CHAPTER 31

Drug-Induced Pulmonary Diseases

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KEY CONCEPTS

1. Select populations may be more susceptible to toxicities associated with specific agents.
2. Primary treatment is discontinuation of the offending agent and supportive care.

The manifestations of drug-induced pulmonary diseases span the entire spectrum of pathophysiologic conditions of the respiratory tract. As with most drug-induced diseases, the pathologic changes are nonspecific. Therefore, the diagnosis is often difficult and, in most cases, is based on exclusion of all other possible causes. In addition, the true incidence of drug-induced pulmonary disease is difficult to assess as a result of the pathologic nonspecificity and the interaction between the underlying disease state and the drugs.

Considering the physiologic and metabolic capacity of the lung, it is surprising that drug-induced pulmonary disease is not more common. The lung is the only organ of the body that receives the entire circulation. In addition, the lung contains a heterogeneous population of cells capable of various metabolic functions, including *N*-alkylation, *N*-dealkylation, *N*-oxidation, reduction of *N*-oxides, and *C*-hydroxylation.

Evaluation of epidemiologic studies on adverse drug reactions provides a perspective on the importance of drug-induced pulmonary disease. In a 2-year prospective survey of a community-based general practice, 41% of 817 patients experienced adverse drug reactions.[1] Four patients, or 0.5% of the total respondents, experienced adverse respiratory symptoms. Respiratory symptoms occurred in 1.2% of patients experiencing adverse drug reactions. In a recent retrospective analysis of clinical case series in France, 898 patients had reported drug allergy, with a bronchospasm incidence of 6.9%. When these patients were rechallenged with the suspected drug, only 241 (17.6%) tested positive. The incidence of bronchospasm in patients with positive provocation test was 7.9%.[2]

Adverse pulmonary reactions are uncommon in the general population but are among the most serious reactions, often requiring intervention. In a study of 270 adverse reactions leading to hospitalization from two populations, 3.0% were respiratory in nature.[3] Of the reactions considered to be life-threatening, 12.3% were respiratory. An early report on death caused by drug reactions from the Boston Collaborative Drug Surveillance Program indicated that 7 of 27 drug-induced deaths were respiratory in nature.[4] This was confirmed in a followup study in which 6 of 24 drug-induced deaths were respiratory in nature.[5]

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DRUG-INDUCED APNEA

Apnea may be induced by central nervous system depression or respiratory neuromuscular blockade (Table 31–1). Patients with chronic obstructive airway disease, alveolar hypoventilation, and chronic carbon dioxide retention have an exaggerated respiratory depressant response to narcotic analgesics and sedatives. In addition, the injudicious administration of oxygen in patients with carbon dioxide retention can worsen ventilation-perfusion mismatching, producing apnea.[6] Although the benzodiazepines are touted as causing less respiratory depression than barbiturates, they may produce a profound additive or synergistic effect when taken in combination with other respiratory depressants. Combining intravenous diazepam with phenobarbital to stop seizures in an emergency department frequently results in admissions to an intensive care unit for a short period of assisted mechanical ventilation, regardless of the drug administration rate. Too rapid intravenous administration of any of the benzodiazepines, even without coadministration of other respiratory depressants, will result in apnea. The risk appears to be the same for the various available agents (diazepam, lorazepam, and midazolam). Respiratory depression and arrests resulting in death and hypoxic encephalopathy have occurred following rapid intravenous administration of midazolam for conscious sedation prior to medical procedures. 1 This has been reported more commonly in the elderly and the chronically debilitated or in combination with opioid analgesics. Concurrent use of inhibitors of cytochrome P450 3A4 with benzodiazepines are likely to lead to greater risk of respiratory depression.

1 Prolonged apnea may follow administration of any of the neuromuscular blocking agents used for surgery, particularly in patients with hepatic or renal dysfunction. In addition, persistent neuromuscular blockade and muscle weakness have been reported in critically ill patients who are receiving neuromuscular blockers continuously for more than 2 days to facilitate mechanical ventilation.[7] This has resulted in delayed weaning from mechanical ventilation and prolonged intensive care unit stays. The prolonged neuromuscular blockade has been confined principally to pancuronium and vecuronium in patients with renal disease. Both agents have pharmacologic active metabolites that are excreted renally. The persistent muscular weakness is less-well defined but appears to represent an acute myopathy.[7] High-dose corticosteroids appear to produce a synergistic effect, supported by animal studies showing that corticosteroids at dosages ≥2 mg/kg per day of prednisone produce atrophy in denervated muscle.[8] The fluorinated corticosteroids (e.g., triamcinolone) appear to be more myopathic.[9] Dose-dependent respiratory muscle weakness has been reported in chronic obstructive pulmonary disease (COPD) and asthma patients receiving repeated short courses of oral prednisone in the previous 6 months.[10]

TABLE 31-1 Drugs That Induce Apnea

	Relative Frequency of Reactions
Central nervous system depression	
Narcotic analgesics	F
Barbiturates	F
Benzodiazepines	F
Other sedatives and hypnotics	I
Tricyclic antidepressants	R
Phenothiazines	R
Ketamine	R
Promazine	R
Anesthetics	R
Antihistamines	R
Alcohol	I
Fenfluramine	R
l-Dopa	R
Oxygen	R
Respiratory muscle dysfunction	
Aminoglycoside antibiotics	I
Polymyxin antibiotics	I
Neuromuscular blockers	I
Quinine	R
Digitalis	R
Myopathy	
Corticosteroids	F
Diuretics	I
Aminocaproic acid	R
Clofibrate	R

F, Freguent; I, infrequent; R, rare.

Respiratory failure has been known to occur following local spinal anesthesia. Apnea from respiratory paralysis and rapid respiratory muscle fatigue has followed the administration of polymyxin and aminoglycoside antibiotics.[6] The mechanism appears to be related to the complexation of calcium and its depletion at the myoneural junction. Intravenous calcium chloride has been variably effective in reversing the paralysis.[6] The aminoglycosides competitively block neuromuscular junctions. This has resulted in life-threatening apnea when neomycin, gentamicin, streptomycin, or bacitracin has been 1 administered into the peritoneal and pleural cavities.[6] The aminoglycosides will produce an additive blockade and ventilatory paralysis with curare or succinylcholine and in patients with myasthenia gravis or myasthenic syndromes.[6] Intravenous administration of aminoglycosides has resulted in respiratory failure in babies with infantile 2 botulism. Treatment consists of ventilatory support and administration of an anticholinesterase agent (neostigmine or edrophonium).[6]

DRUG-INDUCED BRONCHOSPASM

Bronchoconstriction is the most common drug-induced respiratory problem. Bronchospasm can be induced by a wide variety of drugs through a number of disparate pathophysiologic mechanisms 1 (Table 31–2). Regardless of the pathophysiologic mechanism, drug-induced bronchospasm is almost exclusively a problem of patients with preexisting bronchial hyperreactivity (e.g., asthma, chronic obstructive lung disease).[11] By definition, all patients with nonspecific bronchial hyperreactivity will experience bronchospasm if given sufficiently high doses of cholinergic or anticholinesterase agents. Severe asthmatics with a high degree of bronchial reactivity may wheeze following the inhalation of a number of particulate substances, such as the lactose in dry-powder inhalers and inhaled corticosteroids, presumably through direct stimulation of the central airway irritant receptors. Other pharmacologic mechanisms for inducing bronchospasm include β_2-receptor blockade and nonimmunologic histamine release from mast cells and basophils.[11] A large number of agents are capable of producing bronchospasm through immunoglobulin (Ig) E-mediated reactions.[11] These drugs can become a significant occupational hazard for pharmacists, nurses, and pharmaceutical industry workers.[11]

TABLE 31-2 Drugs That Induce Bronchospasm

	Relative Frequency of Reactions
Anaphylaxis (IgE-mediated)	
Penicillins	F
Sulfonamides	F
Serum	F
Cephalosporins	F
Bromelin	R
Cimetidine	R
Papain	F
Pancreatic extract	I
Psyllium	I
Subtilase	I
Tetracyclines	I
Allergen extracts	I
Ll-Asparaginase	F
Pyrazolone analgesics	I
Direct airway irritation	
Acetate	R
Bisulfite	F
Cromolyn	R
Smoke	F
N-acetylcysteine	F
Inhaled steroids	I
Precipitating IgG antibodies	
β-Methyldopa	R
Carbamazepine	R
Spiramycin	R
Cyclooxygenase inhibition	
Aspirin/nonsteroidal antiinflammatory drugs	F
Phenylbutazone	I
Acetaminophen	R
Anaphylactoid mast-cell degranulation	
Narcotic analgesics	I
Ethylenediamine	R
Iodinated-radiocontrast media	F
Platinum	R
Local anesthetics	I
Steroidal anesthetics	I
Iron–dextran complex	I
Pancuronium bromide	R
Benzalkonium chloride	I
Pharmacologic effects	
α-Adrenergic receptor blockers	I–F
Cholinergic stimulants	I
Anticholinesterases	R
β-Adrenergic agonists	R
Ethylenediamine tetraacetic acid	R
Unknown mechanisms	
Angiotensin-converting enzyme inhibitors	I
Anticholinergics	R
Hydrocortisone	R
Isoproterenol	R
Monosodium glutamate	I
Piperazine	R
Tartrazine	R
Sulfinpyrazone	R
Zinostatin	R
Losartan	R

F, frequent; I, infrequent; R, rare.

Epidemiologic studies demonstrate an increase in the prevalence of asthma and COPD with increased use of acetaminophen. The use

of aspirin or ibuprofen is not associated with asthma or COPD. The acetaminophen–asthma/COPD association may be explained by reduction of glutathione, an endogenous antioxidant enzyme in the airway epithelial lining fluid, with high doses of acetaminophen resulting in oxidant damage in the lung.[12]

ASPIRIN-INDUCED BRONCHOSPASM

Aspirin sensitivity or intolerance occurs in 4% to 20% of all asthmatics.[13] The frequency of aspirin-induced bronchospasm increases with age. Patients older than age 40 years have a frequency approximately four times that of patients younger than 20 years.[13] The frequency increases to 14% to 23% in patients with nasal polyps.[13] Women predominate over men, and there is no evidence for a genetic or familial predisposition.[14]

The classic description of the aspirin-intolerant asthmatic includes the triad of severe asthma, nasal polyps, and aspirin intolerance. The typical patient experiences intense vasomotor rhinitis, which may or may not be associated with aspirin exposure, beginning during the third or fourth decade of life.[15] Over a period of months, nasal polyps begin to appear, followed by severe asthma exacerbated by aspirin. Bronchospasm typically begins within minutes to hours following ingestion of aspirin and is associated with rhinorrhea, flushing of the head and neck, and conjunctivitis.[15] The reactions are severe and often life-threatening.

All aspirin-sensitive asthmatics do not fit the classic "aspirin triad" picture, and not all patients with asthma and nasal polyps develop sensitivity to aspirin.[14] In most cases, aspirin-sensitive asthmatics are clinically indistinguishable from the general population of asthmatics except for their intolerance to aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs). Aspirin-induced asthmatics are not at higher risk of having fatal asthma if aspirin and other NSAIDs are avoided.[16]

Diagnosis of aspirin-induced asthma requires a detailed medical history. The definitive diagnosis is made by aspirin provocation tests, which may be done via different routes.[14,17] An oral provocation test is used commonly where threshold doses of aspirin induce a positive reaction measured by a drop in forced expiratory volume in the first second of expiration (FEV_1) and/or the presence of symptoms.[17,18] A nasal provocation test is done by the application of one dose of lysine-aspirin, and aspirin sensitivity is manifested with clinical symptoms of watery discharge and a significant fall in inspiratory nasal flow.[17,18] When lysine-aspirin bronchoprovocation was compared with oral aspirin provocation, both methods were equally sensitive.[19]

PATHOGENESIS

Aspirin-induced asthma is correctly classified as an idiosyncratic reaction in that the pathogenesis is still unknown. Patients with aspirin intolerance have increased plasma histamine concentrations after ingestion of aspirin and elevated peripheral eosinophil counts.[14,15] All attempts to define an immunologic mechanism have been unsuccessful. Chemically similar drugs such as salicylamide and choline salicylate do not cross-react, whereas a large number of chemically dissimilar NSAIDs do produce reactions.[14,15] Table 31–3 lists the analgesics that do and do not cross-react with aspirin.

The currently accepted hypothesis of aspirin-induced asthma is that aspirin intolerance is integrally related to inhibition of cyclooxygenase. This is supported by the following evidence: (a) All NSAIDs that inhibit cyclooxygenase produce reactions, (b) the degree of cross-reactivity is proportional to the potency of cyclooxygenase inhibition, and (c) each patient with aspirin sensitivity has a threshold dose for precipitating bronchospasm that is specific for the degree of cyclooxygenase inhibition produced, and once established, the dose of another cyclooxygenase inhibitor needed to induce bronchospasm can be estimated.[15]

TABLE 31-3 Tolerance of Antiinflammatory and Analgesic Drugs in Aspirin-Induced Asthma

Cross-Reactive Drugs	Drugs with No Cross-Reactivity
Diclofenac	Acetaminophen[a]
Diflunisal	Benzydamine
Fenoprofen	Chloroquine
Flufenamic acid	Choline salicylate
Flurbiprofen	Corticosteroids
Hydrocortisone hemisuccinate	Dextropropoxyphene
Ibuprofen	Phenacetin[a]
Indomethacin	Salicylamide
Ketoprofen	Sodium salicylate
Mefenamic acid	
Naproxen	
Noramidopyrine	
Oxyphenbutazone	
Phenylbutazone	
Piroxicam	
Sulindac	
Sulfinpyrazone	
Tartrazine	
Tolmetin	

[a]A very small percentage (5%) of aspirin-sensitive patients react to acetaminophen and phenacetin.

The mechanism by which cyclooxygenase inhibition produces bronchospasm in susceptible individuals is unknown. Arachidonic acid metabolism through the 5-lipoxygenase pathway may lead to the excess production of leukotrienes C_4 and D_4.[16] Leukotrienes C_4, D_4, and E_4 produce bronchospasm and promote histamine release from mast cells.[15] The precise mechanism by which augmented leukotriene production occurs is unknown, and available hypotheses do not explain why only a small number of asthmatic patients react to aspirin and NSAIDs.

DESENSITIZATION

Patients with aspirin sensitivity can be desensitized. The ease of desensitization correlates with the sensitivity of the patient.[15] Highly sensitive patients who react initially to less than 100 mg aspirin require multiple rechallenges to produce desensitization.[14] Desensitization usually persists for 2 to 5 days following discontinuance, with full sensitivity reestablished within 7 days.[14] Cross-desensitization has been established between aspirin and all NSAIDs tested to date. Because patients may experience life-threatening reactions, desensitization should be attempted only in a controlled environment by personnel with expertise in handling these patients. In addition, there are reports of patients who have failed to maintain a desensitized state despite continued aspirin administration.[14] In one open followup trial in 172 aspirin-sensitive asthmatics who had undergone desensitization and continued daily aspirin treatment (1,300 mg/day) an improvement in nasal-sinus and asthma symptoms occurred after 6 months of treatment, which persisted up to 5 years.[20]

CROSS-SENSITIVITY WITH FOOD AND DRUG ADDITIVES

1 Up to 80% of aspirin-sensitive asthmatics will have an adverse reaction to the yellow azo dye tartrazine (FD&C Yellow No. 5), which is used widely for coloring foods, drinks, drugs, and cosmetics.[13] However, the studies reporting high cross-reactivity were poorly controlled and often used only subjective criteria.[13,21] In double-blind, placebo-controlled trials using pulmonary function testing, sensitivity to tartrazine has proved to be a rare event.[21] Tartrazine sensitivity appears to occur only in aspirin-intolerant patients at a prevalence of 2%.[21] Although rare, owing to the severity of reaction and widespread use of tartrazine, the U.S. Food and Drug Administration (FDA)

requires labeling for the products containing this dye.[22] The likely mechanism is dose-related histamine release, and the clinical presentation is the same as the reaction to aspirin in aspirin-sensitive patients.[22]

Reactions to other azo dyes, monosodium glutamate, parabens, and nonazo dyes have been reported much less frequently than reactions to tartrazine and have been equally difficult to confirm with controlled challenges.[21] Positive reactions to sodium benzoate, a food preservative, have been reported in as many as 23% of aspirin-sensitive individuals.[13] Acetaminophen is a weak inhibitor of cyclooxygenase. As such, approximately 5% of aspirin-sensitive asthmatics will experience reactions to acetaminophen.[13] Most aspirin-sensitive asthmatics can use acetaminophen as a safe alternative to aspirin. There is a growing body of evidence that selective cyclooxygenase-2 inhibitors may be used safely in aspirin-sensitive patients,[23–26] but long-term studies with these agents should be undertaken to confirm their safe use in aspirin-sensitive patients. At this point, the package inserts of these agents state that they are contraindicated for aspirin-sensitive asthmatics.[23–26] Sporadic cases of worsening bronchospasm and anaphylaxis have been reported in aspirin-sensitive asthmatics receiving intravenous hydrocortisone succinate, but such reactions have not been reported with use of other corticosteroids.[14] It is not known whether it is the hydrocortisone or the succinate that is the problem.

TREATMENT

Aspirin-Sensitive Asthma

2 Therapy of aspirin-sensitive asthmatics takes one of two general approaches: desensitization or avoidance. Avoidance of triggering substances seldom alters the clinical course of patients' asthma. The therapy of asthma has been nonspecific; however, in theory, 5-lipoxygenase inhibitors such as zileuton or leukotriene antagonists should provide specific therapy. A few studies have investigated use of leukotriene modifiers to prevent aspirin-induced bronchospasm in aspirin-sensitive asthmatic patients.[27–29] Pretreatment with zileuton in eight aspirin-sensitive asthmatic patients protected them from the same threshold-provoking doses of aspirin.[27] However, larger, escalating doses of aspirin above the threshold challenge doses were not examined in this study. Furthermore, when doses of aspirin were escalated above the threshold provocative doses, zileuton did not prevent formation of leukotrienes.[28] In a similar study, pretreatment with montelukast 10 mg/day did not protect patients when aspirin doses were increased above their threshold doses.[29] In another study, the mean provoking dose of aspirin did not differ in the asthmatics who were taking leukotriene modifiers and the control group (60.4 mg vs. 70.3 mg, respectively).[30] Although initial studies suggested that leukotriene modifiers blocked aspirin-induced reactions, it is now apparent that they merely shift the dose–response curve to the right, leaving the patient at risk at higher doses. Thus even patients who might benefit from leukotriene modifiers should avoid aspirin and all NSAIDs. A case of ibuprofen 400-mg–induced asthma was reported in an asthmatic patient on zafirlukast 20 mg twice daily.[31] Furthermore, most of the challenge studies are based on incremental doses of aspirin or NSAIDs, and exposure of patients to full clinical doses of aspirin or NSAIDs can overcome the antagonistic effect of leukotriene modifiers. The respiratory symptoms can be decreased but not prevented by pretreatment with antihistamines, cromolyn, and nedocromil.[14,32] The long-term asthma control of patients with aspirin sensitivity does not differ from that for other asthmatics. There is no evidence to support that aspirin-sensitive asthmatics respond better to leukotriene modifiers. In a double-blind, randomized, placebo-controlled study, aspirin-sensitive asthmatic patients on montelukast showed a 10% improvement in FEV_1 compared with the placebo group.[33] Similar results were reported when montelukast was compared with placebo in patients with intermittent or persistent asthma.[34]

β-BLOCKERS

1 β-Adrenergic receptor blockers comprise the other large class of drugs that can be hazardous to a person with asthma. Even the more cardioselective agents such as acebutolol, atenolol, and metoprolol have been reported to cause asthma attacks.[11] Patients with asthma may take nonselective and β_1-selective blockers without incident for long periods; however, the occasional report of fatal asthma attacks resistant to therapy with β-agonists should provide ample warning of the dangers inherent in β-blocker therapy.[11]

If a patient with bronchial hyperreactivity requires β-blocker therapy, one of the selective β_1-blockers (e.g., acebutolol, atenolol, metoprolol, or pindolol) should be used at the lowest possible dose. Celiprolol and betaxolol appear to possess greater cardioselectivity than currently marketed drugs.[35,36] Fatal status asthmaticus has occurred with the topical administration of the nonselective timolol maleate ophthalmic solution for the treatment of open-angle glaucoma.[37] Early investigations with ophthalmic betaxolol suggest that it is well tolerated even in timolol-sensitive asthmatics.[38,39]

SULFITES

Severe, life-threatening asthmatic reactions following consumption of restaurant meals and wine have occurred secondary to ingestion of the food preservative potassium metabisulfite.[21] Sulfites have been used for centuries as preservatives in wine and food. As antioxidants, they prevent fermentation of wine and discoloration of fruits and vegetables caused by contaminating bacteria.[40] Previously, sulfites had been given "generally recognized as safe" status by the FDA. Sensitive patients react to concentrations ranging from 5 to 100 mg, amounts that are consumed routinely by anyone eating in restaurants. Consumption of sulfites in U.S. diets is estimated to be 2 to 3 mg/day in the home with 5 to 10 mg per 30 mL of beer or wine consumed.[21] Anaphylactic or anaphylactoid reactions to sulfites in nonasthmatics are extremely rare. In the general asthmatic population, reactions to sulfites are 1 uncommon. Approximately 5% of steroid-dependent asthmatics demonstrate sensitivity to sulfiting agents, but the prevalence is only around 1% in non–steroid-dependent asthmatic patients.[40]

MECHANISM

Three different mechanisms have been proposed to explain the reaction to sulfites in asthmatic patients.[40] The first is explained by the inhalation of sulfur dioxide, which produces bronchoconstriction in all asthmatics through direct stimulation of afferent parasympathetic irritant receptors. Furthermore, inhalation of atropine or the ingestion of doxepin protects sulfite-sensitive patients from reacting to the ingestion of sulfites. The second theory, IgE-mediated reaction, is supported by reported cases of sulfite-sensitive anaphylaxis reaction in patients with positive sulfite skin test. Finally, a reduced concentration of sulfite oxidase enzyme (the enzyme that catalyzes oxidation of sulfites to sulfates) compared with normal individuals has been demonstrated in a group of sulfite-sensitive asthmatics.

A number of pharmacologic agents contain sulfites as preservatives and antioxidants. The FDA now requires warning labels on drugs containing sulfites. Most manufacturers of drugs for the treatment of asthma have discontinued the use of sulfites. In addition, labeling is required on packaged foods that contain sulfites at 10 parts per million or more, and sulfiting agents are no longer allowed on fresh fruits and vegetables (excluding potatoes) intended for sale.

Pretreatment with cromolyn, anticholinergics, and cyanocobalamin have protected sulfite-sensitive patients.[40,41] Presumably, pharmacologic doses of vitamin B_{12} catalyze the nonenzymatic oxidation of sulfite to sulfate.

OTHER PRESERVATIVES

Both ethylenediamine tetraacetic acid (EDTA) and benzalkonium chloride, used as stabilizing and bacteriostatic agents, respectively, can produce bronchoconstriction.[42] In addition to producing bronchoconstriction, EDTA potentiates the bronchial responsiveness to histamine.[42] These effects presumably are mediated through calcium chelation by EDTA. Benzalkonium chloride is more potent than EDTA, and its mechanism appears to be a result of mast cell degranulation and stimulation of irritant C fibers in the airways.[42]

The bronchoconstriction from benzalkonium chloride can be blocked by cromolyn but not the anticholinergic ipratropium bromide.[43] Benzalkonium chloride is found in the commercial multiple-dose nebulizer preparations of ipratropium bromide and beclomethasone dipropionate marketed in the United Kingdom and Europe and is presumed to be in part responsible for paradoxical wheezing following administration of these agents.[42–44] Benzalkonium chloride is also found in albuterol nebulizer solutions marketed in the United States and has been implicated as a possible cause of paradoxical wheezing in infants receiving this preparation.[42] The effect of these agents on FEV_1 when used in the amount administered for treatment of acute asthma was evaluated in subjects with stable asthma.[45] Patients were assigned randomly to inhale up to four 600-mcg nebulized doses of EDTA and benzalkonium chloride and normal saline. The change in FEV_1 was not different between EDTA and the placebo group; however, benzalkonium chloride was associated with a statistically significant decrease in FEV_1 compared with placebo. It is important to consider that these agents are always used in combination with bronchodilators and β_2-agonists, which are potent mast cell stabilizers, and the anecdotal reports have not yet been confirmed with controlled investigations.[42,43]

CONTRAST MEDIA

Iodinated radiocontrast materials are the most common cause of anaphylactoid reactions producing bronchospasm.[46] Chapter 91 discusses this topic.

NATURAL RUBBER LATEX ALLERGY

Allergy to natural rubber latex, first reported in 1989 in the United States, is a common cause of occupational allergy for healthcare workers.[47] Natural rubber is a processed plant product from the commercial rubber tree, *Hevea brasiliensis*.[48] Latex allergens are proteins found in both raw latex and the extracts used in finished rubber products. Latex gloves are the largest single source of exposure to the protein allergens.[48]

1 The reported prevalence of latex allergy depends on the sample population. In the general population, latex allergy is less than 1%; however, the prevalence increases in healthcare workers to 5% to 15%.[48] Risk factors for latex allergy include frequent exposure to rubber gloves, history of atopic disease, and presence or history of hand dermatitis. Patients with spina bifida are at an increased risk of latex allergy, with an incidence of 24% to 60% as a result of early and repeated exposure to rubber devices during the surgical procedures.[48]

Clinical manifestations of latex allergy range from contact dermatitis and urticaria, rhinitis and asthma, and reported cases of anaphylaxis.[47,48] The early manifestation of rubber allergy is contact urticaria, which is an IgE-mediated reaction to rubber proteins following direct contact with the medical devices: mainly rubber gloves.[48] Contact dermatitis may occur within 1 to 2 days. Contact dermatitis is a cell-mediated delayed-type hypersensitivity reaction to the additive chemical component of rubber products.[48] Rhinitis and asthma may follow inhalation of allergens by cornstarch powder used to coat the latex gloves. Asthma caused by occupational exposure is seen mostly in atopic patients with histories of seasonal and perennial allergies and asthma.[48] Isolated cases of wheezing secondary to latex exposure in patients without a history of asthma have also been reported.[48]

The diagnosis of latex allergy is based on the presence of latex-specific IgE, as well as symptoms consistent with IgE-mediated 2 reactions.[49] The mainstay of therapy for latex allergy is avoidance. The FDA requires appropriate labeling for all medical devices containing natural rubber latex to ensure avoidance and a latex-free environment. The role of pretreatment with antihistamines, corticosteroids, and allergen immunotherapy remains to be determined.[48,49] Two randomized, placebo-controlled clinical trials have evaluated the role of specific immunotherapy in the treatment of latex allergy.[50,51] Although both studies showed an improvement of cutaneous and rhinitis reactions, systemic reactions were observed, and bronchoconstriction did not improve. At this time, immunotherapy remains investigational for the treatment of latex allergy.

ANGIOTENSIN-CONVERTING ENZYME INHIBITOR–INDUCED COUGH

1 Cough has become a well-recognized side effect of angiotensin-converting enzyme (ACE) inhibitor therapy. According to spontaneous reporting by patients, cough occurs in 1% to 10% of patients receiving ACE inhibitors, with a preponderance of females. In a retrospective analysis, 14.6% of women had cough compared with 6.0% of the men on ACE inhibitors. It is suggested that women have a lower cough threshold, resulting in their reporting this adverse effect more commonly than men.[52] Studies specifically evaluating cough caused by ACE inhibitors report a prevalence of 19% to 25%.[53,54] Patients receiving ACE inhibitors had a 2.3 times greater likelihood of developing cough than a similar group of patients receiving diuretics.[53] Patients with hyperreactive airways do not appear to be at greater risk.[54] African Americans and Chinese have a higher incidence of cough.[52] When different disease states were compared, 26% of patients with heart failure had ACE inhibitor-induced cough compared with 14% of those with hypertension.[52] Cough can occur with all ACE inhibitors.[55]

The cough typically is dry and nonproductive, persistent, and not paroxysmal.[55] The severity of cough varies from a "tickle" to a debilitating cough with insomnia and vomiting. The cough can begin within 3 days or have a delayed onset of up to 12 months following initiation of ACE inhibitor therapy.[55] The cough remits within 1 to 4 days of discontinuing therapy but (rarely) can last up to 4 weeks and recur with rechallenge.[55] Patients should be given a 4-day withdrawal to determine if the cough is induced by ACE inhibitors. The chest radiograph is normal, as are pulmonary function tests (spirometry and diffusing capacity). Bronchial hyperreactivity, as measured by histamine and methacholine provocation, may be worsened in patients with underlying bronchial hyperreactivity such as asthma and chronic bronchitis. However, bronchial hyperreactivity is not induced in others.[55,56] The cough reflex to capsaicin is enhanced but not to nebulized distilled water or citric acid.[55]

The mechanism of ACE inhibitor–induced cough is still unknown. ACE is a nonspecific enzyme that also catalyzes the hydrolysis of bradykinin and substance P (see Chap. 15) that produce or facilitate inflammation and stimulate lung irritant receptors.[55] ACE inhibitors also may induce cyclooxygenase to cause the production of prostaglandins. NSAIDs, benzonatate, inhaled bupivacaine, theophylline, baclofen, thromboxane A_2 synthase inhibitor,[52,57] and cromolyn sodium all have been used to suppress or inhibit ACE inhibitor-induced cough.[55,58] The cough generally is unresponsive to cough suppressants or bronchodilator therapy. No long-term trials evaluating

different treatment options for ACE inhibitor-induced cough exist. Cromolyn sodium may be considered first because it is the 2 most studied agent and has minimal toxicity.[52] The preferred therapy is withdrawal of the ACE inhibitor and replacement with an alternative antihypertensive agent. Owing to their decrease in ACE inhibitor-induced side effects, angiotensin II receptor antagonists often are recommended in place of an ACE inhibitor; however, there are rare reports of this agent inducing bronchospasm.[59] The clinical trials suggest that angiotensin II receptor antagonists have the same incidence of cough as placebo. Furthermore, when angiotensin II receptor antagonists were compared with ACE inhibitors, cough occurred much less frequently. Reduction in the incidence of cough with angiotensin II receptor antagonists is likely caused by the lack of effect on clearance of bradykinin and substance P.[60] The use of alternative therapies to treat ACE inhibitor-induced cough generally is not recommended.[55]

PULMONARY EDEMA

Pulmonary edema may result from the failure of any of a number of homeostatic mechanisms. The most common cause of pulmonary edema is an increase in capillary hydrostatic pressure because of left ventricular failure. Excessive fluid administration in compensated and decompensated heart failure patients is the most frequent cause of iatrogenic pulmonary edema. Besides hydrostatic forces, other homeostatic mechanisms that may be disrupted include the osmotic and oncotic pressures in the vasculature, the integrity of the alveolar epithelium, interstitial pulmonary pressure, and the interstitial lymph flow.[6] The edema fluid in cardiogenic pulmonary edema contains a low amount of protein, whereas noncardiogenic pulmonary edema fluid has a high protein concentration.[6] This indicates that noncardiogenic pulmonary edema results primarily from disruption of the alveolar epithelium.

The clinical presentation of pulmonary edema includes persistent cough, tachypnea, dyspnea, tachycardia, rales on auscultation, hypoxemia from ventilation–perfusion imbalance and intrapulmonary shunting, widespread fluffy infiltrates on chest roentgenogram, and decreased lung compliance (stiff lungs). Noncardiogenic pulmonary edema may progress to hemorrhage; cellular debris collects in the alveoli, followed by hyperplasia and fibrosis with a residual restrictive mechanical defect.[6]

NARCOTIC-INDUCED PULMONARY EDEMA

The most common drug-induced noncardiogenic pulmonary edema is produced by the narcotic analgesics (Table 31–4).[6] Narcotic-induced pulmonary edema is associated most commonly with intravenous heroin use but also has occurred with morphine, methadone, meperidine, and propoxyphene use.[6,61] There also have been a few reported cases associated with the use of the opiate antagonist naloxone and nalmefene, a long-acting opioid antagonist.[62,63] The mechanism is unknown but may be related to hypoxemia similar to the neurogenic pulmonary edema associated with cerebral tumors or trauma or a direct toxic effect on the alveolar capillary membrane.[61] Initially thought to occur only with overdoses, most evidence now supports the theory that narcotic-induced pulmonary edema is an idiosyncratic reaction to moderate as well as high narcotic doses.[61]

Patients with pulmonary edema may be comatose with depressed respirations or dyspnea and tachypnea. They may or may not have other signs of narcotic overdose. Symptomology varies from cough and mild crepitations on auscultation with characteristic radiologic findings to severe cyanosis and hypoxemia, even with supplemental oxygen. Symptoms may appear within minutes of intravenous administration but may take up to 2 hours to occur, particularly following oral methadone.[61] Hemodynamic studies in the first 24 hours have demonstrated normal pulmonary capillary wedge pressures in the presence of pulmonary edema.

TABLE 31-4 Drugs That Induce Pulmonary Edema

	Relative Frequency of Reactions
Cardiogenic pulmonary edema	
Excessive intravenous fluids	F
Blood and plasma transfusions	F
Corticosteroids	F
Phenylbutazone	R
Sodium diatrizoate	R
Hypertonic intrathecal saline	R
β_2-Adrenergic agonists	I
Noncardiogenic pulmonary edema	
Heroin	F
Methadone	I
Morphine	I
Oxygen	I
Propoxyphene	R
Ethchlorvynol	R
Chlordiazepoxide	R
Salicylate	R
Hydrochlorothiazide	R
Triamterene + hydrochlorothiazide	R
Leukoagglutinin reactions	R
Iron–dextran complex	R
Methotrexate	R
Cytosine arabinoside	R
Nitrofurantoin	R
Dextran 40	R
Fluorescein	R
Amitriptyline	R
Colchicine	R
Nitrogen mustard	R
Epinephrine	R
Metaraminol	R
Bleomycin	R
Iodide	R
Cyclophosphamide	R
VM-26	R

F, frequent; I, infrequent; R, rare.

Clinical symptoms generally improve within 24 to 48 hours and radiologic clearing occurs in 2 to 5 days, but abnormalities in pulmonary function tests may persist for 10 to 12 weeks. Therapy consists of naloxone administration, supplemental oxygen, and ventilatory support if required. Mortality is less than 1%.[61]

Cough has been reported with intravenous administration of fentanyl.[64] A cohort of 1,311 adult patients undergoing elective surgery had 120 patients with vigorous cough within 20 seconds after administration of fentanyl.[64] The cough was associated with young age and absence of cigarette smoking.[64] Among anesthetic factors, it was associated with the absence of epidurally administered lidocaine and the absence of a priming dose of vecuronium.[64] A history of asthma or COPD had no predictive effect.[64] Further clinical trials are required to understand the mechanism of paradoxical cough with fentanyl and to identify the means to prevent it.

OTHER DRUGS THAT CAUSE PULMONARY EDEMA

A paradoxical pulmonary edema has been reported in a few patients following hydrochlorothiazide ingestion but not any other benzthiazide diuretic.[6] Acute pulmonary edema rarely has followed the injection of high concentrations of contrast medium into the pulmonary circulation during angiocardiography.[6] Rare occur-

rences of pulmonary edema have followed the intravenous administration of bleomycin, cyclophosphamide, and vinblastine.[6]

The selective β_2-adrenergic agonists terbutaline and ritodrine have been reported to induce pulmonary edema when used as tocolytics.[6] This disorder commonly occurs 48 to 72 hours after tocolytic therapy.[63] This has never occurred with their use in asthma patients, even in inadvertent overdosage. This reaction may result from excess fluid administration used to prevent the hypotension from β_2-mediated vasodilation or the particular hemodynamics of pregnancy. In a review of 330 patients who received tocolytic therapy and were monitored closely for their fluid status, no episode of pulmonary edema was reported.[63]

Interleukin-2, a cytokine used alone or in combination with cytotoxic drugs, has been reported to induce pulmonary edema. Although other cytokines have been associated with pulmonary edema, the problem is most significant with interleukin-2. A weight gain of 2 kg has been reported after treatment with interleukin-2.[63]

Pulmonary edema has occurred occasionally with salicylate overdoses. The serum salicylate concentrations are often greater than 45 mg/dL, and the patients have other signs of toxicity, although some cases have been associated with concentrations in the usual therapeutic range.[61]

PULMONARY EOSINOPHILIA

Pulmonary infiltrates with eosinophilia (Loeffler syndrome) are associated with nitrofurantoin, *para*-aminosalicylic acid, methotrexate, sulfonamides, tetracycline, chlorpropamide, phenytoin, NSAIDs, and imipramine (Table 31–5).[6,65] The disorder is characterized by fever, nonproductive cough, dyspnea, cyanosis, bilateral pulmonary infiltrates, and eosinophilia in the blood.[6] Lung biopsy has revealed perivasculitis with infiltration of eosinophils, macrophages, and proteinaceous edema fluid in the alveoli. The symptoms and eosinophilia generally respond rapidly to withdrawal of the offending drug.

Sulfonamides were first reported as causative agents in users of sulfanilamide vaginal cream.[6] *para*-Aminosalicylic acid frequently produced the syndrome in tuberculosis patients being treated with this agent.[6] There are nine reported cases associated with sulfasalazine use in inflammatory bowel disease.[65] The drug associated most frequently with this syndrome is nitrofurantoin.[6,61] Nitrofurantoin-induced lung disorders appear to be more common in postmenopausal women.[61] Lung reactions made up 43% of 921 adverse reactions to nitrofurantoin reported to the Swedish Adverse Drug Reaction Committee between 1966 and 1976.[65] No apparent correlation exists between duration of drug exposure and severity or reversibility of the reaction.[65] Most cases occur within 1 month of therapy. Typical symptoms include fever, tachypnea, dyspnea, dry cough, and, less commonly, pleuritic chest pain. Radiographic findings include bilateral interstitial infiltrates, predominant in the bases and pleural effusions 25% of the time. Although there are anecdotal reports that steroids are beneficial, the usual rapid improvement following discontinuation of the drugs brings the usefulness of steroids into question. Complete recovery usually occurs within 15 days of withdrawal.

A few cases of pulmonary eosinophilia have been reported in asthmatics treated with cromolyn.[6,65] The significance of this is unknown in light of the occasional spontaneous occurrence of pulmonary eosinophilia in asthmatic patients. Cases of acute pneumonitis and eosinophilia have been reported to occur with phenytoin and carbamazepine therapy.[65] Patients have had other symptoms of hypersensitivity, including fever and rashes. The symptoms of dyspnea and cough subside following discontinuation of the drug.

TABLE 31-5 Drugs That Induce Pulmonary Infiltrates with Eosinophilia (Loeffler Syndrome)

Drug	Relative Frequency of Reactions	Drug	Relative Frequency of Reactions
Nitrofurantoin	F2	Tetracycline	R
para-Aminosalicylic acid	F	Procarbazine	R
Sulfonamides	I	Cromolyn	R
Penicillins	I	Niridazole	R
Methotrexate	I	Gold salts	R
Imipramine	I	Chlorpromazine	R
Chlorpropamide	R	Naproxen	R
Carbamazepine	R	Sulindac	R
Phenytoin	R	Ibuprofen	R
Mephenesin	R		

F, frequent; I, infrequent; R, rare.

OXYGEN TOXICITY

Because of the similarity to pulmonary fibrosis, oxygen-induced lung toxicity is reviewed briefly. More extensive reviews on this topic have been published.[66,67]

The earliest manifestation of oxygen toxicity is substernal pleuritic pain from tracheobronchitis.[67] The onset of toxicity follows an asymptomatic period and presents as cough, chest pain, and dyspnea. Early symptoms usually are masked in ventilator-dependent patients. The first noted physiologic change is a decrease in pulmonary compliance caused by reversible atelectasis. Then decreases in vital capacity occur, followed by progressive abnormalities in carbon monoxide diffusing capacity.[67] Decreased inspiratory flow rates, reflected in the need for high inspiratory pressures in ventilator-dependent patients, occur as the fractional concentration of inspired oxygen requirement increases. The lungs become progressively stiffer as the ability to oxygenate becomes more compromised.

The fraction of inspired oxygen and duration of exposure are both important determinants of the severity of lung damage. Normal human volunteers can tolerate 100% oxygen at sea level for 24 to 48 hours with minimal to no damage.[66] Oxygen concentrations of less than 50% are well tolerated even for extended periods. Inspired oxygen concentrations between 50% and 100% carry a substantial risk of lung damage, and the duration required is inversely proportional to the fraction of inspired oxygen.[66] Underlying disease states may alter this relationship. Lung damage may not be lasting and may improve months to years after the exposure.[68,69]

Oxygen-induced lung damage generally is separated into the acute exudative phase and the subacute or chronic proliferative phase. The acute phase consists of perivascular, peribronchiolar, interstitial, and alveolar edema with alveolar hemorrhage and necrosis of pulmonary endothelium and type I epithelial cells.[66] The proliferative phase consists of resorption of the exudates and hyperplasia of interstitial and type II alveolar lining cells. Collagen and elastin deposition in the interstitium of alveolar walls then leads to thickening of the gas-exchange area and the fibrosis.[66]

The biochemical mechanism of the tissue damage during hyperoxia is the increased production of highly reactive, partially reduced oxygen metabolites (Fig. 31–1).[67] These oxidants normally are produced in small quantities during cellular respiration and include the superoxide anion, hydrogen peroxide, the hydroxyl radical, singlet oxygen, and hypochlorous acid.[67] Oxygen free radicals normally are formed in phagocytic cells to kill invading microorganisms, but they also are toxic to normal cell components. The oxidants produce toxicity through destructive redox reactions with protein sulfhydryl groups, membrane lipids, and nucleic acids.[67]

The oxidants are products of normal cellular respiration that are normally counterbalanced by an antioxidant defense system that prevents tissue destruction. The antioxidants include superoxide dismutase, catalase, glutathione peroxidase, ceruloplasmin, and

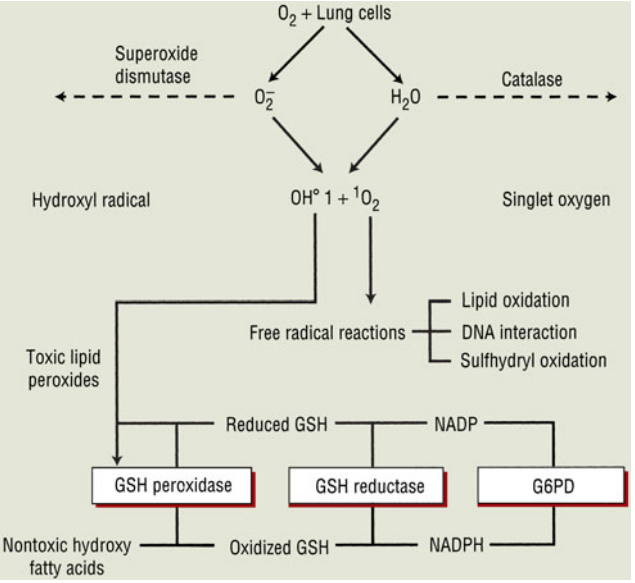

FIGURE 31-1. Schematic of the interaction of oxygen radicals and the antioxidant system. (GSH, glutathione; G6PD, glucose-6-phosphate dehydrogenase; NADP, nicotinamide-adenine dinucleotide phosphate; NADPH, reduced NADP.)

α-tocopherol (vitamin E). Antioxidants are ubiquitous in the body. Hyperoxia produces toxicity by overwhelming the antioxidant system. There is experimental evidence that a number of drugs and chemicals produce lung toxicity through increasing production of oxidants (e.g., bleomycin, cyclophosphamide, nitrofurantoin, and paraquat) and/or by inhibiting the antioxidant system (e.g., carmustine, cyclophosphamide, and nitrofurantoin).[70,71]

PULMONARY FIBROSIS

A large number of drugs are associated with chronic pulmonary fibrosis with or without a preceding acute pneumonitis (Table 31–6). The cancer chemotherapeutic agents make up the largest group and have been the subject of numerous reviews.[70,71] Although the mechanisms by which all the drugs produce pneumonitis and/or fibrosis are not known, the clinical syndrome, pulmonary function abnormalities, and histopathology present a relatively homogeneous pattern.[70] The histopathologic picture closely resembles oxidant lung damage, and in some experimental cases, oxygen enhances the pulmonary injury.[61] Although the terms *pulmonary fibrosis* or *interstitial pneumonitis* have been used widely to describe pneumonia after bone marrow transplantation, in 1991, a National Institutes of Health workshop recommended that the term *idiopathic pneumonia syndrome* (IPS) should be used to avoid histopathologic terms and to define the inherent heterogeneity of this disorder.[72] IPS accounts for more than 40% of deaths related to bone marrow transplantation.[72] Suggested causes of IPS include radiation or chemotherapy regimens prior to transplantation, graft-versus-host disease, unrecognized infections, and other inflammation-related lung injuries.[73,74] IPS is characterized by dyspnea, hypoxemia, nonproductive cough, diffuse alveolar damage, and interstitial pneumonitis in the absence of lower respiratory infection. IPS has been reported early and late, up to 24 months after bone marrow transplantation.[74]

The lung damage following ingestion of the contact herbicide paraquat classically resembles hyperoxic lung damage. Hyperoxia accelerates the lung damage induced by paraquat. Lung toxicity from paraquat occurs following oral administration in humans and aerosol administration and inhalation in experimental animals.[71] The pulmonary specificity of paraquat results in part from its active uptake into lung tissue. Paraquat readily accepts an electron from reduced nicotinamide-adenine dinucleotide phosphate and then is reoxidized rapidly, forming superoxide and other oxygen radicals.[71] The toxicity may be a result of nicotinamide-adenine dinucleotide phosphate depletion (see Fig. 31–1) and/or excess oxygen free radical generation with lipid peroxidation. Treatment with exogenous superoxide dismutase has had limited and conflicting results.[71]

A number of furans have been shown to produce oxidant injury to lungs.[71] Occasionally, patients with acute nitrofurantoin lung toxicity will progress to a chronic reaction leading to fibrosis, and rarely, a patient may develop chronic toxicity without an antecedent acute reaction. Like paraquat, nitrofurantoin undergoes cyclic reduction and reoxidation that may produce superoxide radicals or deplete nicotinamide-adenine dinucleotide phosphate. In addition, nitrofurantoin inhibits glutathione reductase, an enzyme involved in the glutathione antioxidant system (see Fig. 31–1). Table 31–7 lists possible nondrug causes of pulmonary fibrosis.

TABLE 31-6 Drugs That Induce Pneumonitis and/or Fibrosis

Drug	Relative Frequency of Reactions	Drug	Relative Frequency of Reactions
Oxygen	F	Chlorambucil	R
Radiation	F	Melphalan	R
Bleomycin	F	Lomustine and semustine	R
Busulfan	F	Zinostatin	R
Carmustine	F	Procarbazine	R
Hexamethonium	F	Teniposide	R
Paraquat	F	Sulfasalazine	R
Amiodarone	F	Phenytoin	R
Mecamylamine	I	Gold salts	R
Pentolinium	I	Pindolol	R
Cyclophosphamide	I	Imipramine	R
Practolol	I	Penicillamine	R
Methotrexate	I	Phenylbutazone	R
Mitomycin	I	Chlorphentermine	R
Nitrofurantoin	I	Fenfluramine	R
Methysergide	I	Leflunomide	R
Sirolimus	I	Mefloquine	R
Azathioprine, 6-mercaptopurine	R	Pergolide	R

F, frequent; I, infrequent; R, rare.

TABLE 31-7 Possible Causes of Pulmonary Fibrosis

- Idiopathic pulmonary fibrosis (fibrosing alveolitis)
- Pneumoconiosis (asbestosis, silicosis, coal dust, talc berylliosis)
- Hypersensitivity pneumonitis (molds, bacteria, animal proteins, toluene diisocyanate, epoxy resins)
- Smoking
- Sarcoidosis
- Tuberculosis
- Lipoid pneumonia
- Systemic lupus erythematosus
- Rheumatoid arthritis
- Systemic sclerosis
- Polymyositis/dermatomyositis
- Sjögren syndrome
- Polyarteritis nodosa
- Wegener granuloma
- Byssinosis (cotton workers)
- Siderosis (arc welders' lung)
- Radiation
- Oxygen
- Chemicals (thioureas, trialkylphosphorothioates, furans)
- Drugs (see Tables 31-5, 31-6, and 31-8)

DRUGS ASSOCIATED WITH PULMONARY FIBROSIS

ANTINEOPLASTICS

A number of cancer chemotherapeutic agents produce pulmonary fibrosis. In an excellent review,[70] six predisposing factors for the development of cytotoxic drug–induced pulmonary disease were described: (a) cumulative dose, (b) increased age, (c) concurrent or previous radiotherapy, (d) oxygen therapy, (e) other cytotoxic drug therapy, and (f) preexisting pulmonary disease. Drugs that are directly toxic to the lung would be expected to show a dose–response relationship. Dose–response relationships have been established for bleomycin, busulfan, and carmustine (BCNU).[70] Bleomycin and busulfan exhibit threshold cumulative doses below which a very small percentage of patients exhibit toxicity, but carmustine shows a more linear relationship.[71] Older patients appear to be more susceptible, possibly as a result of a decrease in the antioxidant defense system.

Excessive irradiation produces a pneumonitis and fibrosis thought to be caused by oxygen free radical formation.[70] Evidence for synergistic toxicity with radiation exists for bleomycin, busulfan, and mitomycin.[70] Hyperoxia has shown synergistic toxicity with bleomycin, cyclophosphamide, and mitomycin.[70] Carmustine, mitomycin, cyclophosphamide, bleomycin, and methotrexate all appear to show increased lung toxicity when they are part of multiple-drug regimens.

NITROSOUREAS

BCNU is associated with the highest incidence of pulmonary toxicity (20% to 30%).[70] The lung pathology generally resembles that produced by bleomycin and busulfan. Unique to BCNU is the finding of fibrosis in the absence of inflammatory infiltrates. BCNU preferentially inhibits glutathione reductase, the enzyme required to regenerate glutathione, thus reducing glutathione tissue stores.[70,71] The patients present with dyspnea, tachypnea, and nonproductive cough that may begin within a month of initiation of therapy but may not develop for as long as 3 years.[70] Most patients receiving BCNU develop fibrosis that may remain asymptomatic or become symptomatic any time up to 17 years after therapy.[75] The cumulative dose has ranged from 580 to 2,100 mg/m^2.[71] The disease is usually slowly progressive with a mortality rate from 15% to greater than 90% depending on the study and period of followup. In a retrospective study, the risk factors for development of IPS and prognostic factors for outcomes were evaluated in 94 patients with relapsed Hodgkin disease treated with BCNU containing high-dose chemotherapy and hematopoietic support. The risk factors for pulmonary fibrosis and mortality were female sex and dose of BCNU, with all deaths reported in those who received BCNU at doses of more than 475 mg/m^2.[76] Rapid progression and death within a few days occur in a small percentage of patients.[70] Corticosteroids do not appear to be effective in reducing damage.[70] Other nitrosoureas, lomustine, and semustine also have been reported to produce lung damage in patients receiving unusually high doses.[70]

BLEOMYCIN

Bleomycin is the best-studied cytotoxic pulmonary toxin. Because of its lack of bone marrow suppression, pulmonary toxicity is the dose-limiting toxicity of bleomycin therapy. The incidence of bleomycin lung toxicity is approximately 4%, which may be affected by the following risk factors: bleomycin cumulative dose, age, high concentration of inspired oxygen, radiation therapy, and multidrug regimens, particularly those with cyclophosphamide.[63] Age at the time of treatment with bleomycin also may be a risk factor; patients younger than 7 years of age at the time of receiving bleomycin therapy are more likely to develop pulmonary toxicity compared with older subjects.[63] The cumulative dose above which the incidence of toxicity significantly increases is 450 to 500 units.[70] However, rapidly fatal pulmonary toxicity has occurred with doses as low as 100 units.[70]

Experimentally, bleomycin generates superoxide anions, and the lung toxicity is increased by radiation and hyperoxia.[70] Pretreatment with superoxide dismutase and catalase reduces toxicity in experimental animals.[70] Bleomycin also oxidizes arachidonic acid, which may account for the marked inflammation. Bleomycin also may affect collagen deposition by its stimulation of fibroblast growth.[70] Combination of bleomycin with other cytotoxic agents, particularly regimens containing cyclophosphamide, may predispose patients to pulmonary damage.

There are two distinct clinical patterns of bleomycin pulmonary toxicity. Chronic progressive fibrosis is the most common; acute hypersensitivity reactions occur infrequently. Patients present with cough and dyspnea. The first physiologic abnormality seen is a decreased diffusing capacity of carbon monoxide.[70] Chest radiographs show a bibasilar reticular pattern, and gallium scans show marked uptake in the involved lung.[70] Chest radiographic changes lag behind pulmonary function abnormalities. Spirometry tests before each bleomycin dose are not predictive of toxicity. The single-breath diffusing capacity of carbon monoxide is the most sensitive indicator of bleomycin-induced lung disease. Although it is not absolutely predictive, a drop of 20% or greater in the diffusing capacity of carbon monoxide is an indication for using alternative therapies.[70] The prognosis of bleomycin lung toxicity has improved as a consequence of early detection, but the mortality rate is approximately 25%. Mild cases respond to discontinuation of bleomycin therapy.[63] Corticosteroid therapy appears to be helpful in patients with acute pneumonitis, although there have been no controlled trials. Patients with chronic fibrosis are less likely to respond. Although corticosteroids have been used for a number of drug-induced pulmonary problems, a study in mice showing a potential for worsening of lung damage when administered early during the repair stage should sound a word of caution against their indiscriminate use.[77]

MITOMYCIN

Mitomycin is an alkylating antibiotic that produces pulmonary fibrosis at a frequency of 3% to 12%.[70] The mechanism is unknown, but oxygen and radiation therapy appear to enhance the development of toxicity.[70] The clinical presentation and symptoms are the same as for bleomycin. The mortality rate is approximately 50%. Early withdrawal of the drug and administration of corticosteroids appear to improve the outcome significantly.

ALKYLATING AGENTS

A number of alkylating agents are associated with pulmonary fibrosis (see Table 31–5). The incidence of clinical toxicity is around 4%, although subclinical damage is apparent in up to 46% of patients at autopsy. The mechanism of toxicity is unknown; however, epithelial cell damage that triggers the arachidonic acid inflammatory cascade may be the initiating event.[70] The clinical presentation is insidious, with 4 years being the average duration of therapy before the onset of symptoms.[70] Patients present with low-grade fever, weight loss, weakness, dyspnea, cough, and rales.[70] Pulmonary function tests initially show abnormal diffusion capacity followed by a restrictive pattern (low vital capacity). The histopathologic findings are nonspecific. The prognosis is one of slow progression with a mean survival of 5 months following diagnosis.[70] Although there is no direct dose-dependent correlation, patients receiving less than 500 mg of busulfan do not develop the syndrome without concomitant radiation or use of other pulmonary toxic chemotherapeutic agents.[70] There are anecdotal

reports of beneficial responses to corticosteroids, but no controlled studies have been done.

Cyclophosphamide infrequently produces pulmonary toxicity. More than 20 well-documented cases have been reported to date. In animal models, cyclophosphamide produces reactive oxygen radicals. High oxygen concentrations produce synergistic toxicity with cyclophosphamide. The duration of therapy before the onset of symptoms is highly variable, and there may be a delay of several months between the onset of symptoms and discontinuation of the drug.[70] Cyclophosphamide may potentiate carmustine lung toxicity.[70] Clinical symptoms usually consist of dyspnea on exertion, cough, and fever. Inspiratory crackles and the bibasilar reticular pattern typical of cytotoxic drug-induced radiographic changes are present. Histopathologic changes are also nonspecific. Approximately 60% of patients recover. Corticosteroid therapy has been reported to be beneficial; however, death despite corticosteroid administration also has been reported.

Chlorambucil, melphalan, and uracil mustard also are associated with pulmonary fibrosis. Of the alkylating agents, only nitrogen mustard and thiotepa have not been reported to cause fibrotic pulmonary toxicity.[70]

ANTIMETABOLITES

Methotrexate was first reported to induce pulmonary toxicity in 1969.[70] The pulmonary toxicity to methotrexate is unique in that discontinuation is not always necessary, and reinstitution of the drug may not produce recurrence of symptoms.[6] Methotrexate pulmonary toxicity most commonly appears to result from hypersensitivity,[65] and it can occur 3 or more years following methotrexate therapy.[78] Age, sex, underlying pulmonary disease, duration of therapy, or smoking is not associated with an increased risk of pneumonitis with methotrexate.[78] Serial pulmonary function tests did not help to identify pneumonitis in patients receiving methotrexate before the onset of clinical symptoms.[78] Reductions in diffusing capacity of carbon monoxide and lung volumes are the most common manifestations of methotrexate lung toxicity.[63] Pulmonary edema and eosinophilia are common, and fibrosis occurs in only 10% of the patients who develop acute pneumonitis.[70] Systemic symptoms of chills, fever, and malaise are common before the onset of dyspnea, cough, and acute pleuritic chest pain. Methotrexate also is associated with granuloma formation.[70]

The prognosis of methotrexate-induced pulmonary toxicity is good, with a 1% or less mortality rate.[65] Pulmonary toxicity has followed intrathecal as well as oral administration and has occurred after single doses as well as long-term daily and intermittent administration.[70] Pneumonitis has been reported to occur up to 4 weeks following discontinuation of therapy.[70] Numerous anecdotal reports have claimed dramatic benefit from corticosteroid therapy. It is unknown whether intermittent (weekly) dosing, as is done for rheumatoid arthritis, decreases the risk of methotrexate-induced pulmonary toxicity because pneumonitis has occurred with this form of dosing.

Rarely, azathioprine and its major metabolite 6-mercaptopurine have been reported to produce an acute restrictive lung disease. Procarbazine, a methylhydrazine associated more commonly with Loeffler syndrome, rarely has been associated with pulmonary fibrosis.[65] The vinca alkaloids vinblastine and vindesine have been reported to produce severe respiratory toxicity in association with mitomycin. The incidence with the combination is 39% and may represent a true synergistic effect between these agents.[70]

NONCYTOTOXIC DRUGS

Pulmonary fibrosis associated with the ganglionic-blocking agent hexamethonium was first reported in 1954 (see Table 31–6).[6] Patients developed extreme dyspnea after several months on the drug. Pathologic findings were consistent with bronchiectasis, bronchiolectasis, and fibrosis.[6] This phenomenon has occurred occasionally with use of the other ganglionic blockers (i.e., mecamylamine and pentolinium).[6]

In 1959, radiographic changes characteristic of diffuse pulmonary fibrosis were reported in 27 (87%) of 31 patients who had taken phenytoin for 2 years or more.[61] Since then, studies have been conflicting. If phenytoin does produce chronic fibrosis, it would appear to be a relatively rare event.

Gold salts (sodium aurothiomalate) used in the treatment of rheumatoid arthritis have produced pulmonary fibrosis with cough, dyspnea, and pleuritic pain 5 to 16 weeks following institution of therapy.[61] Pulmonary function tests show a restrictive defect, and patients generally have an eosinophilia. The reactions improve on discontinuation of the gold therapy and recur promptly on reexposure. The pulmonary deficit may not resolve completely.

AMIODARONE

Amiodarone, a benzofuran derivative, produces pulmonary fibrosis when used for supraventricular and ventricular arrhythmias (see Table 31–6).[79] The duration of amiodarone therapy before the onset of symptoms has ranged from 4 weeks to 6 years.[61,79] The estimated incidence is 1 in 1,000 to 2,000 treated patients per year. The clinical course is variable, ranging from acute onset of dyspnea with rapid progression into severe respiratory failure and death caused by slowly developing exertional dyspnea over a few months. Patients generally improve on discontinuation of the drug.[79] The majority of patients develop reactions while taking maintenance doses greater than 400 mg daily for more than 2 months or smaller doses for more than 2 years. The risk of amiodarone pulmonary toxicity is higher during the first 12 months of therapy even at a low dosage.[80] Other risk factors include cardiopulmonary surgery combined with the administration of high concentrations of oxygen.[80] Routine spirometry does not appear to be predictive of patients at risk.[81] Carbon monoxide diffusing capacity studies are sensitive indicators of amiodarone pulmonary toxicity but have only a 21% positive predictive value.[81] Clinical findings include exertional dyspnea, nonproductive cough, weight loss, and occasionally low-grade fever.[61,81] Radiographic changes are nondiagnostic and consist of diffuse bilateral interstitial changes consistent with a pneumonitis. Pulmonary function abnormalities include hypoxia, restrictive changes, and diffusion abnormalities.

The mechanism of amiodarone-induced pulmonary toxicity is multifactorial. Amiodarone and its metabolite can damage lung tissue directly by a cytotoxic process or indirectly by immunologic reactions.[80] Amiodarone is an amphiphilic molecule that contains both a highly apolar aromatic ring system and a polar side chain with a positively charged nitrogen atom.[79] Amphiphilic drugs characteristically produce a phospholipid storage disorder in the lungs of experimental animals and humans.[71] Chlorphentermine, an anorectic, is the prototype amphiphilic compound. The mechanism is currently believed to be the inhibition of lysosomal phospholipases.[71] The inflammation and fibrosis are thought to be a late finding resulting from nonspecific inflammation following the breakdown of phospholipid-laden macrophages.[79]

In a review of 39 cases, 9 patients died, and the remaining 30 patients had resolution of abnormalities after withdrawal of the drug.[79] Some patients have had resolution with lowering of the dosage, and therapy has been reinstituted at lower doses without problems in others. Of the patients who died, one-half had received corticosteroids. There are reports of a protective effect with prophylactic corticosteroids and other reports of patients developing amiodarone lung toxicity while on corticosteroids.[79] At this time, any benefit of corticosteroids is unclear because most patients improve after stopping the drug.

PULMONARY HYPERTENSION

Pulmonary hypertension is a rare disorder, occurring with an approximate incidence of 1 to 2 cases per 1 million in the general population.[82] With progression of the disease, right ventricular afterload increases, and the ability to increase cardiac output with activity decreases. This progresses to right-sided heart failure and death.[83]

Patients with pulmonary hypertension often complain of exertional dyspnea, chest pain, and syncope. Because of the nonspecific nature of these symptoms and lack of a noninvasive diagnostic test for detecting pulmonary hypertension, there are often delays in the diagnosis of the disease, frequently up to a year after the onset of symptoms.[83]

The factors leading to the development of pulmonary hypertension are unclear, although associations with portal hypertension and pregnancy have been detected. Obesity by itself may double the risk of pulmonary hypertension.[84] Additionally, the use of cocaine or oral contraceptives, infection with the human immunodeficiency virus (HIV), the use of anorexic agents,[85] hepatic cirrhosis, genetic susceptibility, and female sex in the third to fourth decades of life also are implicated as predisposing factors.[84] Exposure of patients to fenfluramine or dexfenfluramine is associated with 20% of all diagnosed cases of pulmonary hypertension.[84]

The first reports of the association between pulmonary hypertension and the use of anorexic agents occurred in the late 1960s and early 1970s in Western Europe when the drug aminorex was used for weight reduction.[86] The incidence of pulmonary hypertension returned to baseline after the drug was removed from the market. In the early 1990s, an association between fenfluramine use and pulmonary hypertension was established.[87] Shortly thereafter, the International Primary Pulmonary Hypertension Study Group investigated the potential role of anorexic agents in causing pulmonary hypertension.[85] Included in this multinational case-control study were 95 patients with pulmonary hypertension and 355 controls from general practices matched for gender and age. The use of anorexic agents, primarily fenfluramine and dexfenfluramine, within the last year was associated with an increased risk of pulmonary hypertension with an odds ratio of 10:1. When anorexic drugs were used for a total of more than 3 months, the odds ratio increased to 23:1.

In a 12-year observational study, 62 patients with fenfluramine-associated pulmonary hypertension were compared with 125 sex-matched patients with pulmonary hypertension unrelated to the use of fenfluramine derivatives. In most of the cases (81%), fenfluramine derivatives were used for at least 3 months. The time frame between the initiation of the therapy and the onset of dyspnea ranged from 27 days to 23 years. Both the fenfluramine-associated pulmonary hypertension group and the control group had similar levels of New York Heart Association functional class and symptoms, as well as an overall survival rate of 50% in 3 years.[88]

The mechanism by which anorexic agents cause pulmonary hypertension is unknown. Studies show that fenfluramine, dexfenfluramine, and aminorex inhibit potassium channels in isolated pulmonary artery smooth muscle cells in rats, which results in vasoconstriction. Potassium channel activity is altered in pulmonary artery smooth muscle cells obtained from patients with pulmonary hypertension, leading to speculation that anorexic agents may cause vasoconstriction followed by vascular growth and remodeling.[83] Another potential mechanism involves serotonin, which has been found in increased levels in patients with pulmonary hypertension.[83] Serotonin can be stored in the platelet when serotonin plasma concentration is high. Serotonin acts as a pulmonary vasoconstrictor when it is released from the platelets.[84]

Patients with pulmonary hypertension associated with anorexic use may experience a considerable improvement in their condition or possibly even remission within 1 to 3 months following discontinuation of the drug.[84,89] Pharmacologic agents used in the treatment of pulmonary hypertension include high dosage of calcium channel blockers and anticoagulants.[82] Epoprostenol, also known as *prostacyclin,* a strong vasodilator of all vascular beds was approved for the long-term therapy of pulmonary hypertension in 1995.[90] Additionally, lung and heart-lung transplantations have played a role in the treatment of pulmonary hypertension. However, the 4-year survival rate is less than 60% in pulmonary hypertension patients receiving any transplant.[90] Bosentan, an endothelin receptor antagonist indicated for primary pulmonary hypertension, also may have a role, but no studies currently exist describing its use.

In September 1997, the FDA requested the manufacturers of fenfluramine and dexfenfluramine to voluntarily withdraw their products from the market. This was done following case reports of valvular heart disease in patients taking either medication as monotherapy or in combination with another anorexic agent, phentermine. Because no association has been found between phentermine alone and valvular heart disease, it is still available. Isolated case reports of pulmonary hypertension and phentermine monotherapy have been reported,[91,92] but present data do not support an association. Although fenfluramine and phentermine were both approved by the FDA to be used as anorectic agents, the combination therapy, "fen-phen," was never approved.

MISCELLANEOUS PULMONARY TOXICITY

Drugs may produce serious pulmonary toxicity as part of a more generalized disorder. The pleural thickening, effusions, and fibrosis that occur as an extension of the retroperitoneal fibrotic reactions of methysergide and practolol or as part of a drug-induced lupus syndrome are the most common examples (Table 31–8).

Methysergide therapy for prophylaxis of poorly controlled migraine headache occasionally results in pulmonary toxicity associated with pleural effusions. The patients develop pleural pain, dyspnea, and fever. Chest radiography reveals a uniform hazy shadowing over the lower lung fields, and a loud pleural rub is heard on auscultation.[6] The mechanism is unknown, and most patients improve with discontinuation of the drug. Pleural and pulmonary fibrosis has been reported in one patient taking pindolol, a β-blocker structurally similar to prac-

TABLE 31-8 Drugs That May Induce Pleural Effusions and Fibrosis

	Relative Frequency of Reactions
Idiopathic	
Methysergide	F
Practolol	F
Pindolol	R
Methotrexate	R
Nitrofurantoin	R
Drug-induced lupus syndrome	
Procainamide	F
Hydralazine	F
Isoniazid	R
Phenytoin	R
Mephenytoin	R
Griseofulvin	R
Trimethadione	R
Sulfonamides	R
Phenylbutazone	R
Streptomycin	R
Ethosuximide	R
Tetracycline	R
Pseudolymphoma syndrome	
Cyclosporine	R
Phenytoin	R

F, frequent; I, infrequent; R, rare.

tolol, an agent known to produce fibrosis.[61] Acute pleuritis with pleural effusions and fibrosis is a prominent manifestation of drug-induced lupus syndrome. Procainamide is associated with the largest number of pulmonary reactions, with 46% of patients with the lupus syndrome developing pulmonary complications.[6] Symptoms include pleuritic pain and fever with muscle and joint pain. Chest radiographs show bilateral pleural effusions and linear atelectasis. Patients have a positive antinuclear antibody test. Symptoms usually resolve within 6 weeks of drug withdrawal.[6]

Hydralazine is the next most common cause of lupus syndrome. Most patients who develop pleuropulmonary manifestations have antecedent symptoms of generalized lupus.[6] Other drugs that produce the lupus syndrome include isoniazid and phenytoin. Phenytoin also can produce hilar lymphadenopathy as part of a generalized pseudolymphoma or lymphadenopathy syndrome.[6]

MONITORING THERAPEUTIC OUTCOMES

Monitoring for drug-induced pulmonary diseases consists primarily of having a high index of suspicion that a particular syndrome may be drug-induced. Most hypersensitivity or allergic reactions (bronchospasm) occur rapidly, within the first 2 weeks of therapy with the offending agent, and reverse rapidly with appropriate therapy (e.g., withdrawal of the offending agent and administration of corticosteroids and bronchodilators). Dyspnea associated with Loeffler syndrome and acute pulmonary edema syndromes also improve rapidly in 1 to 2 days. However, some residual defect in diffusion capacity and the roentgenogram may persist for a few weeks. It is probably unnecessary to do followup spirometry or diffusion capacity determinations in these patients unless there is some concern that the syndrome will progress to pulmonary fibrosis (through the use of bleomycin or nitrofurantoin).

The routine monitoring of patients receiving known pulmonary toxins with dose-dependent toxicity such as amiodarone, bleomycin, or carmustine is still controversial. For chronic fibrosis, the diffusing capacity of carbon monoxide is the most sensitive test and may be useful in patients receiving bleomycin for detecting and preventing further deterioration of lung function with continued administration. Carmustine lung toxicity may be delayed up to 10 years following administration, and routine monitoring has not proved preventive. Monitoring patients receiving amiodarone in doses greater than 400 mg/day every 4 to 6 months may prove useful in detecting early disease that requires lowering the amiodarone or stopping the drug. Because there is no evidence of a cumulative dose effect once it has been established that the patient can tolerate the elevated dose, continued routine monitoring past the first year is unnecessary.

ABBREVIATIONS

ACE: angiotensin-converting enzyme

COPD: chronic obstructive pulmonary disease

EDTA: ethylenediamine tetraacetic acid

FDA: Food and Drug Administration

FEV_1: forced expiratory volume in the first second of expiration

IPS: idiopathic pneumonia syndrome

NSAIDs: nonsteroidal antiinflammatory drugs

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