Pathology of Pulmonary Disease, edited by Mario J. Saldana.
J. B. Lippincott Company, Philadelphia © 1994.

16

Drug-Induced Pulmonary Disease

Charles M. Lombard

An ever-increasing number of drugs are implicated in the production of pulmonary disease. This chapter focuses on the various histologic patterns of drug-induced lung injury and the mechanisms underlying the production of these changes (Display 16-1). Drug-induced pulmonary injury can manifest as a variety of clinical syndromes (Display 16-2).

Before ascribing causality, the physician should understand when drugs are likely to be implicated in the pathogenesis of pulmonary disease. The following guidelines are an adaptation of some of the principles set forth by Irey.[1] First, to establish that a drug is a cause of disease, the physician must document that the patient is in fact taking the suspected drug. Second, there must be an appropriate temporal association; the drug use must antedate disease, and the latent period must be appropriate. Third, there must be a reasonable line of clinical evidence linking the drug in question to the disease, because there is no diagnostic test that can definitively establish the linkage.

The physician must exclude other natural and iatrogenic causes of disease before diagnosing a drug reaction. Several lines of evidence can suggest that a particular drug is the cause of disease: discontinuation of the drug leads to clinical improvement; rechallenge with the drug leads to recurrent disease; the clinicopathologic presentation is consistent with a known drug reaction; there is precedence in the literature for such a reaction; and quantitation of the drug, if possible, which is particularly important in toxic overdose cases.

USUAL INTERSTITIAL PNEUMONIA AND FIBROSIS

Cytotoxic Drugs

The most frequent pattern of disease with cytotoxic drugs is usual interstitial pneumonia (UIP) with fibrosis (see Chap. 31).[1–3] UIP with fibrosis has been associated with virtually all chemotherapeutic agents known to cause lung disease (Display 16-3). Some of these drugs may be associated with other patterns of lung disease.

There are several key histologic features of drug-induced UIP. Patchy chronic inflammation consists of interstitial infiltrates of lymphocytes, plasma cells, histiocytes, and scattered eosinophils, which vary in intensity from case to case. Fibrosis can be an active cellular fibroblastic proliferation of the Masson type, or a well-established collagenous fibrosis. A patient may have one or both types of fibrosis. The appearance and distribution of these types of fibrosis are nonspecific and may be seen in other conditions.

Alveolar pneumocyte hyperplasia with cytologic atypia is usually the only histologic clue that the lung lesions may be related to cytotoxic drugs. The features include cytomegaly, multinucleation, and pleomorphic and bizarre nuclei with hyperchromasia and prominent nucleoli. Comparable atypia may also be seen in bronchial lining cells. In some cases, the atypia is minimal or absent, and the diagnosis of a drug-associated lung disease must depend entirely on clinicopathologic correlation. Most specimens have a mild to moderate degree of cytologic atypia. The physician should be aware that atypia is also associated with viral infections, oxygen exposure, and irradiation, and these possibilities must be excluded by appropriate history. Some specimens reveal such bizarre atypia that the change is virtually diagnostic of cytotoxic drug-associated disease.

Color Figure 16-1 illustrates the UIP pattern of cytotoxic drug-associated disease. Patients with this pattern of disease present with slowly progressive dyspnea over weeks or months. Dyspnea may be accompanied by cough, fatigue, and malaise. On chest x-ray films, the most common abnormality is a diffuse reticulonodular infiltrate; effusions are uncommon. Treatment consists of drug withdrawal and the administration of corticosteroids. The efficacy of steroids has never been proved in a systematic way, but anecdotal cases have documented favorable responses.

DISPLAY 16-1. PATTERNS OF DRUG-INDUCED LUNG DISEASE

Usual interstitial pneumonia and fibrosis
- Cytotoxic drugs
- Noncytotoxic drugs

Diffuse alveolar damage

Hypersensitivity reactions
- Allergic alveolitis
- Eosinophilic pneumonia
- Lymphoid hyperplasia
- Sarcoidal reaction
- Bronchiolitis obliterans

Vasculopathy
- Pulmonary hypertension
- Vasculitis
- Pulmonary venoocclusive disease
- Alveolar hemorrhage

Miscellaneous

Noncytotoxic Drugs

The histologic findings of noncytotoxic drug-associated pulmonary toxicity are indistinguishable from the changes of UIP (see Display 16-3). They include cellular interstitial infiltrates with lymphocytes, plasma cells, histiocytes, and scattered eosinophils; patchy interstitial fibrosis; and a variety of nonspecific findings, including alveolar pneumocyte hyperplasia, desquamative changes, and metaplastic bronchiolar epithelium. The hyperplastic pneumocytes lack the cytologic atypia seen in many cases of cytotoxic drug-associated disease. Examples of this pattern are shown in Figure 16-1. Amiodarone, a highly effective antiarrhythmic agent, unfortunately is associated with a significant risk (5%–20%) of pulmonary toxicity.[4,5] A variety of patterns of lung disease are associated with this drug; the most common is UIP and fibrosis. Diffuse alveolar damage (DAD) and bronchiolitis obliterans have also been reported. Amiodarone induces peculiar laminated lysosomal inclusion bodies in alveolar macrophages. However, this change is also seen in patients taking the drug without evidence of pulmonary toxicity.

DISPLAY 16-2. DISORDERS THAT DRUG-INDUCED LUNG DISEASE CAN MIMIC

- Allergic alveolitis
- Alveolar hemorrhage syndromes
- Asthma
- Bronchiolitis obliterans
- Chronic cough
- Diffuse alveolar damage
- Emphysema
- Eosinophilic pneumonia
- Fibrosing alveolitis
- Lymphoid interstitial pneumonia
- Pulmonary hypertension
- Septic shock
- Systemic lupus erythematosus
- Vasculitis

DISPLAY 16-3. DRUGS ASSOCIATED WITH USUAL INTERSTITIAL PNEUMONIA AND FIBROSIS

Cytotoxic Drugs	Noncytotoxic Drugs
Azathioprine	Amiodarone
Bleomycin	Cephalosporins
Busulfan	Cotrimoxazole
Chlorambucil	Diphenylhydantoin
Cyclophosphamide	Gold salts
Lomustine	Methysergide
Melphalan	Nitrofurantoin
Methotrexate	Penicillamine
Methyl-lomustine	Sulfasalazine
Mitomycin	Tocainide

DIFFUSE ALVEOLAR DAMAGE

DAD has been reported with a variety of cytotoxic and noncytotoxic drugs (Display 16-4).[6–8] DAD has also been reported as the result of toxic exposure to several industrial agents, most notably paraquat.[9] Regardless of the cause, the histopathologic changes are similar. A key element is temporally uniform damage evenly distributed throughout the lung. In the early exudative phase occurring 1 to 3 days after injury, the pathologist can identify interstitial edema, sloughing of alveolar lining cells, and hyaline membrane formation. In the later proliferative phase occurring 3 to 14 days after injury, there is progressive incorporation of hyaline membranes into the alveolar interstitium, proliferation of fibroblasts, hypertrophy and hyperplasia of alveolar lining cells, and restructuring of the normal alveolar architecture. Subsidiary findings include obliterative bronchiolitis, squamous metaplasia of bronchiolar and peribronchiolar areas, and vascular thrombi. Although cellular inflammation can occur, it is usually inconspicuous. Figure 16-2 illustrates the important features of this pattern of disease. Correct diagnosis requires close clinicopathologic and radiographic correlation.

Patients with DAD present with rapidly progressive, fulminant respiratory failure. Attribution of this pattern of disease to a drug requires excluding the many other causes of DAD in acute respiratory distress syndrome (see Chaps. 14 and 15).

DISPLAY 16-4. DRUGS ASSOCIATED WITH DIFFUSE ALVEOLAR DAMAGE

Amiodarone	Interleukin-2
Aspirin	Lidocaine
Chlordiazepoxide	Methadone
Colchicine	Methotrexate
Cyclophosphamide	Naloxone
Cytosine arabinoside	Nitrogen mustard
Ethchlorvynol	Propoxyphene
Heroin	Vinca alkaloids
Hydrochlorothiazide	

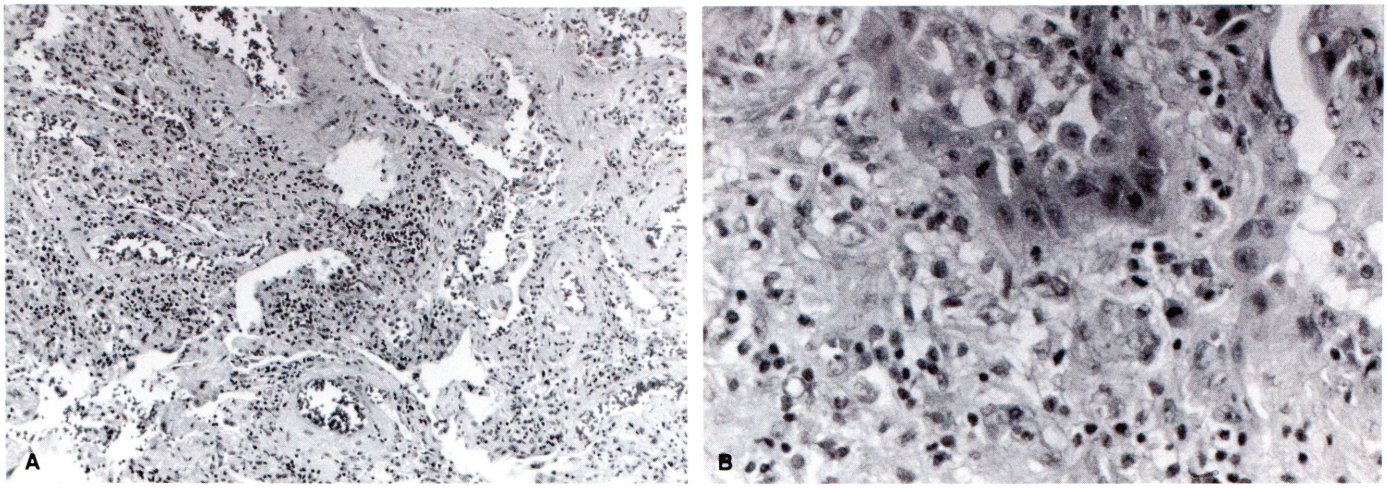

FIGURE 16-1. Noncytotoxic-drug–associated patchy interstitial inflammation and fibrosis. (**A**) Patchy interstitial chronic inflammation and fibrosis in a patient receiving chronic nitrofurantoin therapy. (H & E stain; low magnification.) (**B**) Alveolar lining cell hyperplasia with patchy interstitial inflammation and fibrosis in a patient receiving tocainide therapy. (H & E stain; intermediate magnification.)

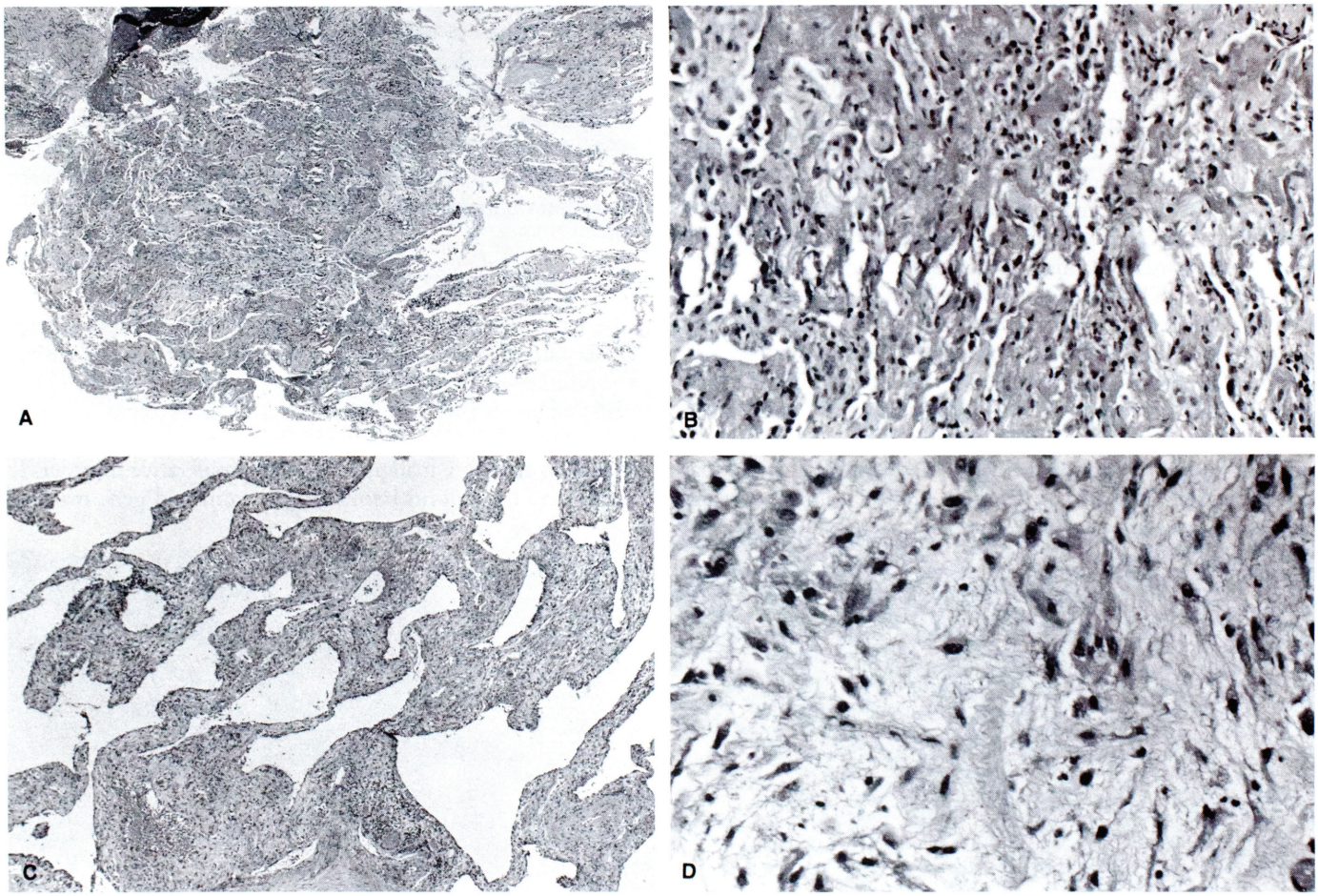

FIGURE 16-2. Diffuse alveolar damage. (**A**) Transbronchial biopsy demonstrated a diffuse pattern of interstitial damage. The patient presented with sudden onset of acute respiratory failure and bilateral interstitial and alveolar infiltrates while taking methotrexate for treatment of psoriasis. (H & E stain; panoramic view.) (**B**) A microscopic view of the same patient demonstrated alveolar interstitial edema and diffuse fibrinous exudates with hyaline membrane formation. (H & E stain; low magnification.) (**C**) The patient developed fulminant respiratory failure after ingestion of paraquat. The biopsy showed diffuse restructuring of normal lung architecture with marked interstitial widening. (H & E stain; low magnification.) (**D**) A closer view of the same case demonstrated the organizing phase of diffuse alveolar damage with interstitial edema, proliferating fibroblasts, and mild inflammation. (H & E stain; intermediate magnification.)

HYPERSENSITIVITY REACTIONS

Patients with hypersensitivity reactions to drugs present with an acute or subacute onset of fever, cough, and dyspnea. Some patients present with concurrent evidence of a systemic hypersensitivity reaction, peripheral eosinophilia, skin rash, and arthritis or arthralgia. Chest radiographs for interstitial or alveolar infiltrates are nonspecific, and pleural effusions may be detected. Treatment consists of drug withdrawal and steroids.

If identified early in the course of their illness, patients usually have a good response to therapy and have little or no permanent lung damage. However, if a drug remains unsuspected and is therefore not withdrawn, irreversible pulmonary fibrosis may ensue. As the cases become chronic, their hypersensitivity nature becomes more obscure and indistinguishable from the patchy inflammation and fibrosis type of drug-associated lung disease (*e.g.*, UIP). A variety of histologic patterns may be seen in cases of drug-associated hypersensitivity lung disease.

Allergic Alveolitis

The histologic features of allergic alveolitis include cellular bronchiolitis, cellular interstitial pneumonia, and granulomas.[6,10] This pattern of disease is seen most commonly with hypersensitivity reactions to inhaled antigens, as in extrinsic allergic alveolitis (see Chap. 65). In many cases of hypersensitivity reactions to ingested or parenteral drugs, inflammation is frequently prominent around small airways, and areas of obliterative bronchiolitis may be seen. The reason for this sensitivity of the small airways is unknown, but it is important to be aware of this fact and not to automatically attribute this pattern of injury to inhaled pathogens.

As in cases of allergic alveolitis as a result of inhaled antigens, lung biopsy may not reveal granulomas. If detected, they are frequently loosely formed microgranulomas and commonly contain no multinucleated giant cells. The interstitial infiltrate consists predominantly of lymphocytes and plasma cells, and in some cases, eosinophils are prominent. Intraalveolar histiocytes are a common finding and may resemble desquamative interstitial pneumonia (see Chap. 32). As lesions become chronic, interstitial fibrosis may ensue. An example of this pattern of disease is shown in Figure 16-3. Drugs associated with allergic alveolitis include bleomycin, chlorambucil, methotrexate, nitrofurantoin, penicillamine, procarbazine, and sulfonamides.

Eosinophilic Pneumonia

Display 16-5 is a partial record of drugs implicated in the pathogenesis of eosinophilic pneumonia (see Chap. 64).[2–4] Patients present with cough, chills, dyspnea, and fever, and some have a skin rash and arthralgia. Peripheral blood eosinophilia is common but does not occur in all cases. Chest x-ray films usually show patchy interstitial and alveolar infiltrates, and nodular infiltrates have also been observed. The onset of disease is unrelated to the cumulative dose and duration of therapy, but most patients present within the first month of therapy.

Because the disease is thought to be caused by hypersensitivity, the latent period is usually at least 7 to 10 days. If the association with the drug is recognized and the drug withdrawn, most patients experience regression of disease with or without steroid therapy. If unrecognized, progressive pulmonary fibrosis may develop.

The pathology of drug-related eosinophilic pneumonia varies among patients. Some have an interstitial infiltrate of mixed inflammatory cells with prominent eosinophils.[11] In others, the findings are histologically indistinguishable from chronic eosinophilic pneumonia (Color Fig. 16-2; Fig. 16-4).[12] In both situations, there are prominent perivenular collections of inflammatory cells, and obliterative bronchiolitis is a common finding.

Lymphoid Interstitial Pneumonia

The lymphoid interstitial pneumonia (LIP) or lymphoid hyperplasia pattern of disease is characterized by a diffuse infiltration of the pulmonary interstitium by lymphocytes admixed with plasma cells and histiocytes. A granuloma is sometimes found, and germinal centers are commonly found. The most important differential diagnosis is with a malignant lymphoproliferative disorder. It is imperative to perform immunologic stains and gene rearrange-

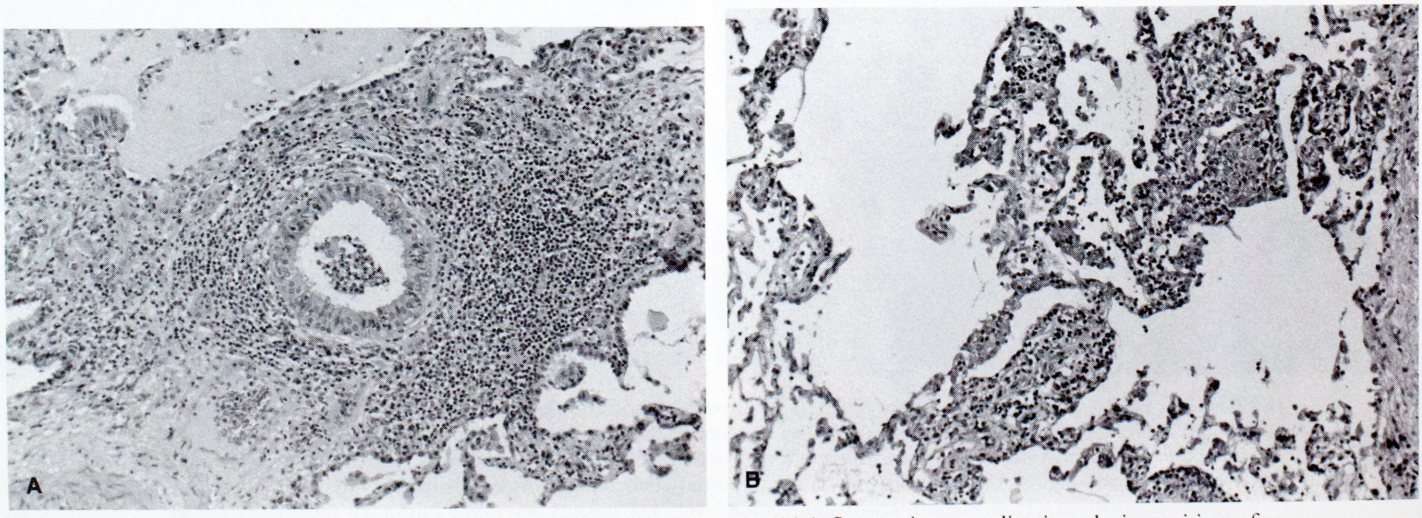

FIGURE 16-3. Allergic alveolitis. (**A**) Cellular bronchiolitis with inflammation spreading into the interstitium of the lung in a patient with rheumatoid arthritis taking methotrexate. (H & E stain; low magnification.) (**B**) Patchy, chronic interstitial inflammation and small, poorly formed granuloma (*upper right corner*) are present. (H & E stain; low magnification.)

DISPLAY 16-5. DRUGS ASSOCIATED WITH EOSINOPHILIC PNEUMONIA

Cytotoxic Drugs

Bleomycin
Methotrexate
Procarbazine

Noncytotoxic Drugs

Ampicillin
Aspirin
Carbamazepine
Chlorpromazine
Chlorpropamide
Diphenylhydantoin
Imipramine
Gold
Hydralazine
Minocycline
Naproxen
Nitrofurantoin
Para-aminosalicylic acid
Penicillin
Sodium dicromoglycate
Streptomycin
Sulfa-containing drugs
Tetracycline
Tolazamide
Tolbutamide

ment studies of biopsy material for a monoclonal proliferation of lymphocytes (see Chap. 55).

Lymphoid hyperplasia refers to a pattern of florid reactive hyperplasia of the bronchus-associated lymphoid tissues along the bronchovascular stalks, pleura, and interlobular septal lymphatics. This pattern of disease may present as a miliary infiltrate seen on chest x-ray films. Diphenylhydantoin is the drug most commonly responsible for this disease (Fig. 16-5*A, B*). Nitrofurantoin has also caused an LIP-like reaction (Fig. 16-5*C, D*).[13,14]

Sarcoidal Reaction

A nonnecrotizing granulomatous reaction indistinguishable from sarcoidosis has been described in patients treated with β-interferon.[15] This is a rare reaction, and it is unclear whether it represents exacerbation of underlying sarcoidosis or a direct adverse effect of the drug.

DISPLAY 16-6. DRUGS ASSOCIATED WITH BRONCHIOLITIS OBLITERANS

Acebutolol
Amiodarone
Bleomycin
Cephalosporin
Cocaine
Cyclophosphamide
Deferoxamine
Gold salts
Methotrexate
Mitomycin C
Nitrofurantoin
Penicillamine
Sulindac
Sulfasalazine
Sulfametopyrazine

Bronchiolitis Obliterans

Obliterative bronchiolitis can occur as a component of hypersensitivity pneumonitis and eosinophilic pneumonia.[8,16] In these cases, the bronchiolitis is a minor component of the overall pathologic picture. However, when obliterative bronchiolitis is a prominent feature, it may mimic idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP). Although it probably represents one end of the spectrum of histologic changes seen in hypersensitivity pneumonitis, recognition that this pattern may be associated with drugs is important. Withdrawal of the sensitizing drug is the most important component of treatment; steroid therapy may hasten resolution of the disease.

Drugs associated with BOOP are presented in Display 16-6. Examples of BOOP associated with drugs are shown in Figure 16-6. In addition to the BOOP-like pattern of disease, I have observed severe, diffuse, obliterative scarring of small airways associated with continuous infusion of deferoxamine in a child with severe, accidental iron poisoning.

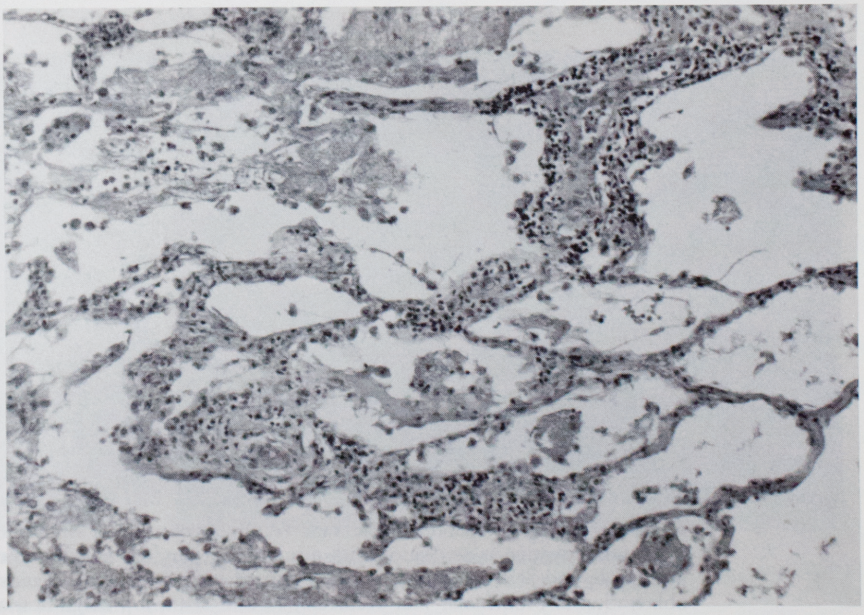

FIGURE 16-4. Eosinophilic pneumonia. Patchy, interstitial inflammatory infiltrates in a patient who developed lung disease while taking sulfonamide (see Color Fig. 16-2). (H & E stain; low magnification.)

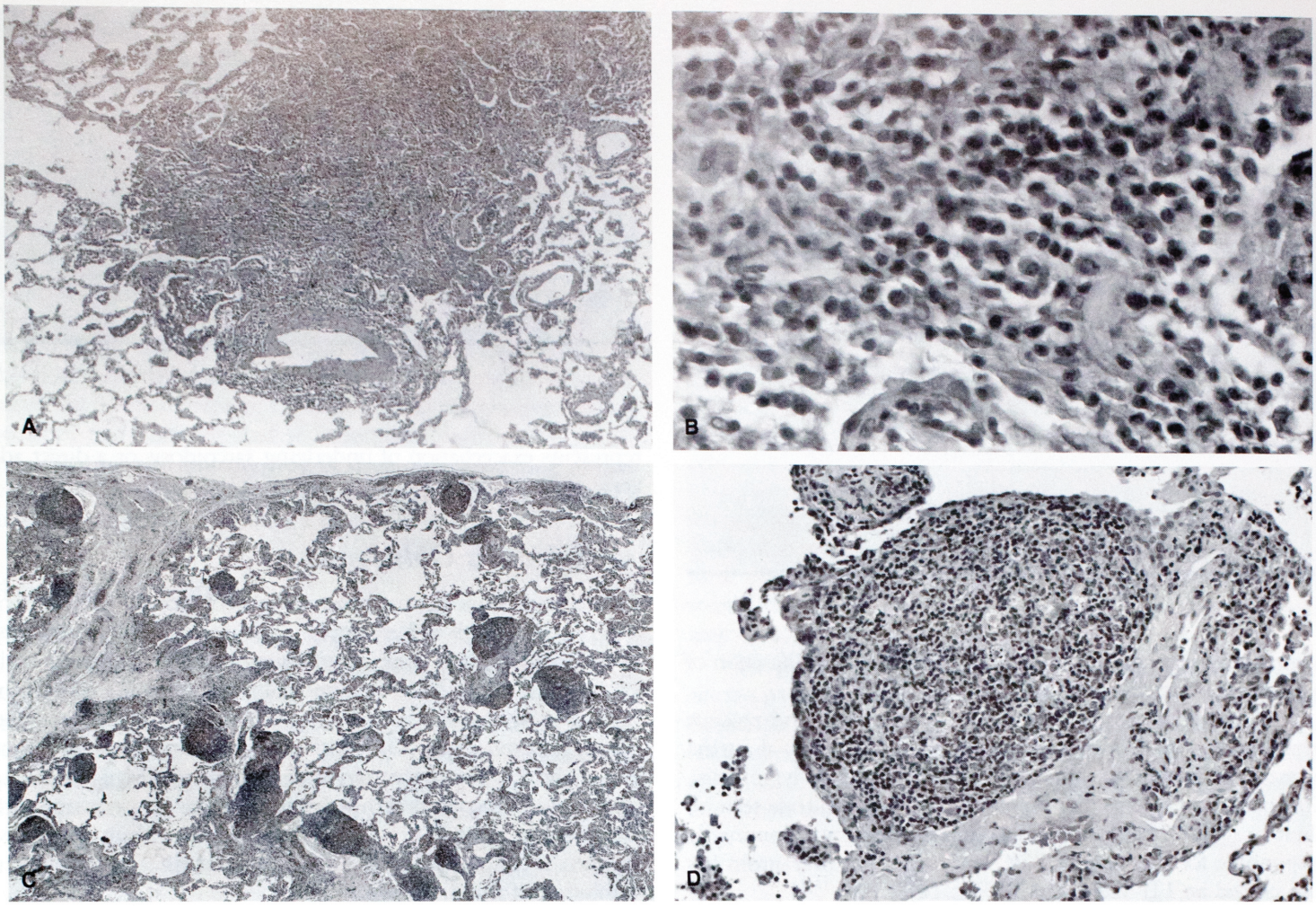

FIGURE 16-5. Lymphoid interstitial pneumonia or lymphoid hyperplasia. (**A**) A patient with diphenylhydantoin-associated lymphoid interstitial pneumonia has an interstitial nodule of lymphocytes with spread into adjacent alveolar septae. (H & E stain; low magnification.) (**B**) A microscopic view of the same patient demonstrates a mixture of cytologically bland lymphocytes associated with plasma cells. (H & E stain; intermediate magnification.) (**C**) A patient with nitrofurantoin-associated lymphoid hyperplasia has numerous follicular centers scattered throughout the lung along lymphatic routes. (H & E stain; low magnification.) (**D**) A microscopic view of the same patient demonstrates reactive follicular hyperplasia. (H & E stain; low magnification.)

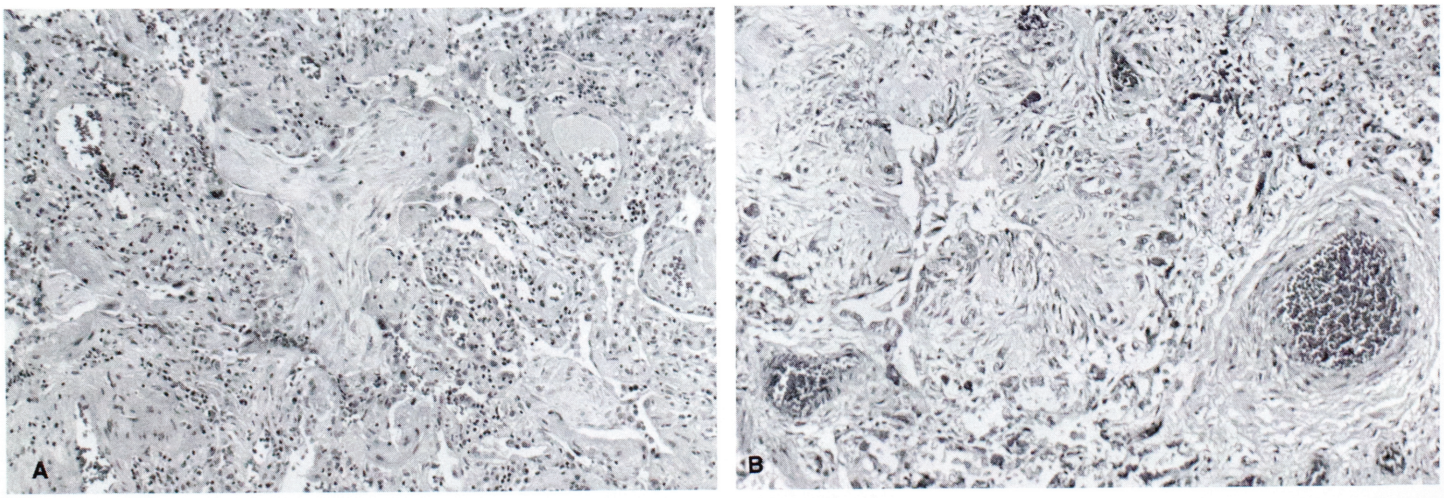

FIGURE 16-6. Bronchiolitis obliterans. (**A**) In nitrofurantoin-associated bronchiolitis obliterans, chronic interstitial inflammation is associated with a branching plug of "Masson-type" granulation tissue in the respiratory bronchiole and alveolar ducts. (**B**) In a patient with deferoxamine-associated bronchiolitis obliterans, fibrous obliteration of bronchiolar wall occurred. (H & E stain; low magnification.)

VASCULOPATHY

Pulmonary Hypertension

Pulmonary hypertension, an unusual complication of drug toxicity, has been best documented with the drug aminorex, an anorexigen used in Germany, Austria, and Switzerland that was withdrawn from the market in 1968.[17] Before its removal, aminorex was responsible for an epidemic of pulmonary hypertension. Some centers in Switzerland reported a 10-fold to 20-fold increase in the incidence of pulmonary hypertension; 1% to 2% of patients taking this drug developed evidence of pulmonary hypertension, usually after 6 to 12 months of drug use. The histologic features, including plexogenic arteriopathy, were indistinguishable from primary pulmonary hypertension.

Although not documented pathologically, chronic use of another anorexigen, fenfluramine, has caused a clinical syndrome of pulmonary hypertension.[18] Chronic abuse of α-adrenergic nasal sprays has been associated with interstitial fibrosis and pulmonary hypertension.[19] The pathogenesis of the hypertensive vascular changes is probably repeated vasoconstriction episodes caused by these agents. Although reports have suggested a link between oral contraceptives and pulmonary hypertension, the association has not been proven.[6,20] L-Tryptophan, associated with the eosinophilic-myalgia syndrome, produces a pulmonary arterial endovasculitis characteristic of this syndrome.[21] There have been cases of advanced pulmonary hypertension associated with chronic use of this drug (Fig. 16-7).[22] Isolated cases of pulmonary hypertension associated with phenformin have been reported. Intravenous drug abuse is associated with a foreign body granulomatosis, vascular destruction, and pulmonary hypertension (see Chap. 22).[23,24]

Vasculitis

Pulmonary vasculitis may occur as a minor component of hypersensitivity reactions, particularly of allergic alveolitis and eosinophilic pneumonia. Pulmonary vasculitis is perhaps better described as vascular inflammation, because the cases lack true destruction of the vessel wall or thromboses. Cases of necrotizing vasculitis attributable to drugs are rare; patients taking propylthiouracil, α-methyldopa, and retinoids have developed a necrotizing vasculitis in the lung resembling Wegener granulomatosis.[25–27]

Pulmonary Venoocclusive Disease

Pulmonary venoocclusive disease (PVOD) is a rare form of pulmonary hypertension that has been associated with multiple etiologic agents, including prior viral infection, inhaled toxins, immune complex deposition, chemotherapeutic drugs, irradiation, and bone marrow transplantation.[8,28] Familial cases have also been reported (see Chap. 23). Because chemotherapeutic agents are commonly used in combination, it has been difficult to pinpoint individual drugs that cause PVOD. However, BCNU as single-agent chemotherapy for the treatment of malignant gliomas has been implicated; other drugs that may produce PVOD include bleomycin, cisplatin, cyclophosphamide, etoposide, mitomycin C, and vincristine.

The difficulty in diagnosing PVOD has been stressed, and the routine use of elastic van Gieson stains in cases of chemotherapy-associated pulmonary fibrosis to examine the pulmonary veins is strongly recommended. Another important diagnostic clue is provided by intraalveolar hemosiderin-laden histiocytes. An example of drug-associated PVOD is shown in Figure 16-8.

Alveolar Hemorrhage

Alveolar hemorrhage is a rare complication attributable to drugs such as anticoagulants, D-penicillamine, Ethiodol, inhaled crack cocaine, and moxalactam disodium. When associated with anticoagulant therapy, the prothrombin time is generally outside of the therapeutic range. Ethiodol is a radioactive iodine (^{131}I) contrast medium used in lymphangiography, and cases of alveolar hemorrhage and subsequent anemia have been reported as a complication of its use.[29] Rare cases of moxalactam-associated pulmonary hemorrhage have been reported.[30] D-Penicillamine is associated with a variety of pathologic changes in the lung, including Goodpasture syndrome (see Chap. 62).[31] Cases of diffuse alveolar hemorrhage due to inhalation of crack cocaine have been reported.[32]

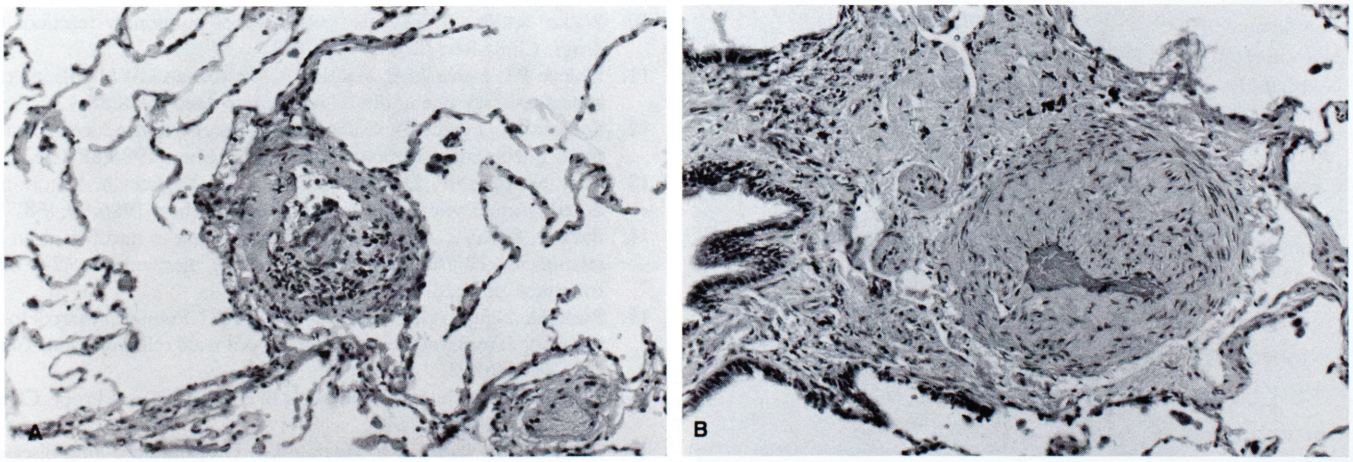

FIGURE 16-7. Pulmonary hypertension. (**A**) The pulmonary artery shows endovasculitis in a patient receiving chronic L-tryptophan therapy. (**B**) The same patient shows the advanced changes of pulmonary hypertension. The patient required lung transplantation. (H & E stain; low magnification.)

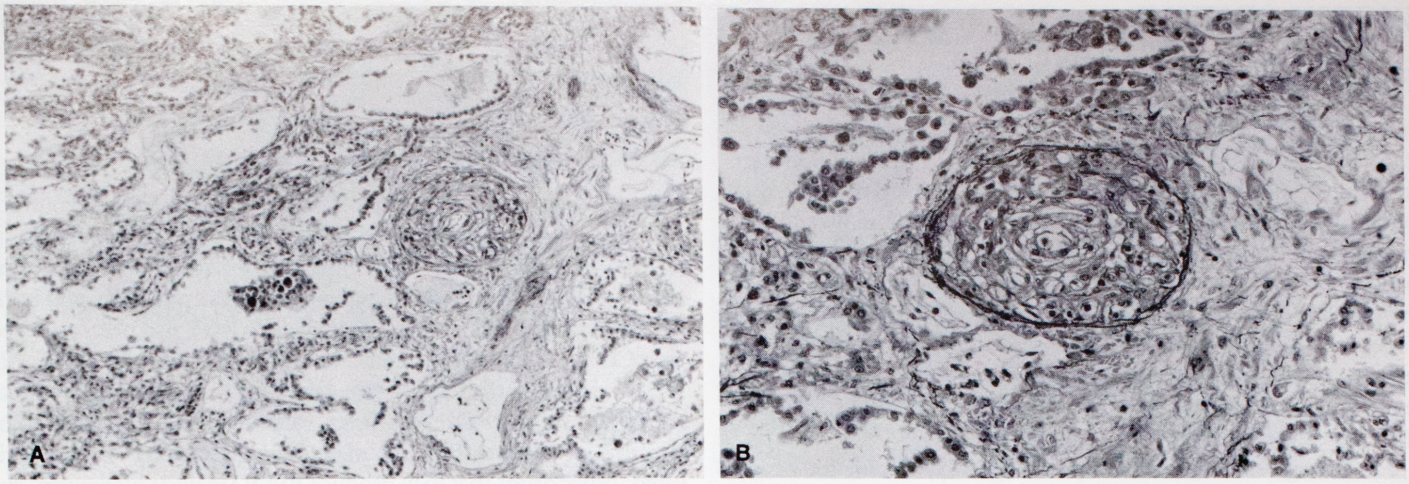

FIGURE 16-8. Pulmonary venoocclusive disease associated with chemotherapy. (**A**) The lung shows an abnormal venule, patchy interstitial inflammation and fibrosis, and intraalveolar hemosiderin-laden macrophages. The patient had MOPP and COPP chemotherapy for Hodgkin disease. (H & E stain; low magnification.) (**B**) The same biopsy specimen prepared with elastic tissue stain outlines the occluded pulmonary venule. (Elastic tissue stain; low magnification.)

MISCELLANEOUS DRUG REACTIONS IN THE LUNG

In addition to the patterns of disease previously discussed, a variety of adverse reactions to drugs can occur (Display 16-7). Unfortunately, in many of these conditions, biopsies of the lung are not obtained for documentation.

DISPLAY 16-7. MISCELLANEOUS ADVERSE DRUG REACTIONS IN THE LUNG

Alveolar Proteinosis
Busulfan
Cyclophosphamide

Bronchospasm
Aspirin
Beta blockers
Dipyridamole
Nitrofurantoin
Nonsteroidal antiinflammatory drugs
Protamine

Chronic Cough
Angiotensin converting enzyme inhibitors

Pulmonary Calcifications
Calcium
Phosphorus
Vitamin D

Pneumothorax
Carmustine
Bleomycin

Pulmonary Effusions
Cytotoxic agents
Nitrofurantoin
Bromocriptine
Methysergide

Systemic Lupus Erythematosus
Chlorpromazine
Penicillamine
Dilantin
Practolol
Isoniazid
Procainamide
Hydralazine
Sulfonamides

Pseudosepsis Syndrome
Aspirin

REFERENCES

1. Irey NS. Tissue reactions to drugs. Am J Pathol 1976;82:617.
2. Sastre J, Ibanez MD, de Shazo RD. Pulmonary reactions induced by drugs: a clinical compendium. Allerg Immunopathol (Paris) 1988; 17:127.
3. Cooper JAD Jr, White DA, Matthay RA. State of the art: drug-induced pulmonary disease, part I. Am Rev Respir Dis 1986;133:321.
4. Cooper JAD Jr, White DA, Matthay RA. Drug-induced pulmonary disease, part II. Am Rev Respir Dis 1986;133:488.
5. Kennedy JI, Myers JL, Plumb VJ, Fulmer JD. Amiodarone pulmonary toxicity: clinical, radiologic, and pathologic correlations. Arch Intern Med 1987;147:50.
6. Demeter SL, Ahmade M, Tomashefski JF. Drug-induced pulmonary disease, part III. Clev Clin Q 1979;46:113.
7. Reed CR, Glauser FL. Drug-induced noncardiogenic pulmonary edema. Chest 1991;100:1120.
8. Rosenow EC, Myers JL, Swensen SJ, Pisani RJ. Drug-induced pulmonary disease: an update. Chest 1992;102:239.
9. Rebello G, Mason JK. Pulmonary histological appearances in fatal paraquat poisoning. Histopathology 1978;2:53.
10. Walker Smith GJ. The histopathology of pulmonary reactions to drugs. Clin Chest Med 1990;11:95.
11. Holoye PY, Luma MA, MacKay B, Bedrossian CWM. Bleomycin hypersensitivity pneumonitis. Ann Intern Med 1978;88:47.
12. Yousem SA, Lifson JD, Colby TV. Chemotherapy-induced eosinophilic pneumonia; relation to bleomycin. Chest 1985;88:103.
13. Chamberlain DW, Hyland RH, Ross DJ. Diphenylhydantoin-induced lymphocytic interstitial pneumonia. Chest 1986;90:458.
14. Back O, Liden S, Abistedt S. Adverse reaction to nitrofurantoin in relation to cellular and humoral immune mechanisms. Clin Exp Immunol 1977;28:400.
15. Abdi EA, Nguyen G, Ludwig R, Dickout WJ. Pulmonary sarcoidosis following interferon therapy for advanced renal cell carcinoma. Cancer 1987;59:896.
16. Costabel U, Teschler H, Schoenfeld B, et al. BOOP in Europe. Chest 1992;102 (Suppl 1):14S.
17. Israel-Biet D, Labrune S, Huchon GJ. Drug-induced lung disease: 1990 review. Eur Respir J 1991;4:465.
18. Douglas JG, Munro JF, Kitchin AH, et al. Pulmonary hypertension and fenfluramine. Br Med J 1981;283:881.

19. Lippmann M. Pulmonary reactions to drugs. Med Clin North Am 1977;61:1353.
20. Pietra GG. Pathologic mechanisms of drug-induced lung disorders. J Thorac Imaging 1991;6:1.
21. Herrick MK, Chang Y, Horoupian DS, et al. L-Tryptophan and the eosinophilia-myalgia syndrome. Pathological findings in eight patients. Hum Pathol 1991;22:12.
22. Tazelaar HD, Myers JL, Drage CW, et al. Pulmonary disease associated with L-tryptophan induced eosinophilic myalgia syndrome: clinical and pathologic features. Chest 1990;97:1032.
23. Fahlen M, Bergman H, Helder G, et al. Phenformin and pulmonary hypertension. Br Heart J 1973;35:824.
24. Heffner JE, Harley RA, Schabel SI. Pulmonary reactions from illicit substance abuse. Clin Chest Med 1990;11:151.
25. Alon U, Hellerstein S, Warady BA. Anti-neutrophil cytoplasmatic (*sic*) antibodies in drug-induced Wegener's-like disease (letter). Pediatr Nephrol 1990;4:299.
26. Matteson EL, Palella TD. Alpha-methyldopa-induced systemic vasculitis confused with Wegener's granulomatosis (letter). Arthritis Rheum 1989;32:356.
27. Dwyer JM, Thompson BT, Labraico J, et al. Vasculitis and retinoids. Lancet 1989;2:494.
28. Lombard CM, Churg A, Winokur S. Pulmonary veno-occlusive disease following therapy for malignant neoplasms. Chest 1987;92:871.
29. Wiertz LM, Gagnon JH, Anthonisen NR. Intrapulmonary hemorrhage with anemia after lymphangiography. N Engl J Med 1971; 285:1364.
30. Brandstetter RD, Tamarin FM, Rangraz MS. Moxalactam disodium-induced pulmonary hemorrhage. Chest 1984;84:644.
31. Zitnik RJ, Cooper J. Pulmonary disease due to antirheumatic agents. Clin Chest Med 1990;11:139.
32. Murray RJ, Albin RJ, Mergner W, Criner GJ. Diffuse alveolar hemorrhage temporally related to cocaine smoking. Chest 1988;93: 427.