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Iatrogenic Diffuse Alveolar Damage: Oxygen Toxicity and Radiation-Induced Injury

Joseph F. Tomashefski, Jr.

OXYGEN TOXICITY

Molecular oxygen (O_2), which comprises approximately 20% of the earth's atmosphere, is life sustaining and essential for cellular metabolism in all mammalian species. However, inhaled in high concentrations, oxygen is paradoxically cytotoxic and potentially lethal. The harmful effects are directly related to the partial pressure at which the gas is breathed. Hyperoxic exposure delivered at up to 1 atm (760 mm Hg, normobaric hyperoxia) is primarily toxic to the lung, and oxygen delivered at hyperbaric pressure (>760 mm Hg) affects the central nervous system, causing convulsions before pulmonary toxicity becomes manifest.[1] Because oxygen is one of the most widely used therapies in clinical medicine, physicians must constantly balance its salubrious against its deleterious effects.

Pulmonary oxygen toxicity in humans takes two main forms: diffuse alveolar damage (DAD) in children and adults, and bronchopulmonary dysplasia (BPD) in premature neonates with respiratory distress syndrome. In this chapter, the pathogenetic mechanisms of pulmonary oxygen toxicity and the lesions produced in experimental animals are reviewed. The evidence for oxygen toxicity in humans is presented, and the pulmonary lesions are defined.

Historical Perspective

Shortly after the discovery of oxygen in 1774, Lavoisier demonstrated its poisonous effects on the lungs of guinea pigs.[2] In the nineteenth century, the observation was confirmed in a variety of species that hyperoxic exposure at ambient pressure produced "tumefied" lungs that were livid and edematous.[2] Paul Bert studied the effects of oxygen at hyperbaric pressure as related to the environmental conditions of caisson workers. He found that oxygen administered above atmospheric pressure produced convulsions resembling strychnine poisoning in mammalian, avian, and cold-blooded species, but he recorded little evidence of pulmonary pathology. Bert's results are recorded in his classic monograph, *La Pression Barometrique*, published in 1876.[2] In 1899, J. Lorraine Smith detailed the pulmonary histopathologic changes of inflammation, congestion, and alveolar consolidation due to granular exudate in the lungs of oxygen-poisoned mice.[2] The first comprehensive, controlled, histopathologic study of pulmonary oxygen toxicity was that of Karsner, who in 1915 exposed rabbits to an environment of 80% to 96% normobaric oxygen; he observed various degrees of pulmonary edema, epithelial desquamation, leukocytic exudate, and fibrin formation.[2]

Interest in the harmful effects of oxygen was further stimulated in the twentieth century as new applications for oxygen were sought in the developing fields of medicine, aeronautics, and space travel. The first controlled study of the effects of normobaric hyperoxic exposure on humans was undertaken by Comròe and colleagues in 1945; they documented respiratory symptoms and decreased lung function in volunteers breathing 100% oxygen for 24 hours.[3] In 1958, Pratt first suggested that capillary proliferation and alveoloseptal fibrosis, observed in the lungs of patients who had received oxygen therapeutically, were manifestations of oxygen poisoning.[4] Subsequently, numerous investigators applied light and electron microscopy and morphometric techniques to elucidate the morphologic features of oxygen toxicity in many animal species.[1] After the introduction of mechanical ventilation and intratracheal delivery of oxygen at high concentrations, lesions similar to those created experimentally in animals were identified in the lungs of humans.[5,6]

In 1967, Northway and colleagues described progressive

pulmonary changes in oxygen-exposed, mechanically ventilated neonates with respiratory distress syndrome and coined the term BPD.[7] The last decade has witnessed an emphasis on investigations of the biochemical pathways of oxygen-induced lung injury. Although oxygen is toxic to the lungs of animals, the role of therapeutically administered oxygen as a cause of lung injury in humans is still controversial.

Mechanisms

FREE-RADICAL THEORY

Molecular oxygen serves as an oxidizing agent and a major source of energy for aerobic organisms.[1] Intracellular oxygen is normally reduced by the transfer of four electrons by means of the mitochondrial cytochrome oxidase system to form water. Partial reduction of oxygen by other enzyme systems results in the formation of hydrogen peroxide (H_2O_2) and superoxide anion (O_2^-), which are readily neutralized by cellular antioxidant enzymes. It is theorized that hyperoxia accelerates the intracellular generation of these reactive oxygen molecules, which overwhelm antioxidant defenses and produce tissue injury. O_2^- in the presence of ferrous iron readily reduces H_2O_2 to form the highly reactive and toxic hydroxyl radical (OH*) by the Fenton reaction. Further chemical interaction between oxygen and lipid peroxyl radicals can yield singlet oxygen ($^1O_2$), an electronically excited state of oxygen that is also extremely toxic to biologic systems.[1] H_2O_2, O_2^-, OH*, and $^1O_2$ are collectively designated "oxygen free radicals" and are the main oxygen metabolites implicated in cellular injury. These molecules can oxidize sulfhydryl enzymes, damage DNA, and peroxidize cellular membrane lipids. Lipid peroxides resulting from membrane peroxidation are also injurious to cellular components (Fig. 15-1).[1]

Oxygen radicals, generated in small amounts during normal aerobic cellular metabolism, are neutralized by endogenous and exogenous antioxidants. Endogenous antioxidant enzymes include superoxide dismutase (SOD), catalase, and the glutathione enzyme system. SOD facilitates the conversion of O_2^- to H_2O_2, and catalase converts H_2O_2 to oxygen and water. Reduced glutathione acts as a preferred substrate to protein sulfhydryl for oxidants, preventing sulfhydryl oxidation. Glutathione peroxidase uses reduced glutathione as a substrate in neutralizing H_2O_2 and lipid peroxides. Glutathione is maintained in its reduced form through coupled reactions governed by glutathione reductase and glucose-6-phosphate dehydrogenase (see Fig. 15-1).[1] Exogenous antioxidants include α-tocopherol (*i.e.*, vitamin E) and ascorbate (*i.e.*, vitamin C), which function as general free-radical scavengers.

ROLE OF NEUTROPHILS

There is evidence that neutrophils play a role in oxygen-induced lung injury. Neutrophils are increased in the interstitial tissue and lung lavage fluid of oxygen-exposed rats, and neutrophil influx has been temporally associated with death of animals used in experiments.[8] Neutropenia conferred protection against pulmonary edema in a rabbit model of oxygen toxicity.[8] Neutrophils potentially contribute to lung injury through the release of oxygen radicals and proteolytic enzymes (see Chap. 14).

In oxygen-exposed neonates with respiratory distress syndrome, a sustained increase in neutrophils, neutrophil elastase activity, and inactivated α-1-proteinase inhibitor occurs in the respiratory secretions of those who ultimately develop BPD.[9] Urinary excretion of elastin degradation products is also increased in children with BPD compared with controls.[10] In neonatal rats exposed to more than 95% oxygen from days 4 to 13 of life (*i.e.*, period of maximal alveolar development), there is reduced total lung elastin fiber length, abnormal alveolar elastin structure, and impaired alveolar development.[11] The data from neonatal humans and experimental animals support the hypothesis that unopposed neutrophil elastase contributes to lung injury and remodeling in BPD (see Chap. 11).

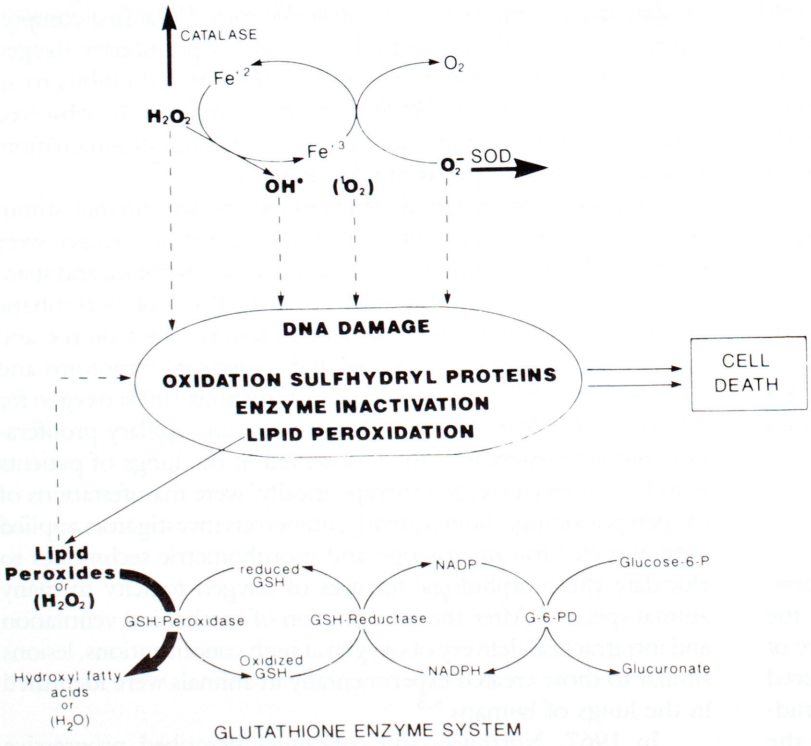

FIGURE 15-1. The cytotoxicity of oxygen free radicals and the major protective endogenous antioxidant enzyme systems. (G-6-PD, glucose-6-phosphate dehydrogenase; GSH, glutathione; H_2O_2, hydrogen peroxide; O_2^-, superoxide anion; $^1O_2$, singlet oxygen; OH*, hydroxyl radical; SOD, superoxide dismutase.)

OXYGEN TOXICITY IN ANIMALS

General Concepts

Most knowledge of oxygen toxicity has been derived from animal experiments. The following discussion summarizes some of the basic concepts of the pathobiology of oxygen-related lung injury.

Although most mammals die when exposed to more than 95% normobaric oxygen, the length of survival differs among species and among individual members of the same species. In general, primates survive longer than rodents in a hyperoxic environment.[1] In some species, immature animals are more resistant to hyperoxic exposure than adults.[1] This resistance is probably conferred by a rapid increase in antioxidant enzymes after oxygen exposure.

Tolerance (*i.e.*, resistance to the toxic effects of oxygen) induced by prior sublethal exposure to oxygen varies among species, but it is especially well developed in the rat. Rats exposed to 85% normobaric oxygen for 5 days can subsequently survive prolonged periods in 100% oxygen.[12] The basis for acquired tolerance in the rat is thought to be increased SOD activity.[12] Chronic exposure to 85% normobaric oxygen does produce significant lung remodeling, including type 2 pneumocyte hyperplasia and a dramatic reduction of the pulmonary capillary bed. The proliferation of type 2 pneumocytes may impart resistance to the toxic effects of oxygen. Tolerance to hyperoxia has also been induced in rats by a variety of other substances, including α-naphthyl thiourea, propylthiouracil, and small doses of endotoxin.[1]

Oxygen damages capillary endothelial and alveolar epithelial cells, but the susceptibility of individual cell types to hyperoxia differs among species. Ultrastructural studies of rats exposed to 100% oxygen confirm extensive destruction of endothelial cells, but similar studies in monkeys demonstrate mainly alveolar epithelial cell damage.[12,13]

Exposure to 60% oxygen for as long as 7 days results in almost no detectable morphologic injury in normal animals.[8] However, biochemical and physiologic evidence of lung injury during this period has been found, and primates exposed to 60% oxygen for 2 weeks developed mild interstitial fibrosis.[1,8] Oxygen toxicity can be enhanced by agents that accelerate free-radical production or impair antioxidant systems. Paraquat is a free-radical–generating compound that occasionally causes fatal poisoning in man. Concomitant exposure to paraquat and oxygen is more lethal to rats than either paraquat or oxygen alone.[1] Similarly, the pulmonary toxicity of bleomycin, a free-radical–generating compound used in anticancer chemotherapy, is increased by hyperoxic exposure.[14] Oxygen exposure appears to have a more deleterious effect on previously injured lung tissue. Hyperoxia exacerbates, by unknown mechanisms, experimental lung injury induced by butylated hydroxytoluene and cyclophosphamide.[14]

Pathology in Subhuman Primates

It is almost impossible to separate the effects of normobaric hyperoxia on the lungs of humans from the antecedent lung injury that necessitated oxygen therapy. Subhuman primates provide an appropriate model for simulating the pure lesion of oxygen toxicity in humans. The progressive morphologic changes after exposure to 100% normobaric oxygen in monkeys consist of an exudative and proliferative phase, identical to DAD in humans (see Chap. 14).[13] Within 48 hours of exposure, no histologic changes are identified. By 4 days, alveolar septa are thickened by edema, neutrophils, and scattered type 2 pneumocytes. Alveoli contain an exudate of erythrocytes, fibrin, leukocytes, and desquamated epithelial cells. At 7 days, there is diffuse proliferation of epithelial cells along the alveolar surface. At 12 days, marked interstitial fibroblast proliferation and collagen deposition accompany epithelial hyperplasia. Animals exposed for 8 to 13 days and allowed to recover in room air demonstrate minimal residual interstitial fibrosis and epithelial hyperplasia.[13]

Ultrastructural morphometric analysis of the primate model confirms extensive, early destruction of type 1 pneumocytes and layering of fibrin on the basement membrane.[13] At 7 days, type 2 pneumocytes cover the alveolar surface and comprise 95% of alveolar epithelial cells, resulting in a 30% increase in epithelial cell volume.[13] There is also evidence of endothelial cell injury. The relative volume of endothelial cells is only 50% of air-exposed controls.[13]

PATHOLOGY OF OXYGEN TOXICITY IN HUMANS

Bronchopulmonary Dysplasia

BPD (*i.e.*, neonatal oxygen toxicity) is the sequela of mechanical ventilation and hyperoxic exposure in premature neonates with respiratory distress syndrome.[7] The histopathologic features of BPD are discussed in Chapter 11. The pathogenesis of BPD is complex, but oxygen toxicity is considered to be one of the most important factors.

In humans and animals exposed to hyperoxic conditions, BPD is characterized by an early exudative phase of edema, fibrinous alveolitis, and necrotizing bronchiolitis and by a proliferative phase of alveolar pneumocyte hyperplasia, interstitial fibroplasia, and bronchiolitis obliterans.[15] Because increasing numbers of premature infants with respiratory distress syndrome have survived the initial stages of BPD, long-standing, healed BPD is now a significant chronic respiratory disease of childhood and is becoming an important chronic respiratory ailment in adults as well.[16,17]

Extended follow-up studies of patients with BPD have documented hypoxemia, airflow limitation, and a high prevalence of airway hyperreactivity.[17] The histologic features of chronic BPD, which were delineated by Stocker, include remodeling of large and small airways, alveolar parenchyma, and lung vasculature.[16] A unique and important feature of severe chronic BPD is marked alveolar hypoplasia. Morphometric studies of fatal chronic BPD by Margraf and colleagues documented a severe reduction in alveolar number, increased mean linear intercept (*i.e.*, an estimate of alveolar diameter), and reduced internal surface area of the lung.[18]

Histologically, the lung in long-standing, healed BPD is composed of large, simplified alveoli (Fig. 15-2). Alveolar elastic fiber architecture is distorted with tortuous, thickened, and irregularly arranged fibers. Similar changes in alveolar morphology and elastin architecture have been described in neonatal rats exposed to more than 95% oxygen during the period of maximal alveolar development.[11] The results of this impaired alveolar development in the human are reduced lung volume and abnormal lobar volume proportions.[18]

The mechanism by which oxygen and other associated factors interfere with alveolar development is unknown, but it probably is related to the destruction and impaired development of alveolar

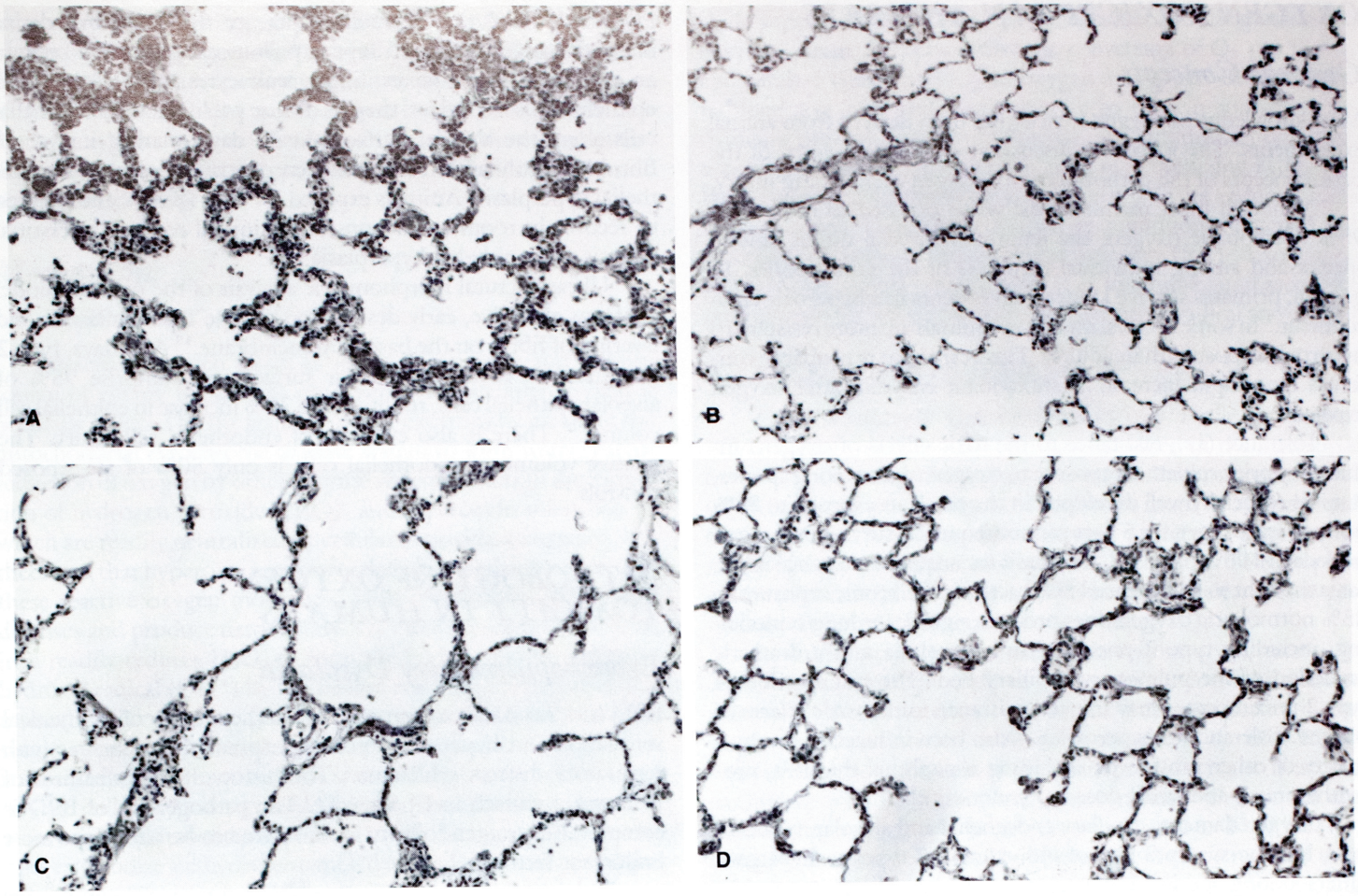

FIGURE 15-2. Alveolar morphology in long-standing, healed bronchopulmonary dysplasia (BPD) can be compared with normal, age-matched control lungs. (**A**) BPD in a 14-month-old patient. (**B**) Normal lung in an 11-month-old child. (**C**) BPD in a 28-month-old patient. (**D**) Normal lung in a 31-month-old child. Alveolar architecture is simplified, and alveoli are larger in patients with BPD. Additionally, alveolar wall thickness and hypercellularity are increased in **A**. (H & E stain; low magnification; from Margraf LR, Tomashefski JF Jr, Bruce MC, Dahms BB. Morphometric analysis of the lung in bronchopulmonary dysplasia. Am Rev Respir Dis 1991;143:391.)

elastin fibers. Because elastic fibers appear to provide the structural framework around which new alveoli develop, proteolytic destruction of these fibers during a period of rapid lung development may contribute to impaired alveolar replication in these infants.[19]

Adult Oxygen Toxicity

Clinical studies of healthy adults exposed to 100% normobaric oxygen for 1 to 3 days have repeatedly demonstrated the typical symptoms of substernal chest pain, seen in almost all persons; cough; sore throat; fatigue; and paresthesias.[3,19] Pulmonary function data indicate reduced vital capacity, reduced diffusing capacity, and hypoxemia. Within 6 hours of exposure, acute tracheitis and decreased tracheal mucus velocity are detected by bronchoscopy. Chest radiographs taken within the first 24 hours are usually normal.[19]

The pathologic features of adult pulmonary oxygen toxicity have largely been discerned from autopsy studies of mechanically ventilated patients given oxygen endotracheally for the management of respiratory failure. The initial causes of respiratory failure in these studies include shock, trauma, and sepsis, which produce acute alveolocapillary injury and noncardiogenic pulmonary edema. The histologic and ultrastructural features attributed to oxygen toxicity are those of DAD, as described in Chapter 14.[5,6]

The near-constant relation between acute respiratory failure and subsequent hyperoxic exposure has raised legitimate questions regarding the importance of oxygen in contributing to human lung injury. Overwhelming evidence from animal data, autopsy studies from the years before ventilators, and numerous studies of patients exposed to oxygen therapy for underlying lung disease leads to the inescapable conclusion that oxygen is an important contributory factor to acute lung injury and progressive respiratory failure in mechanically ventilated patients.[5,20,21]

Because the pulmonary lesions are nonspecific, oxygen toxicity cannot be excluded histologically in a duly exposed patient with DAD in whom the morphologic phase of alveolar damage is commensurate with the duration of oxygen exposure. A mixed pattern of DAD in which hyaline membranes are superimposed on a well-developed fibroproliferative lesion suggests additive injury, such as oxygen toxicity (Fig. 15-3). Regional alveolar damage (RAD), which is localized DAD, is a relatively frequent finding at autopsy, especially in oxygen-exposed patients with other risk factors for the adult respiratory distress syndrome (Fig. 15-4).[22] Sevitt and

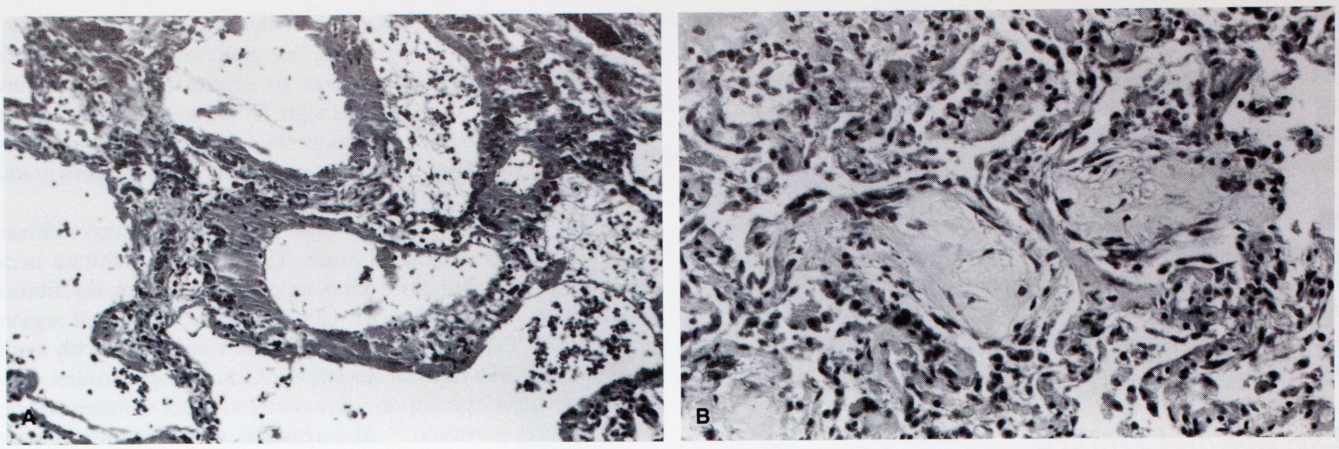

FIGURE 15-3. Mixed-phase diffuse alveolar damage causes (**A**) dense hyaline membranes and (**B**) organizing fibroproliferative changes, as seen in the same histologic section. The hyaline membranes suggest a superimposed acute injury, such as oxygen toxicity. (H & E stain; intermediate magnifications.)

others consider focal hyaline membrane deposition to be a result of exposure to moderate doses of oxygen.[23] RAD often involves the upper lobe and may be associated with radiographic infiltrates that mimic pulmonary edema or pneumonia. The maximal safe level of prolonged oxygen exposure in humans is estimated to be an F_{IO_2} of 60%; but lower inspired concentrations may also be harmful, especially in lungs damaged by prior injury.[1,14]

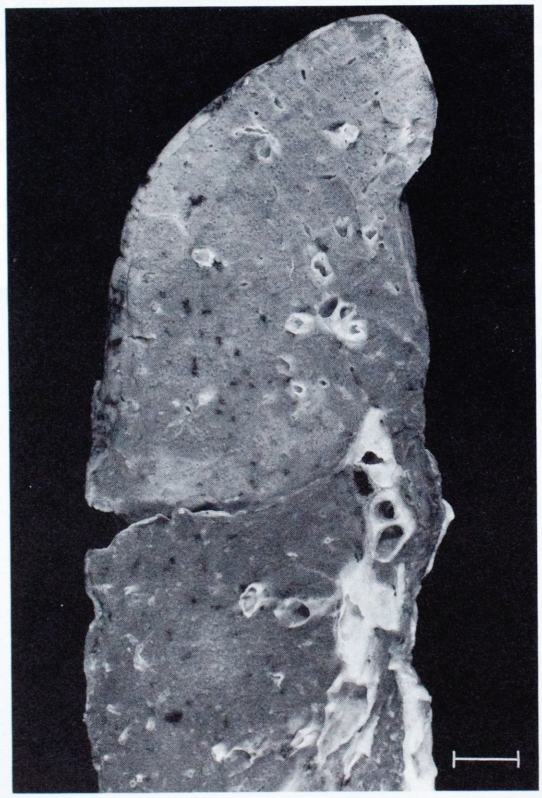

FIGURE 15-4. Regional alveolar damage. Early, proliferative-phase diffuse alveolar damage (DAD) is confined to the upper lobe of the lung, which is pale and firm. DAD is absent in the congested lower lobe. This patient had hypotensive shock, multiorgan failure and septicemia and required mechanical ventilation for 12 days with F_{IO_2} of 60% to 90%. (Scale = 1.3 cm.)

RADIATION PNEUMONITIS

Historical Perspective

The use of irradiation to treat human malignancies rapidly followed Roentgen's discovery of x-rays in 1895. Early reports of lung injury appeared in the 1920s after the therapeutic application of high-energy irradiation.[24] The first clinical documentation was that of Groover, Christie, and Merritt in 1923.[25] In 1922, Hines described the autopsy findings of fibrinous exudate, inflammation, and fibroplasia in the irradiated lungs of a patient with metastatic sarcoma.[26] Comprehensive details of the histopathologic features of radiation-induced lung injury were later provided by Warren and Spencer in 1940[27] and by Jennings and Arden in 1962.[28] Little has been added in the ensuing decades to their anatomic descriptions.

Milestones in the experimental investigation of radiation pneumonitis in a variety of animal species include the studies of Warren and Gates in 1940,[29] Jennings and Arden in 1962,[30] Smith in 1963,[31] and Adamson and colleagues in 1970.[32] Phillips documented the ultrastructural alterations in the irradiated lungs of rats and confirmed the importance of endothelial injury in the pathogenesis of radiation-induced lung damage.[33] The clinical aspects of pulmonary radiation toxicity were accurately summarized by Desjardins in 1926[34] and by Whitfield and colleagues in 1956.[35] A thorough discussion of the general topic of radiation-induced lung injury is provided in an article by Gross.[24]

Mechanisms of Injury

X-rays interact with tissue to produce accelerated electrons that collide with other atoms and molecules to form ion pairs. Ion pairs subsequently react with adjacent molecules, including water, resulting in the formation of free radicals, such as hydroxyl ion (OH^*) and organic free radicals, which are responsible for most of the tissue damage. Organic free radicals undergo secondary reactions with oxygen to form organic peroxides, which are resistant to cellular mechanisms of repair.[24] Consequently, the toxic effects of radiation are exacerbated by elevated tissue oxygen tensions.

The most significant damage induced by radiation is to genetic material, including DNA. Cellular death after irradiation

occurs predominantly during mitosis.[24,33] Within the lung, there is a slow, 2- to 4-month turnover of capillary endothelial cells and alveolar type 2 pneumocytes, which are the stem cells that repopulate the alveolar epithelium. This slow turnover accounts for the latency between radiation exposure and the onset of pneumonitis. As pulmonary cell death occurs, other cell populations are stimulated to proliferate, resulting in increasing waves of mitotic death.[33] The extent of lung injury depends on the volume of lung irradiated and the amount of radiant energy absorbed, which is determined by the total dose of radiation, the fractionation of the dose, and the overall treatment time.[24,33] Formulas have been derived to estimate the biologic effect of radiation delivered on different schedules.[33]

Experimental Features

The most consistent feature of experimental radiation-induced lung injury is damage to the alveolar capillary endothelial cell.[24,30,32,33] In rats, acute endothelial changes occurring within days of exposure include cytoplasmic vacuoles, subendothelial swelling, and cell rupture.[32] Capillary lumens are obstructed by cellular debris and platelet thrombi.[24,32,33] Interstitial edema is also indicative of endothelial injury.[30,32,33] Subsequent changes in the intermediate (2–9 months) and late (>9 months) phases include basement membrane thickening and accumulation of collagen fibers in capillary lumens.[32,33]

Early ultrastructural changes are seen in type 1 epithelial cells. During the intermediate phase, increased numbers of atypical type 2 cells are present, and type 1 cells are reduced. The interstitium is infiltrated by mononuclear cells, mesenchymal cells, and mast cells. After mild injury (600 cGy), there is rapid endothelial repair and minimal interstitial cellular proliferation or fibrosis. With more severe injury (1000 cGy), damage to endothelial cells is prolonged, and there is significant mesenchymal cell proliferation and collagen deposition.[34] At 12 months after irradiation, there is further reduction of type 1 pneumocytes and an increased amount of acellular collagen that expands the alveolar wall and obliterates alveolar lumens.[24,30,33] Hyaline membranes are not a feature of experimental radiation pneumonitis.[24]

Clinical Features

Modern radiation therapy is delivered to the thorax at supervoltage levels in the treatment of patients with breast carcinoma, primary cancers of the lung, or mediastinal tumors such as lymphoma or carcinoma of the esophagus. Between 3% and 5% of patients who receive radiotherapy develop symptomatic pneumonitis.[24] A higher proportion develops radiographic infiltrates but remains asymptomatic. The rate of fatalities due to radiation pneumonitis is low, ranging from 0.7% to 5.8%.[24] Radiation injury is most prevalent among patients with lung cancer. Factors that precipitate or exacerbate radiation injury include administration of selective antineoplastic chemotherapeutic agents (*e.g.*, dactinomycin, doxorubicin, cyclophosphamide, vincristine), rapid withdrawal of corticosteroids, and prior irradiation.[24]

Symptomatic pneumonitis typically occurs at least 6 to 8 weeks after the completion of radiation treatments.[24,33–36] However, radiographic changes may antedate the onset of symptoms by several weeks. Radiation-induced lung injury is often difficult to differentiate from recurrent tumor or infection. The cardinal manifestation is the insidious onset of dyspnea, accompanied by a minimally productive dry cough, low-grade fever, and vague chest pain. Dyspnea rarely progresses to severe respiratory failure. Tachypnea is the main clinical sign. There is no correlation between the presence of radiation skin changes and pulmonary symptoms. The clinical course is protracted, and symptoms gradually resolve over a period of at least 1 month.

The initial finding on the chest radiograph is a hazy infiltrate confined to the irradiated zone. This primary infiltrate occasionally resolves, but more often, it progresses to a streaky, fibrous contraction toward the hilar, apical, or paramediastinal regions (Fig. 15-5). Fibrosis results in ipsilateral volume loss with mediastinal shift and tracheal deviation. Radioisotopic studies done before the development of pulmonary infiltrates demonstrate decreased lung perfusion.[37] Abnormalities of pulmonary function include decreased compliance and reduced lung volumes. In patients with symptomatic pneumonitis, diffusing capacity is reduced and the alveolar-arterial oxygen gradient increased.

Pathology in Humans

There is little information on the pulmonary histologic changes within the first 2 months of radiation exposure.[24] Radiation-induced lung injury in humans is divided histopathologically into acute radiation pneumonitis and radiation fibrosis.

Acute radiation pneumonitis is characterized histologically as DAD. Warren and Spencer identified acute exudative changes and interstitial fibrosis occurring simultaneously within the lung.[27] Characteristic features include intraalveolar fibrinous exudate, dense hyaline membranes, proliferation of highly atypical alveolar epithelial cells, and interstitial and alveolar edema (Fig. 15-6). Atypical epithelial features consist of gigantic cells with one or multiple large, vesicular, pleomorphic nuclei having prominent nucleoli. Inflammation is usually mild (see Fig. 15-6).

Radiation fibrosis is seen grossly as dense, gray scar tissue in a

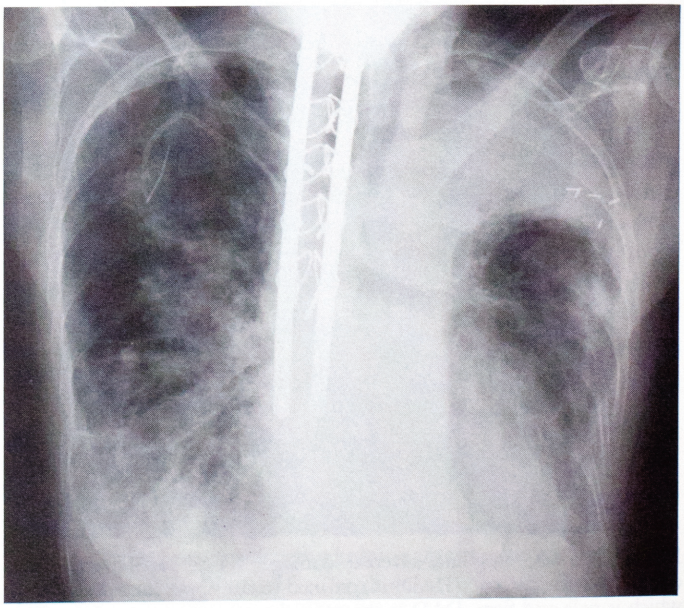

FIGURE 15-5. Diffuse consolidation of the left upper lobe of the lung, 18 months after localized irradiation for metastatic carcinoma of the breast.

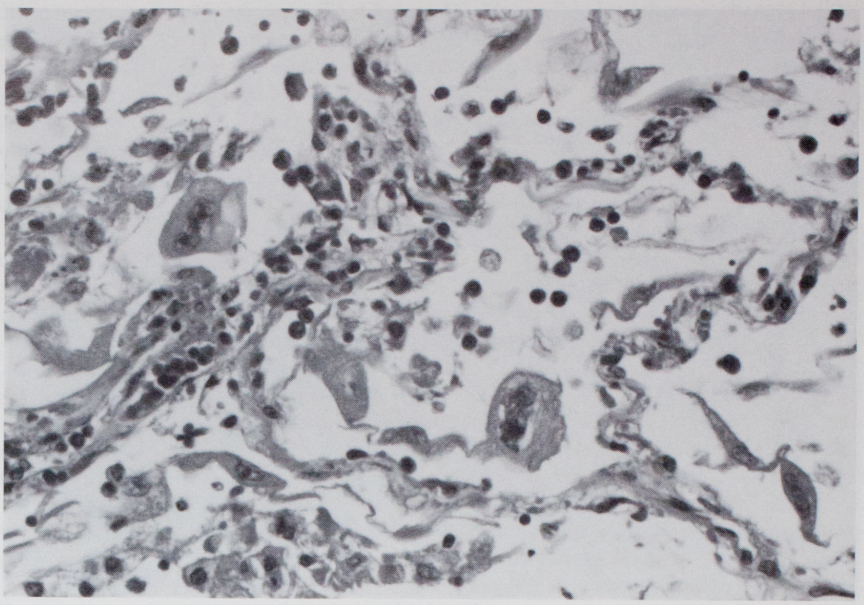

FIGURE 15-6. Histologic features of acute radiation pneumonitis include bizarre epithelial cells, interstitial lymphocytic infiltrates, and some hyaline membranes. The patient completed thoracic irradiation for metastatic carcinoma of the breast 1 month before death. (H & E stain; intermediate magnification.)

distribution that conforms to the ports of radiation delivery. After mediastinal irradiation, a vertical bandlike zone of fibrosis develops subjacent to the medial (*i.e.*, paramediastinal) visceral pleura. After irradiation for carcinoma of the lung, entire lobes are contracted into a fibrous mass (Fig. 15-7). Honeycombing is rare. Histologically, alveolar walls are thickened by sparsely cellular, hyalinized connective tissue.[28,30] Alveolar spaces may be effaced by solid-appearing fibrous tissue (Fig. 15-8). Elastic stains demonstrate distorted, hypertrophic elastic fibers within the fibrous tissue (see Fig. 15-8). There is mural fibrosis and hyalinization of blood vessels, but intimal deposits of foamy macrophages are rarely seen.

The histologic features of radiation fibrosis are frequently obscured by concurrent infection or tumor invasion. Bronchiectasis is occasionally seen, but it usually is the sequela of infection or bronchial obstruction rather than an effect of irradiation. Bronchioles may demonstrate epithelial sloughing, but inflammation and luminal fibrous occlusion are lacking. Pleural inflammation and fibrosis are minimal.

Unusual Complications

Unusual complications of radiation pneumonitis include pleural effusion, pneumothorax, and rib fractures in patients receiving tangential chest wall irradiation for mammary carcinoma.[24] A controversial response to irradiation is lung injury outside of the radiation port clinically presenting as the adult respiratory distress syndrome.[38] This phenomenon may represent errors in radiation dosage or delivery or radiation spillover beyond the delivery port. Some cases probably represent concomitant infection or chemotherapy-induced injury. The hypothesis that diffuse lung injury after localized irradiation is due to lymphatic obstruction is no longer tenable.[33] The possibility that some of the reported cases represent idiopathic diffuse responses to localized irradiation cannot be excluded.

Unilateral hyperlucent lung was originally described by Warren and Spencer as the earliest radiographic change after thoracic radiation—an observation that has not been confirmed in subsequent studies.[27] Unilateral lung hyperlucency has been described as a long-term complication of mediastinal irradiation with subsequent vascular atrophy or occlusion.[39] There have been rare instances of epithelial hyperplasia, carcinoid tumorlets, and primary carcinoma arising in areas of radiation fibrosis, but a causal association has not been proven.[24,40]

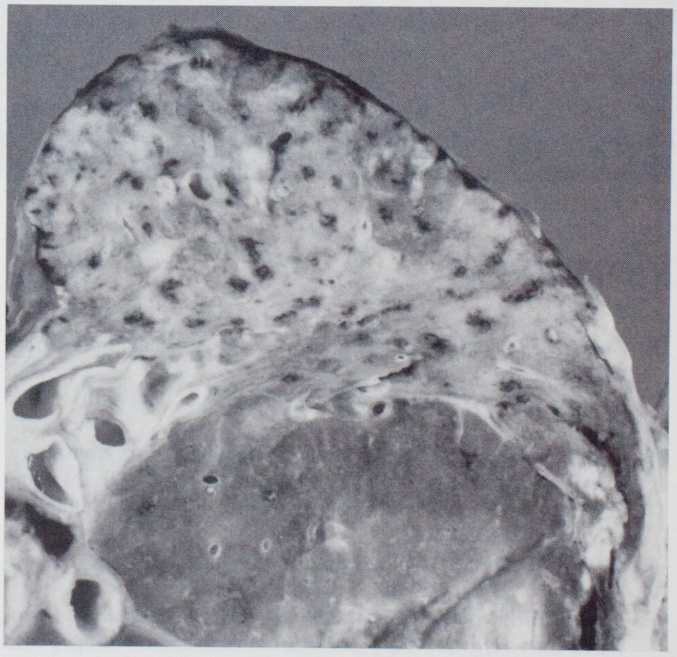

FIGURE 15-7. In the same patient as in Figure 15-5, the left upper lobe of the lung is pale and diffusely fibrotic 18 months after thoracic irradiation. There is a sharp demarcation between the fibrotic area and the darker, uninvolved lung. A fibrous pleural adhesion and metastatic carcinoma are present laterally.

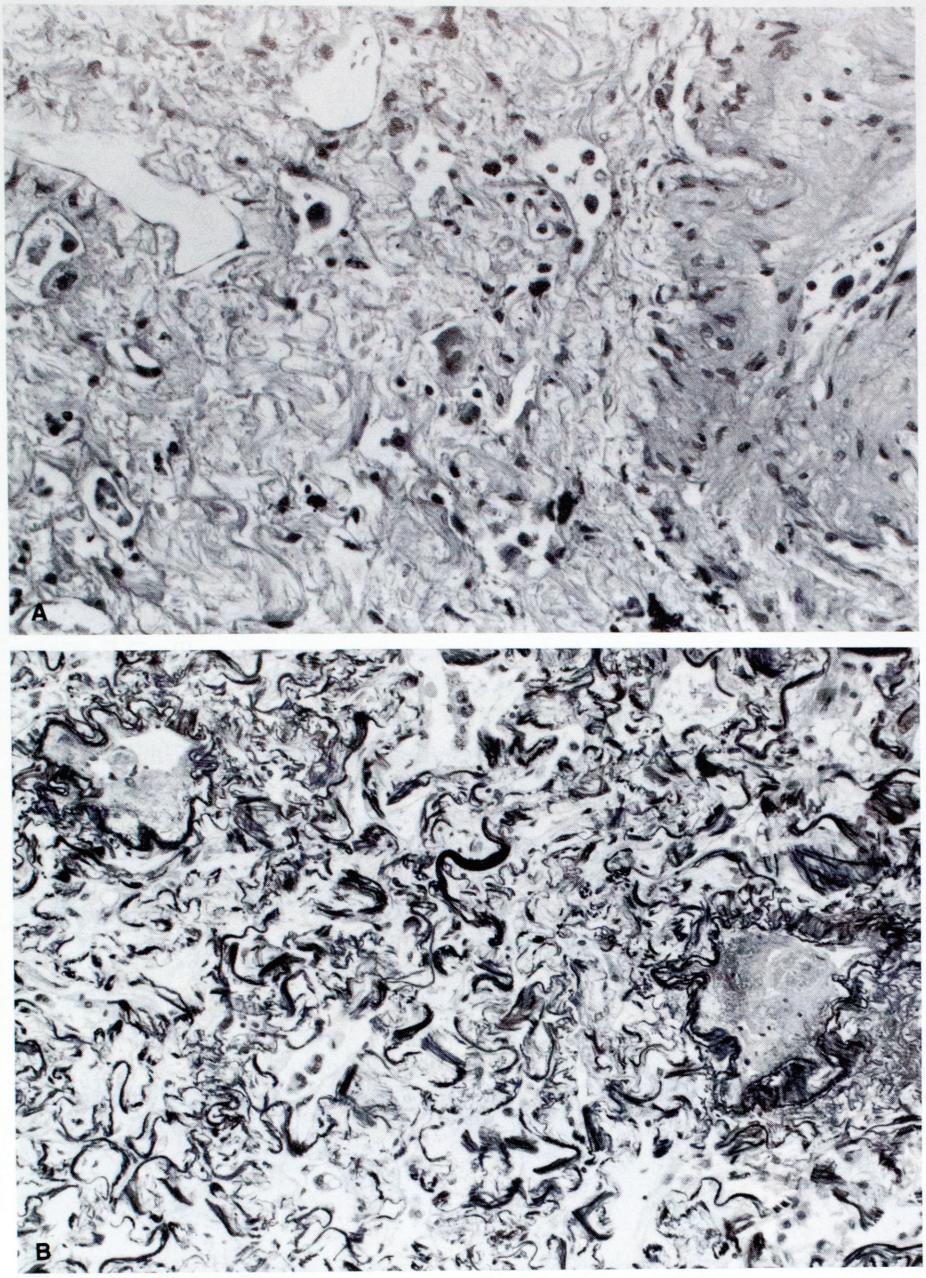

FIGURE 15-8. (**A**) Diffuse radiation fibrosis produces thin-walled blood vessels; a large, sclerotic, hyalinized vessel is present (*right*). (H & E stain; intermediate magnification.) (**B**) Numerous, irregular, thickened elastic fibers traverse the fibrous scar. Two small blood vessels have near-occlusive intimal fibrosis. (Movat pentachrome stain; intermediate magnification.)

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