With an ever-increasing number of therapeutic, and also illicit, drugs available for use, the list of drugs that is responsible for untoward, and, oftentimes, severe pulmonary disease also grows. More than 150 agents are known to cause adverse pulmonary reactions [1]. In many cases, such as a patient who presents with pulmonary infiltrates that are associated with peripheral eosinophilia that coincides with medication that is known to cause eosinophilic pneumonia, lung biopsy may not be necessary and a clinical diagnosis is sufficient. Because most pulmonary drug reactions are not biopsied, the surgical pathologist’s perspective is far from complete. Furthermore, because the criteria for a definitive diagnosis are strict and most cases are considered either probable or possible rather than causative [2], histomorphologic findings ascribed to many antimicrobials, anti-inflammatory agents, cancer chemotherapeutic agents, cardiovascular drugs, and recreational (ie, illicit drugs) are not specific to these drug reactions. Thus, the role of the surgical pathologist in evaluating a tissue sample in suspected cases of drug reaction is limited, but nevertheless useful. The following discussion focuses on the pathologist’s approach to suspected drug-induced lung disease with respect to specimen types and morphologic patterns within various clinical scenarios.

Clinical scenarios relevant to the surgical pathologist

Pulmonary drug reactions result from either direct or indirect effects of a drug. Indirect effects include drug-induced thrombocytopenia, central nervous system depression, and drug-induced immunosuppression with subsequent pulmonary hemorrhage, aspiration pneumonia, or opportunistic infection, respectively [3–5]. The latter consequence is most important because many of the histologic patterns that are seen in drug-induced pulmonary disease also are seen in bacterial, fungal, viral, and even protozoan, infections.

Direct effects can be subclassified into toxic reactions and idiosyncratic categories. For the surgical pathologist, a clinically relevant distinction may not be critical because many drugs (eg, amiodarone and bleomycin), can exert toxic effects and induce immunologic reactions [6–8]. Instead, surgical pathologists contribute mainly by classifying drug reactions according to histologic patterns of disease, rather than according to pharmacologic groupings. Even this approach is not without uncertainty because few drugs produce unique histologic findings. Nitrofurantoin, for example, can present with numerous pulmonary manifestations, including bronchospasm, chronic interstitial pneumonia, diffuse alveolar damage (DAD), organizing pneumonia, pulmonary hemorrhage, eosinophilic pneumonia, granulomatous inflammation, and pleural effusion [9].

Whether the pathologist can discern a drug reaction from an underlying or superimposed disease is dependent on careful clinical and radiographic cor-
relation. Just as the diagnosis of idiopathic pulmonary fibrosis cannot be made without review of detailed clinical information and the high-resolution CT scans, a complete medical history, including current and past medications with details about dosage and timing of therapy relative to onset of symptoms, pulmonary function test results, a history of previous radiotherapy, or recent surgery, are critical pieces of information [10]. These data allow the pathologist to identify broadly the type of respiratory process present and to correlate morphology with the clinical findings to sort out whether the patient primarily has airway dysfunction, an alveolar process, a diffuse parenchymal process, localized or nodular infiltrates, vascular disease, or even pleural or mediastinal abnormalities (Box 1).

The temporal course of the illness is important to convey to a pathologist, in addition to the presenting signs and symptoms and the presence or absence of peripheral eosinophilia, whether the radiographic findings demonstrate localized or diffuse opacities, and the results of pulmonary function tests. The rapidity of onset and rate of progression are probably of the greatest use Anaphylaxis, bronchospasm, and pulmonary edema represent acute reactions that are noted within minutes to hours of drug exposure, whereas hypersensitivity pneumonitis, systemic lupus erythematosus (SLE)-like symptoms, alveolar hemorrhage, DAD, and organizing pneumonia are subacute processes that are seen days to weeks after initiation of therapy. Chronic reactions that manifest as interstitial pneumonitis are seen months to years after either initiation of therapy or a short exposure. Drug reactions also can present as an acute process in an individual who has taken the implicated drug for years; drug effects can develop years after discontinuation of the drug as was reported with bischloroethyl nitrosourea (BCNU) therapy for childhood brain tumors [11]. It is important to be aware of possible drug synergisms, such as bleomycin and oxygen that cause DAD, amiodarone and oxygen that cause DAD, mitomycin and 5-fluorouracil that cause noncardiac pulmonary edema (NCPE), amphotericin B and leukocyte transfusion that lead to NCPE, and vincristine and mitomycin that combine to cause bronchoconstriction [5].

**Methods of diagnosis**

Histologic changes for most drug reactions are nonspecific and diagnosis rests on correlation with clinical, laboratory, and radiologic information. Some type of lung sampling often is required to help establish a diagnosis. Although a surgical (open or thoracoscopic) lung biopsy might allow the pathologist to give a more complete description of the pulmonary process, a minimally-invasive procedure, such as bronchoalveolar lavage (BAL) or bronchoscopic biopsy, can contribute valuable data and aid in a presumptive diagnosis of drug reaction.

Often, BAL is the only material a pathology laboratory will receive from a patient who has a possible drug-induced lung disease. Although BAL can suggest an iatrogenic cause, its greatest usefulness lies in its ability to exclude a more likely pathologic process, such as infection or malignancy. BAL findings that support a drug-related pulmonary process include cytologic atypia (“cytotoxic changes”) with bizarre hyperchromatic cells that include multinucleated forms and prominent macronucleoli, pulmonary hemorrhage with hemosiderin-laden macrophages, or a lymphocytic alveolitis.
In the latter condition, at least 40% of the cells are lymphocytes and an increased percentage of those are CD8+ cells. This inverted CD4+:CD8+ ratio is associated with hypersensitivity reactions as seen in one manifestation of methotrexate-induced pneumonitis [5]. Other BAL findings that are seen in pulmonary drug reactions include increased numbers of eosinophils in eosinophilic pneumonia and lipid-filled macrophages as seen in mineral oil nose-drops or with laxative use.

BAL findings simply may indicate the presence of a drug and not necessarily suggest drug toxicity; gold and amiodarone are illustrative examples. Alveolar macrophages retain gold for long periods of time [15] and amiodarone, which blocks lysosomal enzymes that are involved in the breakdown of complex lipids, is responsible for the accumulation of phospholipids in alveolar macrophages which gives a foamy appearance to the cytoplasm [16,17]. Similar findings were reported in other amphiphilic drugs that block lysosomal phospholipase and sphingomyelinase, including iprindole and chlorphentermine [18,19]. Thus, finding lamellar inclusions in an alveolar macrophage indicates therapy but additional information is required to determine drug toxicity. Furthermore, no BAL result carries prognostic significance [6].

Not unlike BAL, transbronchial lung biopsy (TBB) plays only a limited role in the diagnostic work-up of a suspected drug-related pulmonary process. Because TBB has the greatest diagnostic yield in the setting of diffuse lung infiltrates and greatest accuracy in diagnosing infection and malignancy in immunocompromised patients and sarcoidosis in immunocompetent individuals, its usefulness lies in the exclusion of these processes. Adequate biopsy fragments that demonstrate DAD, organizing pneumonia, or alveolar septal lymphoplasmacytic infiltrates may or may not represent drug reaction, and, furthermore, may not be representative of the entire pathologic process. If a specific process is identified in a bronchoscopic biopsy, correlation with radiologic images and clinical history is particularly critical to ensure that the specimen is representative. Discordance between bronchoscopic biopsy and radiologic or clinical findings may be a strong indication for surgical lung biopsy. Open or thoracoscopic lung biopsy remains the gold standard for diagnosis of most patterns of lung injury. In many cases, extrapolating patterns of lung involvement from small biopsies and cytologic preparations is difficult, if not impossible. A large representative tissue fragment as seen in surgical lung biopsies provides ample material for bacteriology studies and usually allows the pathologist to exclude the presence of underlying disease and infection. Biopsies of more than one lobe are advantageous, given the frequent histologic heterogeneity of diffuse parenchymal lung disorders [22]. If well-sampled, the lung biopsy will indicate a histologic pattern of lung injury; if a drug reaction is under consideration and other causes are excluded, this pattern allows a pathologist to determine whether the pulmonary reaction is appropriate for a particular drug.

**Criteria for diagnosis of drug reaction**

Irey [2] defined a set of criteria for the diagnosis of drug reactions (Box 2). One must identify correctly the drug in question; was the patient taking the drug, and, if so, in what dosage for what duration? Other primary or secondary lung diseases must be excluded, such as infection or pulmonary involvement by collagen vascular disease. The issue of temporal eligibility must be considered; some drugs have well-established latency periods from initiation of therapy to onset of pulmonary symptoms. Is there remission of symptoms after removal

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Box 2. Criteria for diagnosis of drug reactions

- Correct identification of the drug in question. Was the patient taking the drug?
- What dose? What duration?
- Exclusion of other primary or secondary lung diseases
- Temporal eligibility: appropriate latent period (exposure to toxicity)
- Remission of symptoms with removal of challenge
- Recurrence with rechallenge
- Singularity of drug; what other drugs was the patient taking?
- Characteristic pattern of reaction to specific drug; previous documentation?
- Quantification of drug levels that confirm abnormal levels (especially for overdoses)
- Degree of certainty of drug reaction: Causative Probable Possible
of the drug challenge? Ideally, one also should re-challenge the patient to see recurrence of the toxicity, but, in reality, this is done rarely. Singularity of drug therapy is optimal; when a patient is on multiple medications it may be difficult to be certain which drug is causing the toxicity, unless a specific medication has a particular reaction that is being observed in the patient and the other, current medications do not show this type of manifestation. Drugs tend to cause characteristic patterns of lung injury; if a typical pulmonary reaction occurs in a patient who is being treated with a specific drug, this is supportive evidence of drug toxicity. If the histologic pattern of lung injury is not typical of that drug, drug toxicity is less certain. In some cases, quantification of drug levels may confirm abnormal levels, particularly for drug overdoses. Finally, it can be useful to make an overall assessment whether a putative drug reaction is causative, probable, or possible [2].

**Lung injury patterns associated with drug reactions**

The spectrum of clinical syndromes and diseases that is associated with pulmonary drug reactions involves all anatomic compartments of the lung. The major histologic patterns are listed in Box 3. The interstitium, airspaces, vasculature, and pleura may be involved preferentially, but one should be aware that the lung’s response to injury is limited to several recognized reaction patterns; drugs may affect more than one compartment and, thus, lead to overlapping histologic patterns of disease. A reaction may defy classification and evidence of acute and chronic disease processes can be seen in one biopsy.

When considering a diagnosis of drug reaction, it is essential to be aware of the histologic patterns of lung toxicity that were reported in association with the presumed agent. Given the constant introduction of new drugs, one also should be alert for recognition of new forms of pulmonary drug toxicities in the absence of previous documentation. Critical assessment of previous reports is important because the literature is resplendent with pathologic descriptions that predate the current classification of interstitial pneumonias [20]. Many cases that were diagnosed as usual interstitial pneumonia (UIP) currently might be described as nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), or even DAD. With these caveats in mind, one can find exhaustive lists of therapeutic agents that are known to cause iatrogenic lung disease in most pulmonary medicine and surgical pathology textbooks [21–23] and at the continuously updated, user-friendly, online database, www.pneumotox.com.

The following conditions and associated agents are modified from several recently published comprehensive sources [21–23]; the patterns represent histologic, not radiographic, descriptions of lung involvement. Agents known to cause or aggravate bronchoconstriction including, but not limited to, hypotonic nebulized preparations, many β-sympathetic antagonists including propranolol, metoprolol, atenolol and pindolol, iodine-containing contrast media, dipyridamole, protamine, iron dextran, tartrazine, penicillin, trimethoprim-sulfamethoxazole, nitrofurantoin, ketamine, cocaine, vitamins K1 and B12, interleukin (IL)-2, aspirin and other nonsteroidal anti-inflammatory agents, hydrocortisone, acetaminophen, captopril, enalapril, methotrexate, as well as occupational exposure to penicillin, cephalosporins, methyldopa, cimetidine, and piperazine are not included because such reactions never require the expertise of a surgical pathologist [5,24]. L-tryptophan also is not included because it is no longer available.

### Chronic interstitial pneumonia

Histologic findings that resemble UIP, NSIP (Fig. 1), lymphocytic interstitial pneumonia, or even patchy alveolar septal lymphoplasmacytic infiltrates without appreciable airway disease or parenchymal scarring are the most commonly reported morphologic patterns that are associated with pulmonary

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**Box 3. Histologic patterns associated with pulmonary drug reactions**

- Pulmonary edema
- Alveolar hemorrhage
- Alveolar proteinosis–like reaction
- Diffuse alveolar damage
- Organizing pneumonia
- Usual interstitial pneumonia–like pattern
- Diffuse cellular interstitial infiltrates ± granulomas
- Nonspecific interstitial pneumonia
- Lymphocytic interstitial pneumonia
- Acute or chronic eosinophilic pneumonia
- Small vessel angitis
- Pulmonary arterial hypertension
- Pulmonary veno-occlusive disease
drug toxicities [23]. Cytotoxic, antimicrobial, anti-inflammatory, antiarrhythmic, antihypertensive, and anticonvulsant agents, in addition to other miscellaneous drugs, cause such lung disease. Implicated agents include amiodarone, BCNU, busulfan, chlorambucil, cocaine, cyclophosphamide, fluoxetine, gold salts, melphalan, methotrexate, methyl-chloroethyl chlorohexl nitrosourea (CCNU), nilutamide, nitrofurantoin, phenytoin, pindolol, procarbazine, quinidine, sulfasalazine, tocainide, and uracil mustard. In addition, varying patterns of pulmonary fibrosis can develop from drugs whose initial reaction pattern was DAD, bronchiolitis, or even eosinophilic pneumonia.

Diffuse alveolar damage

The pathologist rarely has difficulty recognizing either the acute or exudative phase of DAD with abundant hyaline membranes or the proliferative stage with interstitial inflammation, alveolar septal loose fibrosis, and pneumocyte hyperplasia (Fig. 2). Yet suggesting a drug-related cause is virtually impossible without complete clinical and pharmacologic information. Because infectious agents of all types, shock, sepsis, leukemic cell lysis, SLE and transfusions are recognized causes of DAD, it may be complicated to sort out the specific etiology. Implicated drugs include amiodarone, amitriptyline, azathioprine, BCNU, bleomycin, busulfan, CCNU, cocaine, cochicine, cyclophosphamide, cytosine arabinoside, deferoxamine mysylate, gold salts, heroin, infliximab, melphalan, methotrexate, mitomycin, nitrofurantoin, paraquat, penicillamine, procarbazine, streptokinase, sulfathiazole, teniposide, tocainide, vinblastine, vindesine, and zinostatin.

Organizing pneumonia

The morphologic pattern features fibromyxoid connective tissue plugs that fill distal airspaces, particularly alveolar spaces and alveolar ducts, as well as terminal or respiratory bronchioles (Figs. 3, 4). Interstitial chronic inflammation is usually mild to moderate. OP is a nonspecific histologic reaction that is seen in drug toxicity and in association with...
a wide variety of causes, including hypersensitivity pneumonitis; eosinophilic pneumonia; infection; collagen vascular disease; hemorrhage adjacent to mass lesions, such as infarcts, granulomas, or tumors; as well as in an idiopathic setting. In the latter situation, the clinical term “cryptogenic organizing pneumonia” (COP), formerly known as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) is appropriate [20]. The term “COP” would not be used in the setting of a known drug reaction; in this situation, the term “BOOP” could be used clinically with mention of the specific drug association (ie, BOOP due to amiodarone toxicity). Implicated drugs include amiodarone (see Figs. 3, 4), bleomycin, chlorozotocin, cocaine, cromolyn sodium, cyclophosphamide, gold salts, hemamethonium, interferon, mecamylamine, methotrexate, mitomycin, nilutamide, nitrofurantoin, penicillamine, phenytoin, sulfasalazine, and tocainide.

Pulmonary eosinophilia

Although eosinophilic pneumonia is the most common form of pulmonary eosinophilia (Fig. 5) [25], subclassification into four categories (simple, acute, chronic, and secondary) that is based on clinical features makes this group of entities cumbersome and oftentimes confusing for the pathologist. Drug toxicity is an important cause of acute and chronic eosinophilic pneumonias and patients also may have blood eosinophilia. The “PIE (pulmonary infiltrates with eosinophilia) syndrome” is an older term that is generally no longer used. Drug-induced cases often have a pattern of acute lung injury and can overlap with DAD. The most common agents that are associated with this reaction pattern include several NSAIDs, acetaminophen, ampicillin, bleomycin, captopril, carbamazepine, chlorpropamide, cocaine, cromolyn sodium, hydralazine, imipramine, mephenesin, nabumetone, naproxen, nitrofurantoin, penicillin, phenylbutazone, procarbazine, prontosil, propranolol, pyrimethamine, streptomycin, sulfasalazine, tetracycline, and trazodone.

Pulmonary edema

Most experienced clinicians recognize the temporal relationship between the administration of a new drug and the onset of pulmonary edema, but on rare occasions, lung biopsies are performed. Distinguishing pulmonary edema (Fig. 6) from fibrinous pneumonia or early DAD may not be possible. Recognized drugs that are responsible for noncardiogenic pulmonary edema (NCPE) include albuterol, aspirin, buprenorphine, chlordiazepoxide, cocaine, codeine, cytosine arabinoside, epinephrine, ethchlorvynol, haloperidol, heroin, hydrochlorothiazide, isoxsuprine, lidocaine, magnesium sulfate, methadone, methamphetamine, methotrexate, mitomycin, nalbuphine, naloxone, nifedipine, parafludehyde, paraquat (see Fig. 6), penicillin, propoxyphene, propranolol, radiocontrast material, ritodrine, salbutamol, salicylates, sulindac, and terbutaline.

Pulmonary hemorrhage

Diffuse pulmonary hemorrhage may be easy to diagnose histologically with a preponderance of intra-

Fig. 4. Foamy macrophages associated with amiodarone. The alveolar space contains foamy macrophages that are a marker of amiodarone therapy, but not necessarily toxicity. Hematoxylin and eosin × 40.

Fig. 5. Eosinophilic pneumonia associated with bleomycin. Numerous eosinophils fill the alveolar spaces that also contain fibrin and some red blood cells. Hematoxylin and eosin × 40.
alveolar blood, hemosiderin-laden macrophages, and perhaps foci of small cell vasculitis (ie, capillaritis); however, excluding etiologies, other than drug effect, is a complex task. Infection, immune complex diseases, and pauci-immune complex diseases that are unrelated to drug administration lead the list of causes [26]. Nevertheless, many agents, including amphotericin B, amiodarone, cocaine, cyclophosphamide, haloperidol, hydralazine, mitomycin, nitrofurantoin, paraquat (see Fig. 6), penicillamine, propylthiouracil, sulfonamides, and anticoagulants and thrombolytics, such as streptokinase and urokinase, are recognized as inciting agents.

Vasculitis

Medium-sized vessel vasculitis, seen in Wegener’s granulomatosis (WG) and Churg-Strauss syndrome, usually is not associated with drug reactions, although one recent case points to WG and leukotriene antagonists, and there are several reports of Churg-Strauss syndrome in patients treated with leukotriene antagonists [21–23]. But small vessel injury, so-called “hypersensitivity vasculitis,” may be seen in any of the above discussed histologic patterns, particularly in cases of pulmonary eosinophilia [23].

Vascular thrombosis

Widespread small vessel thrombosis that results in the hemolytic-uremic (thrombotic microangiopathic) syndrome with renal insufficiency and the development of pulmonary hypertension is another vascular process that can be attributed to therapeutic drugs. Mitomycin and combination chemotherapy are implicated [27]. The syndrome can develop during treatment or up to several months after withdrawal of the drug.

Pulmonary hypertension

Although untoward drug effects that afflict individuals who have malignancies, collagen-vascular disease, and infections increase patient morbidity, and, on occasion, mortality, drugs that are responsible for the development of pulmonary hypertension are most unsettling because few of them are therapeutic agents. Arterial intimal and medial thickening may be followed by irreversible plexiform lesions. Aside from mitomycin, aminorex, fenfluramine combined with phentermine (fenphen) and methamphetamine are known causative agents, whereas drugs with sympathomimetic properties, such as cocaine, may cause transient pulmonary vasoconstriction.

Pulmonary veno-occlusive disease

This rare process has been reported as a drug reaction in few cases [5,28]. Pulmonary veno-occlusive disease is characterized by chronic congestive changes, mild to moderate arterial hypertensive changes, and obstruction of small veins. Implicated drugs include chemotherapeutic agents, BCNU, bleomycin, cyclophosphamide, etoposide, mitomycin, and zinostatin.

Granulomatous inflammation

Granulomas of any sort that are identified in lung parenchyma raise the specter of mycobacterial or fungi infection. Yet, in some instances, other etiologies are seriously considered, including drug effect and hypersensitivity pneumonitis to environmental antigens. Necrosis strongly implicates an infectious etiology. Acebutol, cocaine, cromolyn sodium, fluorescein hydrochloride, methotrexate, nitrofurantoin, procarbazone, pentazocine, sirolimus, and triplelenamine are the drugs that are cited most often as being capable of producing a granulomatous pneumonitis with or without the bronchiolitis and interstitial inflammation that are seen in hypersensitivity pneumonitis. Intravesical administration of Bacillus Calmette Guerin for the treatment of bladder carcinoma can lead to granulomas in the lung, yet, it is uncertain whether these lesions represent systemic spread of mycobacteria or an overexuberant host immune response [29].
Unusual pulmonary complications from administered medications include nodular lesions, alveolar proteinosis, and pneumothorax. Multiple, small inflammatory nodules may be radiographically worrisome for malignancy or infection but rare cases represent scattered foci of organizing pneumonia. This morphologic expression of drug toxicity is well-documented with bleomycin and amiodarone. Alveolar proteinosis was reported in patients who received chemotherapy for chronic myelogenous leukemia (CML), most often busulfan. Unlike the idiopathic form of the disease, patients who have CML are less likely to improve with therapeutic lavage [30]. Pneumothorax was reported in a few patients following chemotherapy with bleomycin, BCNU, and amiodarone [31–33]. Given the widespread use of the agents and the not uncommon occurrence of pneumothorax, the rarity of the event prevents confirmation of such an association.

Rarely, one may encounter aspiration of kayexalate (sodium polystyrene sulfonate), which is used as a cation-exchange resin given enterally for the treatment of hyperkalemia. In lung specimens, there is little tissue reaction to the foreign material, which appears as basophilic, irregular, sharply-angled particles of varying size [22].

**Pleural disease**

Although not nearly as well-studied as drug-induced pulmonary disease, drug-associated pleural effusions, pleuritis, and pleural thickening with occasional pleural fluid eosinophilia, have been related causally to drug administration [34]. Acyclovir, amiodarone, bleomycin, bromocriptine, clozapine, cyclophosphamide, dantrolene, D-penicillamine, granulocyte-macrophage colony-stimulating factor, IL-2, isotretinoin, itraconazole, methotrexate, methysergide, mesalamine, minoxidil, mitomycin, nitrofurantoin, proctolol, propylthiouracil, procarbazine, simvastatin, and valproic acid can cause pleural effusions and should be considered if other etiologies are excluded [34]. Pleural thickening also is described in association with ergoline drugs [21–23].

Although more than 75 drugs have been implicated as a cause of lupuslike syndrome or SLE exacerbations, pleuropericardial reactions that usually manifest with fibrinous pleuropericarditis are caused most commonly by procainamide and hydralazine [34]. Chlorpromazine, isoniazid, mesalamine, methyl dopa, penicillamine, and quinidine also may induce lupuslike pleuropericarditis with or without effusions [34].

**Summary**

The surgical pathologist’s role in the diagnosis of adverse pulmonary and pleural drug effect requires an appreciation of the clinico-radiologic scenario and particular knowledge of morphologic patterns of lung injury. Bronchoscopic biopsies may be helpful in some cases of DAD, eosinophilic pneumonia, or OP. Extrapolating patterns of lung involvement from small biopsies and cytologic preparations often is difficult and surgical lung biopsy is required. Although lung biopsies are not pathognomonic for drug toxicity and correlation with clinical, laboratory, and radiologic data is required, they can be a powerful tool in the evaluation of suspected drug-induced pulmonary disease by helping to exclude underlying disease or infection and documenting the pattern of lung injury. The latter information is helpful in making the diagnosis of drug toxicity as well as guiding the optimal management of the patient.

**References**