facilitate percutaneous invasive procedures, including biopsies, aspirations, and tube thoracostomy placement for drainage.

The standard bedside portable chest film frequently fails to adequately define the retrocardiac, costophrenic, juxtadiaphragmatic, and paravertebral infiltrate and the extent of a fluid collection in the pleural space. It has been recognized that CT is a valuable tool for detecting the full extent of noncardiac pulmonary edema as well as the presence of nosocomial, drug, and radiation pneumonias. Complicated pneumonias with pleural involvement, abscess formation, and empyema with bronchopleural fistula are readily defined with CT scanning.

High-resolution CT, defined as thin-section CT optimized by using a high-spatial-resolution algorithm (1- to 2-mm collimation) in contrast to routine thick sections (10-mm collimation) emphasizes the secondary pulmonary lobule. It has been used for the evaluation of hypersensitivity pneumonitis; but unlike the characteristic change in lobular anatomy suggested for chronic interstitial disease, findings have been nonspecific for acute hypersensitivity pneumonitis.

Ultrasonography

The most frequent use of ultrasonography in patients with pneumonia is to identify the extent of pleural fluid collections and facilitate thoracentesis or tube drainage. Furthermore, the nature and aspirability of the pleural collection may be determined. A hypoechoic collection is likely to be "complicated," distributed into fibrin-septated "loculated" subspaces; an anechoic collection is uncomplicated. The more complex the collection, the more likely (but not certain) it is that an empyema is present, whereas an anechoic collection may still be infected.

A significant number of echo-free pleural effusions, up to 20% in some reports, do not yield free fluid. Various explanations include high viscosity of an otherwise hypoechoic effusion that may be simple hemorrhage or pus. More frequently it represents a poorly reported entity first described in group A β -hemolytic streptococcal pneumonia termed *pleural edema*. This is potentially a totally reversible anechoic phenomenon.

Nuclear Radiography

The use of scintigraphy to detect infectious and noninfectious inflammatory lung disease is expanding rapidly, made possible by the development of radiopharmaceuticals and methods as well as by the performance of controlled clinical trials.³⁵ Perfusion lung scans in patients with adult respiratory distress syndrome (ARDS) show nonsegmental focal perfusion deficits, mostly in the peripheral and dorsal portions of the lung, and a shift away from the dependent lung zones as a result of the gravity-dependent distribution of pulmonary edema. This finding is nonspecific for any form of pulmonary edema and reflects increased resistance in the microvasculature secondary to alveolar and perivascular edema with a gravitational gradient.

The use of gallium 67 citrate scans and indium 111 oxine-labeled granulocytes have become standard techniques for evaluating pulmonary infection in immunocompromised hosts, particularly those with AIDS or drug-induced immunosuppression, especially transplant recipients. More recently, technetium diethylenetriamine pentaacetic acid ($^{99m}\text{Tc-DTPA}$) aerosol clearance and thallium 201 chloride scans have been used to a limited extent. Gallium, a group III B metal, behaves like iron in vivo and binds to unsaturated serum transferrin in the serum; and localization of gallium in inflammatory processes may be due in part to the ability of the protein lactoferrin (with a stronger affinity for the radionuclide) to remove gallium from transferrin and its subsequent sequestration intracellularly. As a result of cell lysis, especially of granulocytes, phagocytosis of the protein complex occurs, particularly by lung macrophages. Also as a result of its binding at cellular surface receptors, retention in areas of inflammation occurs, a consequence of protein extravasation due to the associated increased permeability of lung vasculature.

There is nothing specific in the uptake pattern of gallium for any of the disease processes causing ARDS. However, the specificity of gallium uptake in AIDS patients for *Pneumocystis carinii* pneumonia can be as high as 95% when intensity of lung uptake is considered. The evaluation of the heterogeneity of the gallium uptake also increases the positive predictive value to almost 90%.³⁵ Other patterns of gallium uptake also have utility, such as localized uptake, which most often is secondary to bacterial pneumonia and focal regional lymph node uptake, suggestive of mycobacterial infection.

Indium 111-labeled leukocyte scintigraphy, though not as sensitive as gallium 67 for the diagnosis of diffuse opportunistic pulmonary infections (e.g., *Pneumocystis*), has been shown to be superior for identifying focal pulmonary lesions. Neutrophils circulate with an average lifetime of 6 hours, after which they marginate to various tissues, such as the lungs. The labeling procedures for indium is time-consuming and technically demanding; it requires harvesting the leukocytes (the patient must have an adequate leukocyte count, i.e., >4000 cells/ μl) and subsequently labeling the cell suspension, centrifuging it, and delicately resuspending the indium 111-labeled leukocyte pellet for injection. Images are generally obtained within 24 hours of injection. Sequestration in the lung, as with gallium 67, may represent a nonspecific inflammatory response rather than infection. There are both specific and nonspecific sequestration mechanisms related to pulmonary vascular injury and enhanced pulmonary clearance of damaged cells by alveolar macrophages. Focal, in contrast to diffuse, uptake, especially if of high intensity, identifies an infectious etiology in more than 50% of cases.

The disadvantage of gallium scanning is that after intravenous injection of the radiopharmaceutical at least 48 hours and sometimes even 96 hours are required for the blood pool to clear the chest; moreover, other

nuclear radiographic procedures cannot be performed for 10–14 days. For this reason thallium scans have been introduced; not only are they readily available within 2 hours, but other nuclear scanning techniques may be initiated if required. Preliminary data suggest a high correlation with the gallium scans, with similar sensitivity and specificity.

Magnetic Resonance Imaging

The use of magnetic resonance imaging (MRI) for evaluating lung parenchyma has been limited by a poor signal-to-noise ratio and physiologic motion. The high T1-weighted signals seen with airspace consolidation resulting from alveolar hemorrhage was reported to allow differentiation of pulmonary infarction from pneumonia by MRI.³⁶ The aging hemorrhage, because of methemoglobin formation, produces a hyperintense T1-weighted signal. The utility of MRI perfusion scores has also been reported to facilitate the early diagnosis of *Pneumocystis* pneumonia, whereas the T1 and T2 relaxation times were of no predictive value.³⁷ The potential for MRI to monitor disease activity reflecting progression or response to therapy makes it a technology whose expanded role in the assessment of pneumonia is to be anticipated.

Other Methods

Digital imaging, nuclear quantitation of amine receptors, and positron emission tomography scanning have not yet found significant clinical application in pneumonia patients. As technology, methodology, and clinical experience grow, this picture may be expected to change, with the radiologic assessment of pneumonia to be enhanced and the patient's presentation redefined.

Complications

Pleural Effusion

The normal pleural space is nonexistent, and the lung's visceral pleura is in contact with the chest wall's parietal pleura. The few milliliters of fluid normally present simultaneously provide lubrication and enhance the surface adherence properties while allowing mechanical coupling of the lung and chest wall. The mesothelial membranes are highly permeable, offering little resistance to fluid and electrolyte flux and resulting in a pleural fluid composition similar to that of interstitial fluid. The protein content of the liquid is, however, maintained lower than that of lymph and of the interstitial compartment. The parenchymal inflammatory process of pneumonia extending to the pleural surface alters pleural permeability, resulting in an elevated pleural fluid protein con-

centration. Moreover, the associated release of proteases and inflammatory mediators causes degeneration of the oncotic gradient across the pleural membranes.

The arterial blood supply of the parietal pleura is systemic, and primarily, if not entirely, for the visceral pleura via the bronchial arteries in humans (via the pulmonary arteries in the dog).³⁸ The venous return is predominantly to the left side of the heart from the visceral pleura and to the right atrium from the parietal pleura. Drainage of normal or abnormal volumes of fluid, amounts of protein, or quantities of particulate or cellular material in the pleural space is now thought to be primarily via parietal pleural lymphatics.³⁹ The continuity of the parenchyma's interstitium with the visceral subpleural interstitium readily allows escape of fluid from this peripheral portion of the extravascular space of the lung into the pleural cavity.

The pleurolymphatic drainage of the parietal pleura is primarily to the right lymphatic duct. The parietal (in contrast to the visceral) submesothelial lymphatic system communicates directly with the pleural space via a variety of specialized anatomic pleurolymphatic structures in its surface, such as stomata and crevices. Moreover, costomedial and caudocephalic gradients of pleural liquid pressures are maintained and enhanced by diaphragmatic respiratory excursion and cardiac contraction. Thus the setting for bulk flow along a hydraulic pressure gradient exists, and the fluid dynamics are affected by postural gravity-dependent alterations as well. The importance of the rate and depth of respiration in facilitating removal of artificial hydrothorax has been demonstrated in anesthetized animals. Its clinical counterpart is readily apparent in the demonstrated diurnal variation seen in fluid removal via lymphatic absorption during the night.⁴⁰ This variation can be attributed to the relative hypoventilation during sleep, but because the rate of fluid formation persists unabated it may explain the phenomenon of paroxysmal nocturnal dyspnea in noncardiogenic and cardiogenic pleural effusions.

The appearance of a pleural effusion indicates the adverse effects of pneumonia and associated pleural inflammation, immunologic or infectious, on the forces governing the filtration and drainage of pleural fluid. The processes of Starling-dependent filtration and bulk transfer of liquid and protein from the lung interstitium become predominant over the sucking capability of lymphatic-dependent absorption. In this setting, the use of steroids therapeutically may affect the egress or ingress of inflammatory pleural effusions through pleural surfaces. With pneumonia, the high protein concentration of the pleural fluid reflects increased permeability, which may result from inflammatory injury to (1) the visceral pleural mesothelial cells or (2) the visceral pleural microcirculation. However, with increased-permeability pulmonary edema, or ARDS, the alveolar-epithelial barrier is disrupted and the resultant alveolar flooding decompresses the perivascular interstitial space, accounting for the infre-

quency of radiologically detectable or large pleural effusions. However, the frequency of pleural effusions with increased-permeability pulmonary edema has been reported to be nearly the same as that with hydrostatic pulmonary edema.⁴¹

The right and left pleural spaces do not communicate with each other, and their elimination by pleurectomy, pleurodesis, or phylogeny, as in the elephant, does not have a significant effect on respiratory function. Pleural effusion frequently causes a disproportionate degree of dyspnea in comparison to the magnitude of impairment of pulmonary function as reflected by decreases in lung volumes and arterial oxygenation.⁴² The volume of pleural fluid present is partitioned between an increase in chest wall volume and a decrease in lung volume. Therefore although there is a significant relation between the size of the pleural effusion and the decrease in lung volume, the partitioning is apparent by the smaller increases in lung volumes relative to the volume of fluid removed with thoracentesis. This partitioning is determined by the relative compliances of the two structures: the lung and the chest wall (Fig. 7.2). With pneumonia the stiffer lung relative to the chest wall shows a smaller change in functional residual capacity.

The effects of pleural effusion on the lung and chest wall volumes are influenced by both the pleural liquid pressure at the level of the effusion

FIGURE 7.2. Changes in lung volume in patients ($n = 9$) with parenchymal lung disease 2 hours after thoracentesis (mean 1820 ml). The static pulmonary compliance is indicated. TLC = total lung capacity; FRC = functional residual volume; RV = residual volume; VC = vital capacity; C_L = lung compliance. (Data from Estenne et al.⁴²)

and the pleural surface pressure above the pleural effusion. Dyspnea appears to be related to the shortening of inspiratory muscles, which occurs when breathing at an increased chest wall volume. The shortened muscles operate on a disadvantageous portion of their length–tension curve, and neural-mechanical input–output mismatching occurs. This “length–tension inappropriateness” gives rise to the sensation of dyspnea and is alleviated with thoracentesis and lengthening of the inspiratory muscles at end-expiration and their placement on a more advantageous portion of their length–tension curve. The symptomatic alleviation of dyspnea is therefore found to be independent of and to correlate poorly with changes in either lung volumes or blood gases.

The pleural fluid PO_2 and PCO_2 are readily altered by changes in the FI_{O_2} and level of ventilation^{43,44} (Fig. 7.3). This alteration illustrates the dynamic nature of the equilibrium between the pleura, lymphatics, underlying lung, and pleural fluid. Moreover, postural effects on cardiac and pulmonary function are magnified in the presence of a pleural effusion (Fig. 7.4). Thoracentesis is thus a potential effective therapeutic intervention for cardiac and pulmonary insufficiency.

FIGURE 7.3. Pleural fluid oxygenation after varying the FI_{O_2} ($n = 14$). After 20 minutes a significant change in mean PO_2 occurs. The change in pleural fluid PCO_2 is also shown after 10 minutes of hyperventilation in patients ($n = 11$) being mechanically ventilated. The $PaCO_2$ was decreased from 36.7 mm Hg to 28.7 mm Hg. (Data from Zaman and Karetzky⁴³ and Brandstetter et al.⁴⁴)

FIGURE 7.4. Hemodynamic consequences of thoracentesis in 12 patients in the upright and supine postures. The increase in cardiac output was due to an increase in stroke volume in response to decreases in both pulmonary and systemic vascular resistances.

Pneumothorax and Pneumomediastinum

Infection, as with other degenerative diseases of the lung, impairs the integrity of the walls of the distal bronchioloalveolar structures, including existing bullae, or pneumatoceles. It then allows escape (leakage) of air at less than the usual critical pressure gradient of the epithelial barrier, which in normal lungs is approximately 40 cm H₂O. The resulting interstitial air then dissects its way underneath or to the visceral pleural surface. It may remain there under various degrees of tension as a subpleural loculation (bleb, mediastinal emphysema); it may dissect further through extrathoracic tissue planes (subcutaneous emphysema); or it may “rupture” into the pleural cavity (pneumothorax).

The role of interstitial emphysema in pneumothorax formation has been defined in both the laboratory and clinical settings.⁴⁵ It is the transpulmonic pressure gradient between the alveoli and interstitial space due to inadequate venting and an elevated intraalveolar or lowered pulmonary intravascular pressure (or both), rather than the absolute intrathoracic pressure, that is responsible for interstitial air accumulation. Inflammation by damaging the epithelial barrier and impairing its integrity predisposes to infectious interstitial emphysema.⁴⁶

The concurrent cough of pneumonia produces shearing forces that alter the topographic pressure profile along the pleural surface. The cough more importantly causes the critical pressure gradient across epithelium-lined interstitium to be exceeded, as intrathoracic pressures as high as 150mm Hg may be produced. In addition, the extrapulmonary transmission of the airways' positive pressure may significantly impair venous return, serving to lower the pulmonary vascular hydrostatic and thus interstitial pressure. Hence apparent innocuous coughing represents a real determinant of the occurrence of pneumothorax. Consideration must also be given to the increase in surface tension resulting from the impaired synthesis and enhanced inactivation of surfactant that occurs in alveoli affected by pneumonia. Therefore a combination of increased hydrostatic and surface forces exerted on compromised parenchymal structures predisposes to the dissection of air, pneumothorax development, and the entity best termed infectious interstitial emphysema.

The pathophysiology of pneumothorax associated with the classic fluid-filled alveoli of lobar pneumonia is presumably related to the associated airway obstruction. This situation impairs pressure equilibration of entrapped alveolar gases, resulting in interstitial dissection of air and finally decompression into the pleural cavity. Pneumothorax occurs in patients with pneumonia and pulmonary alveolar proteinosis following bronchoalveolar lavage (BAL).⁴⁷ Approximately 40–60% of BAL fluid is not removed with suctioning, depending on the severity of the destructive parenchymal process. The retained fluid may promote local gas trapping as a consequence of the loss of the protective decompression mechanism of collateral ventilation acting via channels at both the alveolar and bronchiolar levels.⁴⁸ Collateral flow has similarly been observed to be impaired in the lung of a dog model when water is injected into a lobe.⁴⁹ Also, obstruction of the sublobar segments at low lung volumes in animal models results in a greater outward acting stress on the alveolar wall (alveolar pressure gradient) as a result of pulmonary interdependence.⁵⁰ The potential significance of these pathogenic mechanisms of pneumothorax are enhanced with middle lobe segmental involvement, as there is only a single interface with another segment.⁴⁷

Attention has been given to the presentation of AIDS-related *Pneumocystis carinii* pneumonia with spontaneous pneumothorax. The occurrence of adventitious air was reported in association with *Pneumocystis* pneumonia in immunocompromised patients prior to the recognition of AIDS. This problem presented spontaneously as mediastinal emphysema, subcutaneous emphysema, or both unilateral and bilateral pneumothorax. Previously, attention to the role of infection in the pathogenesis of infectious interstitial emphysema was most clearly illustrated in patients with tuberculosis. *Mycobacterium tuberculosis* infection long has been considered to be a common cause of pneumothorax, particularly in its cavitary form; and in some reports it has been associated with as many as

60% of cases presenting as apparent spontaneous pneumothorax. Similarly, necrotizing pneumonias associated with aspiration have been shown to have a high incidence of pneumothorax and pneumomediastinum. These infections predispose to barotrauma if ventilatory support is required. Such injury occurs with both pressure and volume ventilators, and the incidence is further promoted with positive end-expiratory pressure (PEEP), though the peak inspiratory pressure is of prime importance.^{51,52} The pressure range of assisted positive pressure or volume ventilators is usually a minimum of 20–25 cm H₂O. This level is often exceeded when patients expire out of phase with the instrument. Overexpansion of small airways and alveoli due to maldistribution of volume and pressure may result in occlusion of thin-walled microcirculatory elements in their walls. Thus mechanical ventilation, by increasing intraalveolar pressure, enhances the development of a local perivascular pressure gradient, which, especially with infection, does not have to exceed 40 cm H₂O to cause alveolar leakage and continuous escape of air from the alveoli to the interstitium and vascular sheaths.

Extrapulmonary air is not pathognomonic of any specific interstitial degenerative, inflammatory, or fibrotic process. However, the occurrence of pneumothorax in AIDS patients serves to demonstrate that a particularly invasive form of infection, with an especially destructive lesion of the distal lobule, alveoli, and terminal bronchioles, such as reported with *Pneumocystis* pneumonia, predisposes to pneumothorax. *P. carinii* pneumonia serves as a model for inflammatory interstitial emphysema originating in the bronchioloalveolar interstitial space as a result of disruption of the alveolar lining due to type I cell necrosis and denudation with breakdown of bronchioloalveolar septa. This situation would predispose to the more widely recognized entity of barotrauma, particularly pneumothorax complicating mechanical ventilation.

Lung Abscess

During the preantibiotic era, lung abscess was reported to be associated with a mortality of 60–100%, with the value of bronchoscopy difficult to assess. Mortality was reduced to 20% with surgical intervention; and for the nontuberculous abscess, thoracotomy for drainage, if not surgical resection, was considered obligatory.⁵³ Antibiotic therapy has reduced mortality to approximately 7%. The outstanding pathologic feature of lung abscess remains the rapidity with which necrosis goes on to liquefaction and sloughing with sphacelus formation at its extreme. The necrotizing pneumonia that progresses to abscess formation cannot be distinguished initially by clinical features to be due to pyogenic or putrefactive organisms.

Aspiration of mouth organisms following states of unconsciousness, allowing for ongoing symbiosis of a polymicrobial flora in the lung, has

long been recognized in the pathogenesis of lung abscess; and the rarity of such a putrid complication in edentulous people and children free of pyorrhea alveolaris has been repeatedly noted.⁵⁴ The unusual virulence demonstrated by the anaerobic organisms involved, which usually are of low pathogenicity, has been explained by synergy and the propitious conditions of the event. They include the liquid nature and volume of the aspirate and the concentration of organisms in the inoculum. Other factors are thought to include impaired upper airway protection (diminished gag reflex), lower mucociliary clearing, and impairment of basic immunologic defense mechanisms. Approximately one-third of lung abscesses are complicated by empyema, with or without bronchopleural fistula formation.

Patients present most frequently with pneumonitis of a dependent lung segment, indicating the importance of the laws of motion, specifically of gravitational forces (Newtonian pneumonia). Empiric definitions differentiate the necrotizing pneumonia, characterized by multiple cavitary lesions measuring less than 1 cm in diameter, from the larger usually solitary lung abscess. The bacterial flora is influenced by the patient's oropharyngeal colonization, which in turn is affected by location (i.e., community versus hospital) and underlying immune status. Radiologic evidence of abscess formation does not appear before 7 days (mean 15 days) from an identified aspiration event. The syndrome of aspiration pneumonia and its consequent stages of progression is considered to be initiated by a chemical pneumonitis followed in approximately one-third of patients by the development of a subsequent superimposed bacterial pneumonia, a phenomenon uninfluenced by antibiotic prophylaxis. An unknown percentage of such events, most of which were minimized by subsequent initiation of antibiotic therapy, develop into a complicated necrotizing suppurative pneumonia; alternatively, in a "select" group, the process degenerates into a lung abscess with the development in some of the final complication of the continuum, empyema.⁵⁵

The bacteriology of the necrotizing pneumonia, lung abscess, and empyema of these patients is similar and has been described under the term anaerobic pleuropulmonary infection. The polymicrobial flora has been shown to be characterized by an overwhelming predominance of anaerobic and mixed anaerobic-aerobic isolates.⁵⁶ Advances in anaerobic technology has presumably clarified the true etiologic agents of the "non-specific lung abscess." With antibiotic therapy, complete resolution is almost uniformly observed at the end of 3 months. The rate and success of resolution depends on the initial size of the cavity and the duration of symptoms. The importance of location has also been inferred with abscesses in the right upper lobe resolving more slowly than those in other locations but with no greater incidence of treatment failure.^{57,58}

It has been observed, however, that, in contrast to the excellent prognosis for primary lung abscess, more than 75% of lung abscesses are

fatal in patients with opportunistic suppurative infections.⁵⁹ With the increasing number of immunocompromised hosts, overall mortality due to lung abscess has been reported to be increasing since the 1960s to 28%,⁶⁰ with a resurgence of the classic pyogenic organisms such as group A β -hemolytic streptococci.⁶¹

Empyema

Infection may not be successfully confined to the parenchyma as simple pneumonia or even a lung abscess but can extend to and through the pleural surface as empyema (empyema thoracis). It may be by contiguous spread or by formation of a bronchopleural fistula. The relation of this pleuropulmonary complication to the anaerobic population of the normal oral flora was clearly established at the turn of the century. However, it was essentially forgotten as a result of the decreased incidence with effective antibiotic therapy of the primary pneumonia. The resurgence of interest and appreciation of the persistent pathogenic role of anaerobes in empyema resulted from the same technologic advances in laboratory methodology that clarified their role in lung abscess. Anaerobic bacteria are recovered in three of every four cases of empyema and are the exclusive isolate in one-third. As with aspiration pneumonia, the polymicrobial nature of the empyematous process is clearly reflected by combined anaerobic and aerobic cultures.⁶² Thus despite the reduced incidence of this complication, the pathogenesis of empyema is little changed from the preantibiotic era, and anaerobic pleuropulmonary infections predominate.

Pleural effusions are common in pneumonia, but empyema is an unusual occurrence, its frequency dependent on definition. It is more than a semantic consideration, though, as treatment is affected and delay alters not only the duration of hospitalization and morbidity but the mortality. Clinical, radiographic, and laboratory criteria have been suggested to detect this complication, differentiate it from lung abscess, and detect the presence of a bronchopleural fistula. Many patients with anaerobic empyema have no other evidence of pneumonia on routine chest roentgenogram. CT scanning is reported to be sufficient to uniformly differentiate lung abscess from empyema. The most reliable CT features are wall characteristics (Table 7.3).⁶³ Xenon 133 gas lends itself well to the detection of bronchopleural fistulas. Detection of radioactive gas in the pleural space and its persistence on washout studies provides a simple and reliable test of communication. The initial characterization of the fluid and noninvasive serial monitoring may be achieved by MRI. Empyemas are more intense and show greater heterogeneity, reflecting the increasing cellular and chemical complexity of the fluid.⁶⁴

The present definition of empyema includes cellular parameters (purulence), microbiologic findings (bacteriologic culture), and chemical charac-

TABLE 7.3. CT characteristics.

Measurement	Lung abscess	Empyema
Wall	Thick	Thin, smooth, uniform
Pleural separation	None	Split pleura
Chest wall angle	Acute	Obtuse
Shape	Round to oblong	Oblong to lenticular
Size	Small	Larger
Lung	Destroyed	Compressed
Luminal margin	Irregular	Smooth
Contrast	No effect	Enhancement
Posture	No effect	Gravitational change in shape
Bronchi/vessels	Abrupt termination	Compressed and distorted

teristics [pH, glucose, lactate dehydrogenase (LDH)] in relation to serum values. The term parapneumonic effusion has been coined to indicate the common occurrence of pleural effusion in association with pneumonia. Its further delineation as an empyema is dependent on criteria meant to suggest that a positive culture does not make an empyema, and an acellular fluid does not rule it out. The lower the pH and glucose, the higher the lactate, protein, and LDH levels and the WBC count; the more positive the Gram stain, the greater is the likelihood of the effusion being an empyema. The metabolic activities of the pathogenic organisms and the cellular components of the fluid play a relatively minor role in determining the pH of the fluid. In contrast, the metabolic activity of the pleural tissue and the ability of its metabolic products, carbon dioxide and lactic acid, to be transported out of and oxygen into the pleural compartment are found to be the primary determinants of the pleural fluid pH, PCO₂, and PO₂.^{65,66}

The anatomic and immunologic barriers to infection of the pleural space are formidable. As with pneumonia presenting with an associated pneumothorax, if the destructive process is aggressive enough, the infected material may extend into the compartment beyond the containment barrier of visceral pleura. A breach in these defenses usually implies a necrotizing process. However, pleura may become infected directly also, via the visceral pleural capillaries, or the organism may be carried along a pressure gradient in the underlying contiguous interstitial space. The pleural lymphatic system provides not only for a dynamic fluid transport mechanism but an effective transport system for infective agents as well as for immunocompetent and phagocyte cells. Organisms are rapidly cleared unless the microbial onslaught is relentless and overwhelming or if the lymphatics of the parietal pleura are damaged by the inflammation process, interfering with their patency and ability to act as a delivery and drainage system.

A variety of immunologic mechanisms have been proposed in an effort to explain the persistence of microorganisms observed in empyema. It has

been suggested that diminished local opsonization occurs because of the decreased complement-mediated opsonic activity, which may result from the release of granulocyte proteases, which inactivate C3 in purulent pleural fluids. Local consumption of complement has been shown to take place with empyema but not with benign parapneumonic effusions. With empyema, low values for hemolytic complement (CH50) along with large amounts of the C3d the Ba complement components have been reported and may prove to be of diagnostic significance.⁶⁷

The likelihood of developing empyema is increased if treatment for pneumonia is delayed. Although postpneumonic empyema is uncommon, it accounts for 60% of the cases of empyema. As many as 40% of patients with bacterial pneumonia have an associated pleural effusion, but fewer than 1% of adults develop empyema. The incidence varies with the type of pneumonia, but its incidence is greatest in anaerobic infections. Aside from antibiotic therapy, management has not progressed much beyond facilitating spontaneous drainage through the chest wall (empyema necessitatis) seen commonly during the preantibiotic era. With all the treatment presently available, the mortality of patients with empyema is still high (variously reported at 9–50%). By excluding cases with underlying diseases, however, the mortality rate is between 2.9% and 5.8%.⁶⁷

Adequate drainage is a prerequisite of successful treatment and may be achieved by repeat thoracentesis for “thin” effusions of small volumes. Small percutaneous catheters have been introduced, rather than large thoracostomy tubes or more extensive thoracostomies, and have been found to be as effective if not more so in selected cases. They may be inserted under ultrasound guidance allowing for multiple placements if necessary for different loculated compartments.⁶⁷

Finally, instillation of streptokinase has been suggested for lysis of loculated effusions in order to avoid decortication. Its efficacy has been reported to be enhanced by instillation into the space around the empyema rather than intrapleurally directly into the loculation.⁶⁸

Delayed Resolution; Chronic and Recurrent Pneumonia

Persistence of the radiologic manifestations of pneumonia for weeks rather than days with or without symptoms characterizes the entity of delayed resolution, or chronic pneumonia. It may be a complication of an infectious or a noninfectious etiology. Agents causing necrotizing acute processes such as gram-negative and anaerobic organisms do not predispose to delayed resolution other than their tendency to recur or persist with repeated aspiration. The underlying immunocompetence of the individual influences not only the specific type of pneumonia but its subsequent course as well.

During evaluation of the possible pathogenesis and etiology of this complication of the initial episode, the patient's environmental exposures

are of prime consideration, including occupational, geographic, and social background (e.g. friends, family, and habitual predisposing factors, particularly use of drugs). Disease processes commonly associated with prolonged resolution are preexisting lung disease such as chronic obstructive pulmonary disease (COPD) and obstructing endobronchial carcinoma, alcoholism, diabetes, and AIDS. Whether aging should also come under the category of disease is a philosophical if not semantic question; it is important nonetheless when correlating the rate of resolution and the incidence of chronic, persistent pneumonia. No studies have been done regarding the incidence or frequency of the various predisposing factors to chronic infection.

The rate of resolution of pneumonia depends on the organisms' numbers and virulence and the hosts' local and systemic defense mechanisms. Defense includes immunologic and structural barriers in addition to the entire mucociliary transport system. The potential role and mechanism must be defined for each contributing factor to the persistent process whether it is of a continuous infectious nature or an inflammatory process that cannot or refuses to be turned off. Thus adding to the uncertainty of resolution is the nature of the process giving rise to a persistently abnormal chest film, usually in the absence of continuing associated signs or symptoms of infection. Delayed radiographic clearing has been poorly differentiated in terms of whether the infection is chronic and persistent or recurrent.

With pneumococcal pneumonia, delayed resolution is common and is associated with initial bacteremia, upper, right, or multilobe involvement, advanced age, heart failure, prolonged leukocytosis, leukopenia, delayed treatment, alcoholism, and underlying COPD.⁶⁹ The presence of multiple factors, moreover, are additive in determining the likelihood of delayed resolution.⁷⁰ Advanced age has been the most consistent predictor, whereas the initial clinical picture is widely variable and does not predict speed of resolution, including the persistence of fever.⁷⁰ It must be emphasized, however, that delayed resolution is not synonymous with recovery; it means only that the chest film appears normal by 120 days rather than the usual 30 days.⁷⁰ Pneumonias uncommonly (approximately 4% of patients) have radiologic progression initially despite an otherwise appropriate clinical response.⁷¹ *Legionella* pneumonia, in contrast to *Mycoplasma* pneumonia, is characterized not only by delayed resolution (up to 6–12 months) but by persistent functional abnormalities, especially in regard to diffusing capacity, fatigue, and dyspnea for up to 2 years after its onset.⁷²

The persistence of radiographic abnormalities and symptoms for more than 1 month conveniently defines chronic pneumonia.⁷³ *Hemophilus influenzae* has been reported to be the most common cause of chronic pneumonia, and smoking is the most common predisposing factor.⁷³ It has been suggested that the course of *H. influenzae* pneumonia may be

more likely to be prolonged because it has an increasing incidence of being the causative organism in the elderly with frequent associated illness and impaired host defense mechanisms.⁷⁴ Other associations are similar to those suggested for delayed resolution, and complete resolution occurs with appropriate long-term antibiotic therapy.

The terms relapsing or recurrent pneumonia are best utilized, then, using a 1-month asymptomatic interval, complete radiographic clearing of the acute infiltrate, or both for distinction.⁷⁵ *Mycoplasma pneumoniae*, the prototype for atypical pneumonia, has in the past also been termed recurrent pneumonia. Weeks to years may separate recurrences, and the location and severity of the recurrence may vary with respect to the initial episode, inferring that immune protection developed to an inadequate degree following the initial infection. The role of antibiotic therapy for recurrence is not clear. The limited number of reports available suggest that recurrence is not rare, necessarily localized to the site of the initial pneumonia, and that there is no specificity for a particular etiologic agent.

The bacteriology of recurrent episodes is similar to that of initial episodes in terms of variability. Specifically, the causative agent of the initial episode does not correlate (other than pneumococcal infection remains predominant) with that isolated from the recurrent infection. Predisposing underlying illnesses are almost uniformly present; 93% of patients in one report had associated predisposing diseases, most commonly COPD and congestive heart failure.⁷⁵ Other considerations include inapparent aspiration of a foreign body, malignancy (especially endobronchial), alcoholism, and underlying immunodeficiency. Treatment remains similar to that for initial events, as does responsiveness and mortality.

In summary, it is important to differentiate delayed resolution from deterioration. Bronchogenic carcinoma is an uncommon cause of delayed resolution or recurrent pneumonia.^{70,75} Continued observation is warranted with otherwise clinical improvement, whereas aggressive diagnostic measures are indicated with persistent or recurrent clinical signs and symptoms of pneumonia. Chronic, persistent inflammation may result in vascular proliferation and recurrent hemoptysis, causing severe anemia.⁷⁶ The fatality rate of recurrent pneumonia, despite the presence of associated illness, has been found to be similar to that of the initial infection.

Adult Respiratory Distress Syndrome

In the past the acute lung injury syndrome (ARDS) was characterized clinically by noncardiogenic (low pressure) pulmonary edema reflected by severe impairment of arterial oxygenation, a decrease in lung compliance, and diffuse infiltrates seen on roentgenography. More recently, it has been appreciated that the uniqueness of the impairment of pulmonary

function is more apparent than real. The hypoxemia resulting from the lungs' failure to exchange oxygen, although a distinguishing feature initially suggesting that the lungs act as the target organ for inflammation, is in fact representative only of coexisting multiorgan dysfunction of varying degree. This defect in pulmonary gas exchange is associated with impaired peripheral oxygen extraction as well, which has been attributed to ill-defined factors of decreased delivery, increased diffusion path, decreased membrane penetration, and finally impaired cellular utilization of oxygen. The oxygen uptake may be increased and is found to be delivery-dependent when the driving pressure in the periphery is increased.

The syndrome is associated with a variety of organ and systemic insults, and the mortality varies greatly, affected by numerous confounders such as age and the primary underlying disease process. Death is only infrequently attributable to hypoxemic respiratory failure. ARDS occurs as a complication of both infectious and noninfectious pneumonia as well as nonpulmonary disease.⁷⁷ Mortality due to ARDS is greatest in patients with pneumonia (Fig. 7.5), which is a leading predisposing event for the development of ARDS. It may occur in patients with no apparent risk factor or preexisting disease. A variety of mediators of this neutrophil-induced lung injury have at different times held the forefront of the proposed variety of mechanisms resulting in an inflammatory cascade

FIGURE 7.5. Mortality among 635 patients with ARDS. The numbers of patients are shown in parentheses. (Data from Zapol et al.⁷⁷)

causing the pathophysiologic findings of ARDS. The unifying hypothesis for the pathogenetic mechanisms responsible for their release and interaction continues to be enigmatic. The migration and aggregation of activated neutrophils and macrophages are thought to play interlocking roles in the destruction and damage of the alveolar epithelial and pulmonary capillary endothelial cells. Recruitment of PMN inflammatory cells appears to be due to directed chemotaxis. Neutrophils release preformed intracellular granules of cytotoxic proteases, generate cyclooxygenase and lipoxygenase metabolites of membrane-bound arachidonic acid, and together with other phagocytic cells have respiratory bursts, releasing cytotoxic reactive oxygen species.

It is becoming clear that although effective concentrations of oxygen at the tissue level allow the freedom of an aerobic life style, too much oxygen or inappropriate metabolism of oxygen can be toxic to cells. These reactive oxygen metabolites have accepted less than the usual four-electron reduction of oxygen to form water. The superoxide anion radical dismutates to produce hydrogen peroxide (H_2O_2). These metabolites in the presence of iron-containing compounds form the hydroxyl free radical; the most reactive free radical produced in biologic systems, it causes lipid peroxidation of polyunsaturated fatty acids of cell membranes, altering membrane fluidity and permeability. Hemoprotein peroxidases combine with H_2O_2 to form a halide or pseudohalide; these substances are potent oxidizing agents that are toxic to cells, bacteria, and viral particles through their actions of sulfhydryl oxidation, hemoprotein inactivation, protein and amino acid degradation, and inactivation of essential metabolic cofactors and DNA.

The naturally occurring antioxidant enzymes and scavengers are superoxide dismutase, catalase, and glutathione peroxidase. A second line of defense is composed of the nonenzymatic scavengers and quenchers, such as phenolic compounds (α -tocopherol), carotenoids (vitamin A), and sulfhydryl and thioether compounds. Activated neutrophils produce large amounts of reactive oxygen species to kill invading microbes. Unrestrained production of prooxidants and their release in the extracellular medium disturbs the delicate oxidant-antioxidant balance, resulting in an "oxidative attack" on the lung tissue. Initial studies in patients with ARDS indicate that plasma and red blood cell glutathione levels are decreased and that *N*-acetylcysteine administration, through its reduced sulfhydryl group, increases the levels of glutathione. There is no evidence, however, that its therapeutic administration decreases mortality or improves pulmonary function.

Previous emphasis has been on preformed proteases and newly generated leukotriene and prostanoid lipid mediators from the cell membrane via the arachidonic acid cascade. Among the various mediators currently being focused on are the numerous cytokines, such as tumor necrosis factor (TNF), which causes endothelial injury, and the interleukins, the

best known of which is IL-1, which alters intrapulmonary hemodynamics. These inflammatory markers, the *cytokines*, are cell-derived peptide molecules that act as mediators of intra- and intercellular communications causing a target cell to alter its activities. The cytokines are immunomodulators that are bound by specific receptors on the membrane surface of the target cells, initiating internal receptor-coupled (signal transduction) second messages to generate a response. The cytokines are derived (secreted) from a variety of cell types, including endothelial cells, monocytes, and macrophages each with their own mediator profiles. The dynamics stimulating their synthesis and release are largely unknown but are related to the action and interaction of endotoxins, bacteria, eicosanoids, and the cytokines themselves on target cells. The arachidonate metabolites appear to be amplifiers or modulators and regulators that fine-tune the evolution and resolution of inflammatory sequences rather than causing them.

The temporal features of diffuse alveolar damage include an initial exudative phase of edema, infiltrating inflammatory cells, and hemorrhage as a result of loss of alveolar-capillary integrity. Destruction and death of the endothelial cells cause widening of the capillary gap junctions. Similarly, damage to the alveolar type I cells results in disappearance of the epithelial tight junctions, with their death and desquamation. In addition, gaps appear in the basement membrane, resulting in direct contact between the interstitium and the alveolar airspace. The diffusion barrier is dissipated with loss of the alveolar epithelial barrier. A subsequent proliferative phase of organization and repair follows, leading finally to a fibrotic phase attributable to the proliferation of fibroblasts and collagen deposition. The proliferative phase is characterized by capillary proliferation and remodeling through organization of intra-alveolar and interstitial exudate with proliferation of type II and cuboidal cells, suggesting an attempt at repair of the air-lung interface. The net intraacinar microvascular cross-sectional area is reduced, and both pulmonary vascular resistance and physiologic deadspace are increased.

The lungs are not synchronously or homogeneously affected; alveoli may be unaffected, nonfunctional, or recruitable. With ARDS the weight of overlying edematous lung on underlying regions induces collapse of healthy, dependent lung units. The beneficial mechanism of the action of PEEP probably consists in recruiting these deflated localized lung regions. Thus measurements of specific compliance in ARDS has been reported to be normal. Alleviation of compression atelectasis by PEEP provides for its primary therapeutic effect, which immediately enhances oxygenation by reducing the venous admixture ("shunt").⁷⁸ Lung mechanics reflect the decreased aerable volume, but the inhomogeneity of the process predisposes to barotrauma such as bronchiolectasis with mechanical ventilation. The chest CT scan shows areas of well aerated, normal-appearing lung interspersed with patches of edematous, infiltrated and

destroyed parenchyma. Patients with ARDS demonstrate increases in both the restrictive and elastic work of breathing. Increased airway resistance results from airway flooding and the reduced lung volume. The increased viscoelastic properties are due to the decrease in aerated lung volume and the diffuse inflammatory process in the lung.

Abnormalities of pulmonary function occur following recovery from ARDS. The extent of impairment apart from minor flow and restrictive changes and decreased DLCO is rarely severe and does not correlate with the extent of histologic abnormalities found with open-lung biopsy performed during the acute stage. This lack of correlation has been attributed to the inhomogeneity of the histopathology as well as to the reversibility of the interstitial fibrotic process.⁷⁹ Similarly, no relation was found between the duration of mechanical ventilation or the amount of oxygen received and the capacity to normalize DLCO, though this subject remains controversial.

High levels of PEEP are harmful and must be balanced against the lack of evidence showing it to reduce mortality.⁸⁰ Although PEEP improves gas exchange in the exudative, and perhaps the proliferative, phase of ARDS, in late-stage ARDS patients, when the fibrosis phase is dominant, a beneficial response to PEEP is not observed. The risk of barotrauma (including pneumothorax, increased lung water, and epithelial damage) and perhaps bronchopulmonary dysplasia is now appreciated to be a matter of magnitude, no longer a question of occurrence. Pulmonary edema due to barotrauma results from increased permeability of the alveolar capillary barrier and is accompanied by alveolar cellular damage.⁸¹ The damage results from distension of the alveolar-capillary unit (high tidal volume), not the associated pressure. The uneven distribution of the ARDS lesions lends itself to regional overdistension with mechanical ventilation. The normal lung is the most susceptible to such injury and would be indistinguishable from ARDS lesions.

Mortality is unpredictable, and prognosis varies with the nature of the initial insult, its severity, and any associated disease. The onset of the syndrome occurs within 24 hours of the precipitating event in 75% of patients, and intubation is required within 72 hours in 90% of patients. Ninety percent of the mortality occurs within 2 weeks, and less than 20% results from irreversible respiratory failure. Isolated respiratory failure as a cause of death is primarily seen in the elderly with superinfection- and sepsis-related multiple organ failure is the primary cause of death both early (<72 hours) and late (>72 hours). Acute lung injury scoring systems based on the severity of impairment of oxygenation, the magnitude of the roentgenographic abnormality, the loss of respiratory compliance, and the level of PEEP required to maintain adequate oxygenation have been developed to suggest a continuum of respiratory dysfunction and to aid prognostication. Other established predictors of survival are the severity of the initial metabolic acidosis, the ability of the bone marrow to release

PMNs in response to the initial inflammatory insult, and the renal reserve as reflected by the blood urea nitrogen level (BUN).

Pneumonia appears to be even more common as a complication of ARDS than as a precipitating event. It is primarily gram-negative in type but may be gram-positive or polymicrobial; the dominant pathogen is *Pseudomonas*. Most late deaths are associated with sepsis, and the primary site of origin of the sepsis is the lung. The diagnosis of pneumonia in ARDS patients is difficult to make on clinical grounds, with high incidences of both false positives and false negatives.⁸² The usual clinical criteria for pneumonia in patients with ARDS are inaccurate. Fever and leukocytosis are present in ARDS patients with or without pneumonia. In a comparison of premortem clinical findings with postmortem examination of the lungs, the clinical diagnosis regarding the presence or absence of pneumonia was correct in only 70% of patients. An apparent response to antibiotic therapy as well as serial chest film findings had no predictive value.⁸² Additionally, the adverse consequence of nosocomial pneumonia is illustrated by its presence in 70% of patients dying with ARDS; and in 80% of the patients with clinical sepsis, the sepsis is attributable to pneumonia.⁸² These observations have prompted studies on the nature of the apparent impairment of the antibacterial defense mechanisms of the lung in ARDS, particularly the antibacterial efficiency of lung phagocytes.⁸³ Alterations have been found in neutrophil function with respect to the production of reactive oxygen products, microbicidal activity, and chemotaxis, which seems to increase susceptibility to pulmonary infection in the patient with ARDS.⁸³

Much of the pathophysiology and management have concentrated on the pathophysiology of the oxygen supply-demand imbalance. This observation has not been universal, and controversy still exists whether it is indeed merely attributable to a methodologic error arising from mathematic coupling.⁸⁴ Reports of studies utilizing independent measures of oxygen consumption and cardiac output have failed to find delivery (supply)-dependent oxygen uptake even in the presence of increased concentrations of plasma lactate (Fig. 7.6). It is similarly subject to methodologic interpretation depending on whether the increased measured or decreased calculated cardiac output is used to determine the oxygen delivery. Aside from central factors of anemia and cardiac dysfunction, local mechanisms of impaired oxygen extraction and decreased recruitable capillary reserve have been suggested. The disordered peripheral vaso-regulation characterized by a decrease in systemic vascular resistance is further complicated, as in the lung, by altered intraorgan distribution of blood flow, which may be further aggravated by PEEP. A theory of multisystem panendothelial injury has been proposed that alters permeability and real if not functional capillary density with interstitial edema and both endothelial and parenchymal cell injury impairing oxygen utilization and extraction. The current strategy of management has thus

FIGURE 7.6. Lack of delivery-dependent oxygen uptake in patients with ARDS ($n = 17$). (A) Comparison of calculated versus measured oxygen uptake. (B) Oxygen delivery before and after transfusion of 600 ml of packed RBCs over a 1-hour period. The measured (thermodilution) cardiac output remains unchanged, whereas the calculated (Fick) cardiac output decreases. (Data from Ronco et al.⁸⁴)

both accepted and focused on the concept that oxygen uptake may not be equal to demand, and that tissues may be hypoxic in the presence of a normal supply.

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