

18.14.13 Drug- induced lung disease 4272 S.J. Bour

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section 18 Respiratory disorders 4272 Symptoms occur in about 5–15% of patients, depending on the treatment regimen used, with the onset of cough, breathlessness, and fever about 2 months after radiotherapy. Pre-existing lung disease may increase the clinical impact of radiation pneumonitis, but symptoms often resolve spontaneously. Fibrosis may result in permanent loss of lung function, with a reduction in total lung capacity and carbon monoxide transfer factor associated with chronic breathlessness. This typically develops about 6 months after radiotherapy and may progress for 6–24 months, but has usually stabilized by 2 years. CT is more sensitive than the chest radiograph in detecting radiation-induced changes such as ground-glass shadowing, septal thickening, and fibrosis, and is useful in differentiating radiation injury from tumour recurrence or infection. Severe acute reactions to radiotherapy are rare but can occasionally result in respiratory failure and the acute respiratory distress syndrome, particularly in patients with pre-existing interstitial lung disease. Patterns of injury that involve the lungs more diffusely are well recognized. Bilateral lymphocytic alveolitis is often present after unilateral radiotherapy in patients with breast cancer, while positron emission tomography has shown increased metabolic activity in nonirradiated areas of the lung in patients who have had radiotherapy for lung cancer. Diffuse bronchiolitis obliterans organizing pneumonia and chronic eosinophilic pneumonia have also been reported in patients with breast cancer treated by radiotherapy. Other short-term risks of chest radiotherapy relate to pneumothorax, pleural reactions, and rib fractures, and in the long term there is an increased risk of lung cancer. Treatment Most cases of radiation pneumonitis are subclinical or cause only minor symptoms that do not require treatment. In more severe cases corticosteroids are usually effective in relieving symptoms during the acute phase, but they do not prevent the subsequent development of fibrosis. Typically, prednisolone 40–60 mg daily is given until there is clinical improvement, at which stage the dose is tapered while watching for signs of recrudescence of the pneumonitis. Prevention of radiation-induced lung injury is particularly focused on refining techniques which increase the radiation dose delivered to the cancer and reduce exposure of normal lung. Radiotherapy lung injury has been reduced in animal models by the administration of agents such as amifostine, captopril, pentoxifylline, and manganese superoxide dismutase, but a clinical role for these agents has not been established. FURTHER

READING Castillo R, et al. (2014). Pre-radiotherapy FDG PET predicts radiation pneumonitis in lung cancer. *Radiation Oncology*, 9, 74–89. Cottin V, et al. (2004). Chronic eosinophilic pneumonia after radiation therapy for breast cancer. *Eur Respir J*, 23, 9–13. Crestani B, et al. (1998). Bronchiolitis obliterans organizing pneumonia syndrome primed by radiation therapy to the breast. *Am J Respir Crit Care Med*, 158, 1929–35. Hanania AN, et al. (2019) Radiation-induced lung injury: assessment and management. *Chest*, 156, 150–62. Heinzelmann F, et al. (2006). Irradiation-induced pneumonitis mediated by the CD95/CD95-ligand system. *J Natl Cancer Inst*, 98, 1248–51. Hesham A, et al. (2005). Positron emission tomography demonstrates radiation-induced changes to non-irradiated lungs in lung cancer patients treated with radiation and chemotherapy. *Chest*, 128, 1448–52. Martin C (1999). Bilateral lymphocytic alveolitis: a common reaction after unilateral thoracic irradiation. *Eur Respir J*, 13, 727–32. Movsas B (1997). Pulmonary radiation injury. *Chest*, 111, 1061–75. Neugut AI, et al. (1994). Increased risk of lung cancer after breast cancer radiation therapy in cigarette smokers. *Cancer*, 73, 1615–20. Palma DA, et al. (2013). Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. *Int J Radiation Oncol Biol Phys*, 85, 444–50. Rowinsky EK, Abeloff MD, Wharam MD (1985). Spontaneous pneumothorax following thoracic irradiation. *Chest*, 88, 703–6. Zhuang H, et al. (2014). Radiation pneumonitis in patients with non-small cell lung cancer treated with erlotinib concurrent with thoracic radiotherapy. *J Thorac Oncol*, 9, 882–5.

18.14.13 Drug-induced lung disease S. J. Bourke ESSENTIALS Drug-induced lung disease is common and needs to be considered in the differential diagnosis of many respiratory conditions. The nature and timing of events often provide an important clue and are

Fig. 18.14.12.1 Chest radiograph showing radiation-induced fibrosis, particularly in the right upper zone. Note the sharply demarcated edge to the fibrosis, which does not conform to any normal anatomical structure.

18.14.13 Drug-induced lung disease 4273 sometimes sufficiently characteristic for drug-induced lung disease to be diagnosed with confidence, with resolution of symptoms on drug cessation providing further supportive evidence. Well-recognized adverse drug effects are listed in formularies and drug data sheets, but it is often helpful to consult a constantly updated website (<http://www.pneumotox.com> is highly recommended). Direct drug effects may arise through toxic, pharmacological, allergic, or idiosyncratic mechanisms, and there may also be indirect effects (e.g. a predisposition to lung infection from cytotoxic and immunosuppressive therapies). From a clinical perspective, adverse effects may be classified according to the induced disorder and the site of involvement. Asthma is the most common airway disorder to be induced or exacerbated by drugs. It may be produced by a predictable effect related to the drug's pharmacological properties (e.g. β -adrenergic antagonists) or as an idiosyncratic reaction (e.g. aspirin). Cough is a well-recognized side effect of treatment with angiotensin-converting enzyme inhibitors. Alveolar and interstitial reactions comprise three main categories: (1) alveolar capillary leakage (e.g. salicylates); (2) interstitial pneumonia and fibrosis (e.g. bleomycin, amiodarone, infliximab); and (3) pulmonary eosinophilia (e.g. sulphonamides). Pulmonary vascular involvement includes venous thrombo-embolism (e.g. oral contraceptive pill), and pulmonary hypertension (e.g. aminorex, now withdrawn), dasatinib, and interferons. Pleural effusions and thickening may result from drugs (e.g. dantrolene, bromocriptine, methysergide, and dasatinib).

Introduction Drug-induced lung disease is common and needs to be considered in the differential diagnosis of many respiratory conditions, and in prescribing drugs for the treatment of diseases in all areas of clinical practice. Direct effects may arise through toxic, pharmacological, allergic, or idiosyncratic mechanisms, although

often the precise mechanism is unknown. There may also be indirect effects (e.g. a pre-disposition to lung infection from cytotoxic and immunosuppressive therapies, and the development of respiratory failure from sedation). Some causes of drug-induced lung disease have now been eradicated (e.g. aminorex pulmonary hypertension) as the causative drug is no longer prescribed. For others, the risks are now so well established that the potential for lung toxicity is considered in the risk-benefit assessment of prescribing (e.g. methotrexate, amiodarone, bleomycin) and the patient is informed of the risks and monitored for the adverse effects. It is for newly introduced drugs that particular vigilance is required: adverse effects must be identified as speedily as possible (e.g. leflunomide, infliximab), early recognition of problems being critical both for the affected individual, so that drug cessation is prompt and the adverse effect is minimized, and also to prevent others coming to harm. Making the diagnosis of drug-induced lung disease The first step in diagnosis is to consider the possibility that a clinical presentation might be drug-induced. The nature and timing of events often provides important clues. In some circumstances they are sufficiently characteristic that drug-induced lung disease can be diagnosed with confidence, with subsequent resolution of symptoms on drug cessation providing further supportive evidence. Reintroduction of the drug is rarely indicated unless it is essential in the management of the underlying disease or there is doubt about the diagnosis of an adverse drug effect. The exclusion of an alternative cause of any clinical events is an important step, with the diagnostic approach adapted to the circumstances of the clinical problem, the likelihood of an adverse drug effect, the possibility of an alternative diagnosis, and the need for a definitive diagnosis to guide management decisions. For example, a patient may develop breathlessness and show diffuse infiltrates on chest radiography when taking immunosuppressive drugs for a connective tissue disease or chemotherapeutic agents for cancer. The clinical features could be due to an adverse drug effect on the lungs, infection, lung involvement by the underlying disease, or the development of coincidental lung disease. Management in these circumstances depends crucially upon accurate diagnosis, and invasive tests such as bronchoscopy, bronchoalveolar lavage, and sometimes lung biopsy may be indicated. Although well-recognized adverse drug effects are listed in formularies and drug data sheets, the field of drug-induced lung disease is continuously evolving, and it is often helpful to consult a constantly updated website: <http://www.pneumotox.com> is highly recommended. It is also important to report possible adverse drug reactions to appropriate local authorities, such as the Committee on Safety of Medicines in the United Kingdom, who may also be able to provide information to aid the management of individual cases. The clinical spectrum of drug-induced lung disease is diverse and complex, and it is therefore advisable to scrutinize the drug list for potential drug causes when patients present with clinical problems for which no other cause is apparent. Drug-induced lung disease may be classified according to the induced disorder and the site of involvement as airways, alveoli/interstitium, pulmonary vasculature, and pleura.

Airways Asthma Drug-induced bronchoconstriction may arise by a number of different mechanisms and sometimes the precise mechanism is uncertain. It most often occurs in patients with pre-existing asthma. In some cases the asthma may not have been recognized until an episode of bronchoconstriction occurs as an adverse effect of a drug, but in these instances clues to pre-existing asthma may be apparent when the appropriate history is taken. Drugs that exacerbate symptoms in subjects with pre-existing asthma may be classified as those that produce an effect which is to some extent predictable from their pharmacological properties, and those which produce bronchoconstriction due to an idiosyncratic effect (Table 18.14.13.1). Less commonly, asthma develops *de novo*, probably because IgE-mediated immunological hypersensitivity has developed. Drug hypersensitivity reactions that include asthma among the manifestations are

often associated with blood eosinophilia and/or eosinophilic pneumonia.

section 18 Respiratory disorders 4274 Drug-induced anaphylaxis The most dramatic presentation of drug-related bronchoconstriction is as part of an acute anaphylactic reaction; penicillin and intravenously administered iron-dextran are particularly noteworthy among the causal agents. An anaphylactic reaction is characterized by swelling of the tongue, laryngeal oedema, upper airway obstruction, and bronchospasm occurring within minutes of exposure to the drug. Immunological hypersensitivity is presumed to underlie most causes of occupational asthma, some of which involve pharmaceutical agents. Most prominent are certain antibiotics (e.g. cephalosporins, isoniazid, penicillins, piperazine, spiramycin, tetracycline,), the H₂-receptor antagonist cimetidine, the laxative psyllium (ispaghula), pancreatic enzymes, and certain hormones (adrenocorticotrophic hormone (ACTH), gonadotropin, pituitary snuff). If an individual sensitized by inhalation in the workplace subsequently uses the relevant drug therapeutically, the potential arises for an asthmatic reaction (Fig. 18.14.13.1). The medical history, when symptoms suggest asthma, should always include details of occupation and medication, and if the patient has ever worked in the pharmaceutical industry the possibility of occupationally induced hypersensitivity to a current medication should be considered.

Cholinergic drugs Cholinergic drugs, such as carbachol, occasionally produced bronchoconstriction when given systemically, and in very sensitive asthmatic patients exacerbations have occurred after use of pilocarpine eye drops for the treatment of glaucoma. Bronchoconstriction can also occur from the cholinergic effect of pyridostigmine used in the treatment of myasthenia gravis. An inhaled anticholinergic agent has been shown to be effective in reversing untoward effects of cholinesterase inhibitors in asthmatic patients with myasthenia gravis.

β-adrenergic antagonists β-adrenergic antagonists aggravate bronchoconstriction in patients with asthma. Although drugs, such as sotalol and metoprolol, which target β₁-receptors have less adverse effects on airway function, patients with asthma can still show a reduction in forced expiratory volume in 1 s (FEV₁) or peak flow which can be severe. By contrast, patients with smoking-induced chronic obstructive pulmonary disease often tolerate β-blockers and derive benefit from their use in treating comorbid conditions such as ischaemic heart disease. Although the adverse effects of oral or systemic β-blockers are well recognized, those of ophthalmic preparations are sometimes

Fig. 18.14.13.1 Results of inhalation and ingestion challenge tests with ampicillin. The inhalation test confirmed that the patient had become sensitized to ampicillin as a consequence of respiratory exposure at work, and the ingestion test showed that asthmatic reactions would be provoked also by oral ingestion at therapeutic dose levels. Data taken from Davies RJ, Hendrick DJ, Pepys J (1974). Asthma due to inhaled chemical agents: ampicillin, benzyl penicillin, 6-amino-penicillanic acid and related substances. Clin Allergy, 4, 227–47.

Table 18.14.13.1 Drugs that may cause or exacerbate asthma

Pharmacological effects Cholinergic agents (e.g. carbachol, pilocarpine) Cholinesterase inhibitors (e.g. pyridostigmine) Prostaglandin F Histamine-releasing agents (e.g. curare derivatives, morphine, taxanes) β-Sympathetic antagonists ACE inhibitors (cough without asthma more common) Sensitizing and idiosyncratic effects Oral Aspirin and other NSAIDs Tartrazine-containing preparations Taxanes (e.g. paclitaxel, docetaxel) Carbamazepine Venlafaxine Parenteral Penicillin Iron-dextran complex Adenosine Hydrocortisone sodium succinate N-Acetylcysteine Inhaled Nebulized pentamidine, colistin Inhaled mannitol, hypertonic saline Eye drops NSAIDs ACE, angiotensin-converting enzyme; NSAIDs, nonsteroidal anti-inflammatory drugs.

18.14.13 Drug-induced lung disease 4275 overlooked. Timolol, which is commonly used in eye drops for the treatment of glaucoma, is a potent nonselective β -blocker. Its use has frequently been associated with worsening asthma. The ophthalmic formulation of a newer β -blocker, betaxolol, appears to be less dangerous, but should only be used in patients with asthma if no suitable alternative is available. Aspirin and nonsteroidal anti-inflammatory drugs Aspirin and nonsteroidal anti-inflammatory drugs cause broncho constriction in about 10% of patients with asthma. This is thought to be caused by a shift of arachidonic acid metabolism away from the cyclooxygenase pathway towards the lipoxygenase pathway, resulting in increased production of leukotrienes which cause bronchoconstriction. Asthmatic deaths have been reported with both aspirin and indomethacin. These patients often have a triad of nasal polyps, asthma, and aspirin-induced bronchoconstriction. Many patients with analgesic-induced asthma are also sensitive to the azo dye tartrazine, which was a commonly used colouring agent in medications and foodstuffs, and—since it is an approved food and drug additive—its presence is not always declared and hence the extent of the problems it may cause is not clear. In the past tartrazine was present, ironically, in some medications used to treat asthma, but most pharmaceutical companies no longer use it in their formulations. The importance of drug formulation Asthmatic symptoms can be a consequence of the particular formulation of a drug or its method of delivery. For example, nebulized solutions of low osmolality can trigger asthmatic reactions if the patient has a high level of airway responsiveness. This appears to have been the main mechanism of bronchoconstriction induced paradoxically by nebulized ipratropium bromide, and since the drug was reformulated in isotonic solution the problem has resolved. A further cause of bronchoconstriction from nebulized drugs has been the presence of certain preservatives or stabilizers (e.g. benzalkonium chloride, edetate disodium) in the excipient solution. Inhaled antibiotics, such as pentamidine for *Pneumocystis jirovecii* infection, or colistin, tobramycin, or aztreonam for treating bronchiectasis and cystic fibrosis, sometimes also provoke bronchoconstriction. Inhaled mannitol, used as a mucolytic agent in treating patients with cystic fibrosis, is known to provoke bronchoconstriction in patients with asthma and patients should be monitored at the start of treatment with serial spirometry after a trial dose to ensure that they do not develop bronchoconstriction. Prior use of a bronchodilator such as salbutamol is useful in increasing the tolerability of such inhaled medications. Other drugs that can cause asthma The bronchoconstrictor prostaglandin $F_{2\alpha}$, used to induce abortion, may be hazardous in asthmatic patients. The occurrence of bronchoconstriction after thiopentone, opiates, and muscle relaxants (tubocurarine, suxamethonium, and pancuronium) is probably due to their capacity to release histamine from basophils. Taxanes, such as paclitaxel or docetaxel, may result in mast cell degranulation, and this can provoke bronchoconstriction. Corticosteroids and antihistamines are therefore routinely given prior to taxane treatment to reduce the occurrence of this adverse effect. Iodinated contrast media used in radiological imaging may activate the complement system, with activation of mast cells and basophils via anaphylatoxins C3a and C5a receptors. Adenosine given intravenously to treat supraventricular tachycardia is a potent constrictor of asthmatic airways. Its effects on the airways are probably due to activation of mast cells via an A₂ receptor. Drug prescribing for patients with asthma The potential exacerbation of asthma by drugs used to treat it presents a special dilemma, as a drug effect may be difficult to dissociate from spontaneous deterioration. There are well-documented reports of worsening asthma after intravenous hydrocortisone. This is a particular problem in asthmatic patients who also show adverse reactions to aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs). The sensitivity to hydrocortisone of these individuals does not extend to other steroids: it appears to be related to the succinate moiety of the hydrocortisone sodium succinate molecule,

as it is not seen with the alternative phosphate salt. Idiosyncrasy probably underlies many asthmatic symptoms related to medication and is the likely explanation for exacerbations following use of intravenous N-acetylcysteine in paracetamol poisoning, use of which requires caution in asthmatic patients. Drugs masking asthma There are rare situations where cessation of a drug may reveal previously undetected asthma. For example, lithium has been shown to reduce airway responsiveness and inhibit the contractile response of airway smooth muscle, and there are rare reports of asthma becoming apparent for the first time when this medication is discontinued. Cough Cough in the absence of asthma is a well-recognized side effect of treatment with angiotensin-converting enzyme (ACE) inhibitors. It develops in 10 to 20% of individuals treated with these drugs and is an effect of the class of drug rather than of specific agents. The cough is nonproductive. There appears to be a weak relation to dose, such that dose reduction may result in some improvement, but in many individuals the symptom remains sufficiently troublesome to necessitate drug withdrawal. Deterioration of pre-existing asthma has also been reported occasionally, but features of asthma are not present in most individuals with cough related to ACE inhibition. The mechanism is unclear; ACE catalyses not only the conversion of angiotensin I to angiotensin II, but also the breakdown of bradykinin and substance P. Since these agents are cough stimulants, their accumulation offers a possible mechanism for this adverse effect. The cough resolves on withdrawal of the drug. Alveoli and the lung interstitium Drug-induced alveolar and interstitial lung disease may occur in different clinical settings, with a diverse range of drugs, and encompasses a broad spectrum of disease from acute noncardiogenic pulmonary oedema to insidiously developing pulmonary fibrosis. These conditions are conveniently considered under three main categories: alveolar capillary leakage, interstitial pneumonitis and fibrosis, and pulmonary eosinophilia (Table 18.14.13.2).

section 18 Respiratory disorders 4276 Alveolar capillary leakage Acute pulmonary oedema is a recognized complication of overdoses of salicylates, opiates, and tricyclic antidepressants. The pulmonary oedema develops as a result of increased permeability of the alveolar capillary membrane, which is thought to arise through various mechanisms, sometimes involving immunoglobulin and complement deposition in the lung, cytokine release from lymphocytes, and activated neutrophils aggregating and adhering to endothelial cells, releasing toxins, oxygen radicals and mediators (arachidonic acid, histamine, kinins). Alveolar capillary leakage has also been described with hydrochlorothiazide as an idiosyncratic reaction which does not occur with other thiazide drugs. Acute pulmonary oedema has also been reported with interleukin-2, used in the treatment of melanoma and renal cell carcinoma, and occasionally after injection of radiocontrast media. Infused β_2 -adrenergic agonists (terbutaline, isoxsuprine), used as tocolytics to relax the uterus and to inhibit premature labour, may also give rise to florid pulmonary oedema. In these cases there is a close temporal relationship between drug administration and the onset of pulmonary oedema. In other circumstances the acute respiratory distress syndrome may result from a reaction to more prolonged use of drugs including amiodarone, anticancer chemotherapy (vinorelbine, mitomycin C, melphalan, paclitaxel, cyclophosphamide) and anti-inflammatory drugs (infliximab, methotrexate). Interstitial pneumonitis and fibrosis Many drugs may provoke an inflammatory reaction in the lungs with interstitial inflammation, alveolitis, and sometimes fibrosis. Many classic causes are very well-known, but vigilance is required as new drugs are introduced into practice. Early recognition of drug-induced interstitial lung disease allows prompt cessation of the drug. Interstitial pneumonitis and fibrosis are particularly well recognized with amiodarone, nitrofurantoin, methotrexate, leflunomide, and certain anticancer drugs. When choosing a drug

which is recognized to have the potential for lung toxicity, it is important to advise patients of the risk so that they can be alert for the onset of any symptoms. It is also advisable to establish accurately whether the patient has any pre-existing lung disease, and to undertake baseline investigations such as a chest radiograph and lung function tests. This is particularly relevant where the disease being treated is itself associated with interstitial lung disease, as in the case of rheumatoid arthritis and connective tissue diseases. Clinical presentation and investigation

Patients experiencing a drug-induced pneumonitis may present acutely with cough, fever, shortness of breath, and occasionally systemic upset. Alternatively, there is slowly progressive fibrosis with gradually worsening dyspnoea and widespread shadowing on the chest radiograph. The mechanisms of such reactions are uncertain, but may include toxicity, hypersensitivity, and often idiosyncrasy.

Table 18.14.13.2 Alveolar and interstitial drug reactions

Alveolar capillary leakage	Hydrochlorothiazide	Interleukin-2	Naloxone	Opiates	Salicylates	Radiocontrast	Tricyclic antidepressants	Tocolytic agents (e.g. isoxsuprine, terbutaline)
Interstitial pneumonitis and fibrosis	Amiodarone	Antiretroviral therapy	Infliximab	Leflunomide	Methotrexate	Nitrofurantoin	Cytotoxic agents	Azathioprine
	Bleomycin	Busulfan	Carmustine (BCNU)	Chlorambucil	Cyclophosphamide	Cytosine arabinoside	Lomustine (CCNU)	Melphalan
	6-Mercaptopurine	Mitomycin C	Biological agents	TNF α inhibitors (e.g. infliximab, etanercept, adalimumab)	Monoclonal antibodies (e.g. rituximab, trastuzumab)	Tyrosine kinase inhibitors (e.g. gefitinib, erlotinib)	Interferon α	Pulmonary eosinophilia
	Aspirin	Carbamazepine	Chlorpropamide	Dapsone	Gold salts	Imipramine	Methotrexate	Naproxen
	Nitrofurantoin	Penicillamine	Penicillins	Phenytoin	Procarbazine	Sulphasalazine	Sulphonamides	Tetracycline

a Pulmonary eosinophilia is a feature of some reactions to these drugs, but adverse effects can also occur by other mechanisms.

18.14.13 Drug-induced lung disease 4277 With some drugs—including bleomycin, carmustine, amiodarone, and nitrofurantoin—there is a relation to dose or duration of treatment. Evidence in cases of nitrofurantoin- and bleomycin-induced pneumonitis suggests a role for the production of toxic oxygen radicals in the lungs, perhaps providing a link with the known pulmonary toxicity of oxygen itself and the synergistic adverse effects of high oxygen concentrations and some cytotoxic agents. A single drug (e.g. amiodarone, methotrexate) may produce a diverse range of histopathological changes in the lungs, including alveolitis, fibrosis, nonspecific interstitial pneumonitis, cryptogenic organizing pneumonia, and diffuse alveolar damage. Lung biopsy therefore tends to show the pattern and severity of interstitial lung disease rather than showing the precise causation, and it is often difficult to establish from biopsy whether fibrosis is due to the underlying disease (rheumatoid or connective tissue lung disease) or a drug reaction. For this reason lung biopsy is of limited value and is rarely performed. Conversely, drugs must always be considered in the differential diagnosis of patients presenting with interstitial lung disease. Histological patterns of nonspecific interstitial pneumonia, usual interstitial pneumonia, and cryptogenic organizing pneumonia have all been associated with many different drugs. Particular clinical circumstances

Amiodarone Much interest has centred on the cardiac antiarrhythmic drug amiodarone. It has been estimated that about 6% of patients taking 400 mg or more per day for 2 months or more will develop overt pulmonary toxicity, but there have been several well-documented cases involving smaller doses. The mechanisms may include both immunologically mediated and direct toxic effects. Histologically the lung shows features of chronic inflammation together with interstitial and intra-alveolar fibrosis (Fig. 18.14.13.2). Characteristic 'foamy' macrophages are seen, but they are not specific for serious toxic reactions as they are also demonstrable in most patients taking the drug without adverse clinical effects. Occasionally the

histo- logical picture is of cryptogenic organizing pneumonia. Symptoms include progressive dyspnoea, a troublesome cough, and (occasionally) pleuritic pain. Radiographic appearances are varied: most frequently there is a diffuse nodular or alveolar filling pattern, sometimes with upper lobe predominance (Fig. 18.14.13.3); sometimes a pleural effusion is present. The differential diagnoses of amiodarone pulmonary toxicity particularly include left ventricular failure and pneumonia. Measurement of serum brain natriuretic peptide (elevated in cardiac failure) and assessment of left ventricular function by echocardiography is helpful. Bronchoalveolar lavage may be necessary to exclude infection: in amiodarone pulmonary toxicity this typically shows a lymphocytic pattern, but the finding of 'foamy' macrophages is insufficient to confirm the diagnosis. If amiodarone lung toxicity is suspected, cessation of treatment is desirable, but the very long half-life of drug metabolites (many weeks) means that elimination is very slow. Corticosteroids probably suppress the reaction and are often used. Rheumatoid arthritis Drug-induced interstitial lung disease is particularly common in the treatment of rheumatoid arthritis and connective tissue diseases. Interstitial disease has been well described in relation to penicillamine, gold salts, and sulphasalazine, but these agents are now much less frequently used than they were in the past. Methotrexate is a particularly well recognized cause of drug- induced interstitial lung disease. This is usually a hypersensitivity reaction which is not directly related to the cumulative dose or duration of treatment. Patients typically present subacutely with cough and dyspnoea, sometimes with fever. Chest radiography and CT show diffuse infiltrates. Bronchoalveolar lavage may be helpful in excluding infection and may show a neutrophilic or lymphocytic alveolitis. Lung function tests usually show a reduction in lung volumes and impairment of gas diffusion, but serial monitoring of lung function has not been shown to be helpful in detecting pneumonitis before the onset of symptoms. Where lung biopsies have been performed they have shown a spectrum of interstitial inflammation, fibrosis, type II pneumocyte hyperplasia and (sometimes) Fig. 18.14.13.2

Histological specimen of the lung of a patient who died from amiodarone pulmonary toxicity, showing (a) alveolar wall thickening and organizing intra-alveolar exudates; and (b) the alveolar exudate with characteristic 'foamy' macrophages, seen at higher magnification. From Adams PC, et al. (1986). Amiodarone pulmonary toxicity: clinical and subclinical features. Quarterly Journal of Medicine, 59, 449-71, by permission of Oxford University Press.

section 18 Respiratory disorders 4278 granulomas. Treatment is by stopping the drug, and corticosteroids are often given. Leflunomide-induced interstitial pneumonitis is thought to be rare, and the incidence may have been exaggerated by the tendency to use leflunomide rather than methotrexate in patients with pre-existing rheumatoid interstitial lung disease. Nonetheless, it can cause severe pneumonitis, possibly aggravating pre-existing rheumatoid lung disease, such that particular care is required in managing such patients. Leflunomide should be discontinued if there is evidence of new or deteriorating interstitial lung disease, when cholestyramine or activated charcoal can be used to aid elimination of the drug. Cytotoxic and immunosuppressive drugs Cytotoxic and immunosuppressive drugs are frequently associated with interstitial pneumonitis. Bleomycin causes problems most frequently, followed by busulfan and mitomycin C. Cyclophosphamide and azathioprine are the most widely used drugs in this group, because of their roles in nonmalignant disease, but produce adverse pulmonary reactions only occasionally. In most cases it is not clear whether the effects are due to direct toxicity or to hypersensitivity. Bleomycin toxicity is dose-related, occurring more commonly at cumulative doses greater than 300 000 units (European pharmacopoeia units). The recorded frequency of adverse reactions varies with the means by which they are detected, with fibrosis occurring in 5 to 10% of patients treated

with busulfan on clinical and functional criteria, but a much higher proportion on the basis of pathological and cytological evidence. Similarly, the increasing use of CT scanning shows an appreciably higher prevalence than found in surveys that employ plain chest radiography. The frequency of overt lung involvement may also be related to length of survival, as determined by the primary disease. With busulfan, the interval between starting treatment and the appearance of toxic effects can be as long as 4 years, and in some cases the lung changes appear to progress after the drug has been discontinued. With carmustine (BCNU), pulmonary fibrosis may first be recognized several years after treatment has finished. Other factors that may increase the toxicity of a given drug include advanced patient age, and synergism with other drugs, lung radiation, or the subsequent inhalation of high concentrations of oxygen. Histologically, most cytotoxic drugs produce evidence of diffuse alveolar damage with destruction of lining cells, formation of hyaline membranes, and variable degrees of inflammatory infiltration and fibrosis. Fibrosis is particularly common with busulfan and bleomycin, but rare with methotrexate. With methotrexate and procarbazine (and very occasionally with bleomycin) there may be blood and tissue eosinophilia, and correspondingly a good therapeutic response to steroids. Biological agents

Biological agents are being increasingly used in the treatment of inflammatory conditions and tumours. Certain drug-induced lung conditions have been reported with these agents, and there have also been several reports of interstitial pneumonitis. Tumour necrosis factor α (TNF α) inhibitors (infliximab, etanercept, adalimumab) are used in the treatment of rheumatoid arthritis and inflammatory bowel disease. Increased susceptibility to respiratory infections, and to tuberculosis in particular, is an important adverse effect, but there have also been several reports of interstitial pneumonitis with these agents. Monoclonal antibodies (rituximab, trastuzumab) are used in the treatment of some cancers and may cause interstitial pneumonitis. Interstitial pneumonitis has also been reported with tyrosine kinase inhibitors (gefitinib, erlotinib). Interferon- α , used to treat hepatitis C, has been associated with the development of a sarcoid-like granulomatous disease. The frequency and severity of interstitial lung disease with these different biological agents is not yet well established, but it is important to be alert to possible adverse effects of treatment in patients developing respiratory symptoms on these medications. Drug-induced sarcoidosis-like reactions

A granulomatous lung disease, mimicking sarcoidosis, has been described after instituting highly active antiretroviral therapy with protease inhibitors in patients with HIV infection. This pattern of lung disease seems to be related to immune reconstitution with enhanced lymphoproliferative responses rather than to any infective organism. Similar drug-induced sarcoidosis-like reactions have also been associated with immune checkpoint inhibitors (e.g. ipilimumab, nivolumab), interferons and TNF α antagonists. Pulmonary eosinophilia

Eosinophilic reactions in the lung include conditions that would be classified as Löffler's syndrome, simple or prolonged pulmonary eosinophilia, and eosinophilic pneumonia (see Chapter 18.14.2).

Fig. 18.14.13.3 Chest radiograph of a patient with amiodarone pulmonary toxicity showing confluent alveolar shadowing in both upper lobes. From Adams PC, et al. (1986). Amiodarone pulmonary toxicity: clinical and subclinical features. *Quarterly Journal Medicine*, 59, 449–71, by permission of Oxford University Press.

18.14.13 Drug-induced lung disease 4279 Tissue eosinophilia is a more consistent feature than peripheral blood eosinophilia. Historically, sulphonamides have been the drugs most frequently reported to cause pulmonary eosinophilia, and sulphonamide sensitivity may also explain some of the reactions to sulphasalazine, which is chemically related. The pulmonary eosinophilia recorded with aspirin appears to be distinct from aspirin-induced asthma. Nitrofurantoin may produce an

acute pulmonary eosinophilic reaction in addition to more insidious fibrosis. The roles of gold salts and penicillamine in eosinophilic reactions have been a matter of some debate, but the evidence suggests that both are involved. It seems unlikely, however, that drugs are responsible for many of the cases of lung fibrosis associated with rheumatoid arthritis. Penicillamine has been incriminated in two other types of adverse pulmonary reaction: (1) pulmonary haemorrhage (Goodpasture's syndrome) when used in high doses for the treatment of Wilson's disease, and (2) obliterative bronchiolitis in patients treated for rheumatoid arthritis. The clinical severity of eosinophilic reactions is very variable, ranging from a transient and asymptomatic radiographic opacity to a severe eosinophilic pneumonia with dyspnoea, cough, fever, and hypoxaemia. Concomitant asthma is not uncommon. Chest radiography and CT show fluffy opacities, frequently with a peripheral or predominantly upper lobe distribution (Fig. 18.14.13.4). The prognosis is usually good: the changes often subside spontaneously on withdrawal of the drug, while in more severely ill patients there is usually a dramatic improvement on instituting treatment with corticosteroids. Although repeated exposure to the offending agents continues to produce reactions, the severity of these may progressively decrease.

Pulmonary vasculature Several drugs and toxins have been shown to be associated with the development of pulmonary arterial hypertension (Box 18.14.13.1).

Appetite suppressants In the 1960s there was a major outbreak of pulmonary hypertension in relation to the use of aminorex as an appetite suppressant in Switzerland, Germany and Austria, and the drug was withdrawn. Aminorex resembles adrenaline and ephedrine in its chemical structure. Fenfluramine and dexfenfluramine were associated with pulmonary hypertension in the 1980s and 1990s. These are serotonin uptake inhibitors and were used also as appetite suppressants. They increase circulating levels of serotonin (5-hydroxy tryptamine, 5HT), which is usually stored in platelets. Serotonin is a direct pulmonary artery vasoconstrictor and promotes growth of smooth muscle. These drugs inhibit the uptake and promote release of serotonin from platelets. Genetic factors seem to be important, and patients who developed pulmonary hypertension on fenfluramine were more likely to be carriers of bone morphogenetic protein type 2 (BMP2) mutations. Benfluorex was used in France until 2009 and was also shown to be associated with pulmonary hypertension. Illicit stimulants Amphetamines, methamphetamines, and cocaine are also considered to be risk factors for pulmonary hypertension based on case reports, epidemiological studies, and pharmacological similarities to fenfluramine. Epidemiological studies showed that patients with idiopathic pulmonary hypertension were 10-fold more likely to have a history of having used these stimulants. Biological agents Dasatinib is a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia. Several reports of pulmonary hypertension have been published in patients receiving this drug. It is thought to act by inhibiting the Src family kinases which play a critical role in smooth muscle cell proliferation and vasoconstriction. There have also been reports of interferon- α and interferon- β causing pulmonary hypertension.

Fig. 18.14.13.4 Eosinophilic pneumonia due to dapsone. CT shows extensive patchy air space opacification in the upper lobes with subpleural predominance. Bronchoalveolar lavage showed eosinophilia and no infection. Blood eosinophil count was elevated at $1.43 \times 10^9/\text{litre}$ (0.04–0.4).

Box 18.14.13.1 Drugs associated with pulmonary arterial hypertension

Appetite suppressants • Aminorex • Fenfluramine, dexfenfluramine • Benfluorex

Illicit stimulants • Amphetamines • Methamphetamine • Cocaine

Biological agents • Dasatinib • Interferon- α , interferon- β

section 18 Respiratory disorders 4280 Other drug effects on the pulmonary circulation Pulmonary thromboembolism related to use of the contraceptive pill is well established; its frequency

correlates with the oestrogen content and has been reduced since the introduction of low-oestrogen preparations. Pulmonary veno-occlusive disease has been reported after carmustine (BCNU), mitomycin and bleomycin. NSAIDs and selective serotonin-reuptake inhibitors are associated with persistent pulmonary hypertension in the newborn. This condition is due to an increased pulmonary vascular resistance that prevents normal pulmonary blood flow and causes a right-to-left shunt through a patent foramen ovale and patent ductus arteriosus. Analgesics given during labour have also been implicated in the development of pulmonary hypertension in the newborn; drugs such as aspirin, indomethacin, and naproxen delay premature labour but, by their inhibitory effects on prostaglandin synthesis, may also cause constriction of the ductus arteriosus leading to pulmonary hypertension in utero. This persists into the postpartum period and causes respiratory distress.

Pleura Some drugs that have been associated with pleural effusions or fibrous thickening are shown in Table 18.14.13.3. Sometimes this arises as part of a syndrome of drug-induced systemic lupus erythematosus (SLE): the antiarrhythmic procainamide was most often implicated, but other agents include gold, hydralazine, isoniazid, penicillamine, captopril, and sulphonamides. When drug-induced SLE affects the respiratory system it particularly involves the pleura, but there is often some fibrosis of the underlying lung. Practolol, a now obsolete selective β -sympathetic antagonist, produced a characteristic 'oculomucocutaneous' syndrome. This differed from drug-induced SLE in that autoantibodies to histones were not usually present, and ocular symptoms (not usually a feature of drug-induced SLE) were common. Pleural effusions and subsequent pleural thickening occurred in association with characteristic corneal ulceration, discoid rash, and fibrinous peritonitis. Affected patients sometimes developed effusions months or years after discontinuing the drug, and in some the chronic changes led to significant respiratory disability. Exudative pleural effusions and pleural thickening have been reported with ergot-like drugs, including bromocriptine, cabergoline, ergotamine, methysergide, and pergolide. The pleural effusion may be an isolated manifestation of drug-induced disease or may occur with some lung fibrosis. The precise mechanisms involved are uncertain, but may include hypersensitivity reactions, direct toxic effects, or chemical-induced inflammation. There is a suggestion that previous asbestos exposure may be a promoting factor in some cases. The pleural fluid characteristically contains a high proportion of lymphocytes. The frequency of this reaction is uncertain, but it may be relatively common. Methotrexate has also been associated with pleurisy, independent of its alveolar effects. Dasatinib, a tyrosine kinase inhibitor used in the treatment of chronic myelogenous leukaemia, is frequently associated with exudative pleural effusions, possibly by an immune-mediated mechanism. Eosinophilic pleural effusions have been reported with drugs such as dantrolene, valproate, fluoxetine, propylthiouracil, and sulphasalazine. In these eosinophilic effusions there is usually no evidence of any parenchymal abnormality, and although the changes gradually resolve on withdrawing the drug some residual pleural fibrosis may remain. Pleuroparenchymal fibroelastosis is a distinctive condition characterized by bilateral apical pleural thickening on chest radiography and CT with breathlessness and restriction of lung volumes. It is often complicated by pneumothorax. There is usually also dense subpleural fibrosis involving the underlying lung parenchyma, with abrupt transition to normal architecture deeper in the lung. It is often idiopathic but has been reported as a late complication of chemotherapy with drugs such as cyclophosphamide and carmustine (BCNU).

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Table 18.14.13.3 Drugs associated with pleural effusions and thickening Clinical presentation Drug
Drug-induced lupus Procainamide, etanercept, gold, hydralazine, isoniazid, penicillamine, sulphonamides
Oculomucocutaneous syndrome Practolol
Isolated pleural effusion Methysergide, bromocriptine, methotrexate, dantrolene, acebutolol, dasatinib
Pleuroparenchymal fibroelastosis Cyclophosphamide, carmustine (BCNU)

18.14.13 Drug-induced lung disease 4281 Pneumotox. Drug-induced lung diseases. <http://www.pneumotox.com> Quinta-Cardama A, et al. (2007). Pleural effusions in patients with chronic myelogenous leukaemia treated with dasatinib after imatinib failure. J Clin Oncol, 25, 3908–14. Salpeter SR, Ormiston TM (2001). Cardioselective beta-blockers in patients with reversible airways disease. Cochrane Database, 2, CD002992. Szczeklik A, Picado C (2003). Aspirin-induced asthma. Eur Respir Monogr, 23, 239–48. Simonneau G, et al. (1998). Primary pulmonary hypertension associated with use of fenfluramine derivatives. Chest, 114, 195–9s. Takeishi M, et al. (2005). Leflunomide induced acute interstitial pneumonia. J Rheumatol, 32, 1160–3. Vahid B, Marik PE (2008). Pulmonary complications of novel antineoplastic agents for solid tumours. Chest, 133, 528–38.

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