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Drug-Induced Respiratory Disorders

Incidence, Prevention and Management

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Abstract

Various drugs are associated with adverse respiratory disorders (ARDs) ranging in severity from mild, moderate to severe and even fatal. Cardioselective and nonselective β-blockers, calcium antagonists and dipyridamole can induce asthma. ACE inhibitors are mainly associated with cough. Amiodarone is related to a form of interstitial pneumonitis (IP) which can be fatal, tocainidine and flecainidine to a form of IP, and hydrochlorothiazide to a form of IP and pulmonary oedema. Antiasthmatic drugs can be associated with a paradoxical bronchospasm, while leukotriene antagonists are linked to the development of Churg-Strauss syndrome. Nonsteroidal anti-inflammatory drugs including aspirin (acetylsalicylic acid) may induce asthma. Gold is mainly related to IP, penicillamine to IP, systemic lupus erythematosus, bronchiolitis obliterans, and Goodpasture's syndrome.

Acute respiratory reactions to nitrofurantoin include dyspnoea, cough, IP, and pleural effusion while IP and fibrosis are common in chronic reactions. Other antibacterials mainly evoke pneumonitis, pulmonary infiltrates and eosinophilia, and bronchiolitis obliterans. ARDs are similar for most categories of cytotoxic agents, with chronic pneumonitis and fibrosis being the most common. Noncardiogenic pulmonary oedema occurs as the most common respiratory complication in opioid agonist addiction. Psychotropic drugs such as phenothiazides, butyrophenones and tricyclic antidepressants can also induce pulmonary oedema. Oral contraceptives may produce asthma exacerbation, while long term use and/or high doses of postmenopausal hormone replacement therapy increase the risk of asthma. Bromocriptine is mainly associated with pleural effusion, while methysergide is usually associated with pleural effusion and fibrosis. Some anorectic agents have been linked to the development of primary pulmonary hypertension.

The possibility of the occurrence of ARDs should be taken into account in each individual patient. Although in most cases the adverse effects are unpredictable, they can be reduced to a minimum or prevented if some drugs are avoided or stopped in time.

Drug-induced adverse respiratory disorders (ARDs) are common iatrogenic illnesses. Their clinical presentation may be mild to severe and even fatal. Knowledge of these adverse effects is important in providing an appropriate medical treatment. In drug-related adverse respiratory effects a symptomatology complex and/or an abnormality on the chest x-ray film may highlight the suspicion of this disorder. Sometimes biopsy is needed to prove a diagnosis. This review summarises the relevant information regarding various main categories of drug-induced ARDs.

1. Data Collection

A comprehensive search of all biomedical literature from 1966 to 1998 was conducted using Medline. Terms included in the search, alone or combined, were drug-induced adverse respiratory disorders or effects. Some reports were identified from bibliographies of selected articles and book chapters. All articles were critically evaluated and all relevant available publications on the incidence, mechanism of action, prevention, and management of drug-induced ARDs were included.

2. Cardiovascular Drugs

2.1 β-Blockers

β-Blockers (β-adrenoceptor antagonists) are widely used to treat cardiovascular diseases, hypertension, anxiety syndromes, glaucoma, tremor and hyperthyroidism. The β-adrenergic system is clas-

sified as having β_1- and β_2-receptor activities. Stimulation of β_1-receptors results in an increase in heart rate and force of cardiac contraction, while β_2-receptor stimulation leads to bronchodilatation. β-blockers may induce bronchoconstriction by blocking the β_2-adrenergic receptors in bronchial smooth muscle.[1-3] Adverse respiratory reactions were observed in 0.5% of patients following the ocular administration of timolol.[4] Furthermore, 5.3% of 38 patients receiving oral and ophthalmic β-blockers were hospitalised for asthma.[5] Respiratory difficulties may be associated with a nonselective β-blocker, such as timolol, and a cardioselective β-blocker, such as betaxolol.[6-9] Even topical preparations of β-blockers (such as timolol), used to treat glaucoma, can cause significant and severe respiratory distress.[6] Pneumonitis, pulmonary fibrosis, and pleurisy have also been related to these agents.[10]

β_1-selective agents are tolerated best, independently of the other associated properties, but they do cause increased airway resistance, suggesting the need for caution when giving β-blockers to patients with asthma.[6]

Celiprolol is a novel agent that represents a new generation of β-blockers. It combines cardioselective β-adrenergic antagonism (β_1-receptor) with mild vasodilatation via vasoselective β-adrenergic agonism (β_2-receptor). Celiprolol has β_1-receptor antagonist potency similar to that of propranolol and atenolol, and cardioselectivity slightly greater than that of atenolol. This agent distinguishes itself from other β-blockers by virtue of its cardioselectivity, vasorelaxation via β_2-receptor agonism, and the lack of bronchoconstriction and cardiodepression.[11] It is effective and well tolerated for the treatment of essential hypertension and angina pectoris, demonstrating favourable haemodynamic activity and minimal effects on other cardiovascular risk factors.[12,13] In addition, this agent has no effect on forced expiratory volume in one second (FEV_1) either before or after administration of inhaled β_2-receptor agonists in patients with asthma.[14,15]

The use of β-blockers, regardless of their degree of selectivity, should be avoided in patients with asthma. If a β-blocker is essential, a short acting β_1-receptor selective agent should be used, at the lowest possible dose (table I).[6]

Table I. β-Blockers and associated half-lives[a][16]

Agents	Half-life (hours)
Nonselective (β_1/β_2)	
Nadolol	22
Sotalol	12
Timolol	4
Propranolol	4
Selective (β_1)	
Betaxolol	20
Bisoprolol	20
Atenolol	10
Metoprolol	8
Esmolol[b]	5
Selective (β_1) with intrinsic sympathomimetic activity	
Acebutolol	4
Celiprolol	4-5
Nonselective (β_1/β_2) with intrinsic sympathomimetic activity	
Carteolol	6
Penbutolol	4
Pindolol	4
Nonselective (β_1/β_2) with α-adrenoceptor blocker function	
Labetolol	7

a Arranged by activity.
b Intravenously administered only.

2.2 Calcium Antagonists

The incidence of ARDs with calcium antagonists is unknown, however, serious adverse respiratory reactions to these agents seem to be rare. The activation of the mast cell and the liberation of chemical mediators such as histamine, slow reacting substance of anaphylaxis, and prostaglandins are associated with an influx of free calcium ions.[17] Calcium antagonists selectively inhibit calcium ion influx across the cell membrane and suppress calcium-dependent smooth muscle excitation and contraction.[18] Bronchoconstriction can be explained by the fact that human lung mast cells are lacking voltage-dependent calcium channels and are not influenced by calcium antagonists, as well as the empirical observation that verapamil at concentrations as high

as 10^4 mol/L does not inhibit the immunological release of chemical mediators from sensitised basophil preparations.[19]

Dyspnoea, bronchoconstriction, and acute asthma attacks associated with these agents have been reported in single cases.[19-23] Treatment consists of discontinuation of the drug and administration of antiasthmatic medications.

2.3 ACE Inhibitors

ACE inhibitors are widely used in the treatment of cardiovascular diseases, diabetic microalbuminuria and nephropathy, and nondiabetic nephropathy.[24-26] ARDs such as unspecific airway hyperreactivity, dyspnoea, bronchospasm, and asthma are related to these drugs.[27-38] The incidence of cough attributed to ACE inhibitors is estimated to be from 0.1[31] to 62.7%,[32] dyspnoea 4.5%, bronchospasm 1.4%, and asthma 2.6%.[33]

ACE is responsible for the degradation of bradykinin, substance P, and other biologically active peptides in the kallikrein-prostaglandin system. The mechanism of ACE inhibitor–induced cough is thought to be related to increased bronchial reactivity caused by reduced degradation of proinflammatory mediators such as bradykinin and substance P, stimulation of pulmonary C fibre receptors by elevated levels of substance P,[29,39] enhanced cough reflex, prostaglandin-mediated effects, and the presence of the sulfhydryl group in the ACE molecule.[29,32,33] Angiotensin II receptor antagonists have no effect on the kallikrein-kinin-prostaglandin system and do not increase the levels of bradykinin and other peptides because of high substrate specificity, bypassing these undesirable adverse effects of ACE inhibitors.[39] However, cough can also be induced by angiotensin II receptor antagonists, but it occurs significantly less during treatment with these agents than during ACE inhibitor treatment.

Management of ACE inhibitor–induced cough includes discontinuation of the ACE inhibitor and replacement by another ACE inhibitor,[40] angiotensin II receptor antagonist,[39] or by a drug from another therapeutic class. Alternatively, the cough can be treated with nonsteroidal anti-inflammatory drugs (NSAIDs),[41-43] benzonatate,[44] theophylline,[45,46] or inhaled sodium cromoglycate[47-49] while treatment with the current ACE inhibitor continues.[40]

2.4 Antiarrhythmic Drugs

2.4.1 Amiodarone

Amiodarone, a benzofuran derivative is an antiarrhythmic drug used for supraventricular and ventricular arrhythmias. The incidence of pulmonary toxicity related to this drug varies from 4 to 6%.[50-52] The mechanism of amiodarone-induced pulmonary toxicity is explained by at least 2 different pathways: (i) an indirect mechanism characterised by influx of inflammatory or immune effector cells to the lung and (ii) a direct toxic mechanism that results in lung parenchymal cell injury and a subsequent fibrotic response. There is potential for much crossover interaction between the pathways of toxicity in any given patient.[53] The adverse effects of amiodarone, especially pulmonary toxicity, are thought to be dose and time related.[53,54]

Symptoms of pulmonary toxicity consist of exertional dyspnoea, nonproductive cough, bodyweight loss, occasionally low grade fever,[55,56] pneumonitis which can lead to pulmonary fibrosis,[52] postoperative adult respiratory distress syndrome,[57] respiratory failure,[52] and death.[50,51,58] Physical examination commonly shows bibasilar rales, with decreased breath sounds and pleural friction rubs reported rarely. Laboratory findings are nonspecific. The white blood cell count is usually normal, and peripheral eosinophilia is rare. The erythrocyte sedimentation rate may be elevated and returns to normal with the resolution of pneumonitis.[59] Chest x-rays have revealed both reticular infiltrates and patchy acinar infiltrates in patients with amiodarone-induced lung disease.[60,61] Less common findings include pleural thickening, pleural effusion, focal consolidation, diffuse acinar infiltrates, and nodular lesions.[60,61] Gallium scans may show uptake in the lungs.[62,63]

In all previous studies in which amiodarone toxicity has been documented, patients treated with amiodarone had received high maintenance dosages (375

to 685 mg/day), usually for a prolonged time.[54] Recently, it has been shown that patients receiving lower dosages of amiodarone (100 to 420 mg/day) did not have significant pulmonary toxicity.[54] Thus, amiodarone is considered to be a well tolerated and effective antiarrhythmic drug when used in lower doses.[64]

Treatment consists of discontinuation of the drug. If required, corticosteroids may be used for a brief time (e.g. weeks) or long term, as long as the patient receives amiodarone.[65]

2.4.2 Tocainide and Flecainide

Tocainide is used in the treatment of refractory ventricular arrhythmias while flecainide is used for ventricular and supraventricular arrhythmias. The incidence of tocainide-associated pulmonary fibrosis is estimated to be 0.3%.[66] Dyspnoea is reported to occur in 5 to 6% of patients treated with flecainide.[67] Acute interstitial pneumonitis (IP) and pulmonary fibrosis[68] associated with tocainide therapy, and pneumonitis,[69] and adult respiratory distress syndrome[70] related to flecainide use have been reported in small numbers of patients.

Treatment consists of discontinuing the drug concerned; corticosteroids may be necessary in some cases.

2.5 Dipyridamole

Dipyridamole is a vasodilator and an antithrombotic agent. The incidence of dipyridamole-induced bronchospasm was reported to be 0.15% in patients who underwent dipyridamole-thallium myocardial perfusion imaging. In patients who developed a bronchospastic reaction a history of asthma or wheezing was obtained. Those patients were successfully treated with intravenous administration of aminophylline.[71] Although the mechanism of dipyridamole-induced bronchospasm is uncertain, it seems that dipyridamole blocks transiently raised levels of endogenous adenosine uptake, available for interaction with adenosine receptors. Exogenously inhaled adenosine has been shown to induce bronchospasm which can be prevented with either antihistamine or sodium cromoglycate. This suggests that the effect of adenosine is executed through a mediator release.[72]

2.6 Hydrochlorothiazide

ARDs associated with hydrochlorothiazide use are rare. This drug can cause acute onset IP and noncardiogenic pulmonary oedema in some patients.[73-78] Patients present with dyspnoea, cough, wheezing and a low grade fever within a few hours of taking this medication. Chest x-ray findings are consistent with pulmonary oedema and include reticular and acinar infiltrates.[77] Treatment is supportive, and aminophylline and corticosteroids are employed. Mechanical ventilation is sometimes required.[77] Patients with hydrochlorothiazide-induced ARDs should avoid this drug.

Interestingly, another diuretic, furosemide, given in inhaled solutions, can prevent exercise-induced bronchoconstriction in patients with asthma.[79] Furosemide can inhibit both early and late reactions induced by specific allergen challenge in allergic patients with asthma.[80] The mechanism is most probably attributable to changes in the local osmotic and ionic environment which leads to reduced responsiveness of epithelial receptors to inflammatory stimuli,[79,80] release of bronchodilatory prostaglandins,[81] inhibition of inflammatory mediators,[82] resolution of mucosal oedema,[83] or inhibition of epithelial nerves.[80,84]

3. Anti-Inflammatory Agents

3.1 Aspirin (Acetylsalicylic Acid) and Other Nonsteroidal Anti-inflammatory Drugs

Aspirin and other NSAIDs can induce dose-dependent asthma exacerbation.[6] Other severe adverse effects related to overdoses of aspirin are central respiratory stimulation, noncardiogenic pulmonary oedema, respiratory failure and death.[85] The incidence of aspirin-induced asthma (AIA) in children is estimated to be between 1.9[86] and 13%,[87] but incidences as high as 28% have been reported.[88] In adults, the incidence is estimated to be between 4%[89] and 25%.[90-94]

The triad of asthma, nasal polyposis, and AIA was identified in 1968.[95] Aspirin intolerance has also been shown to occur in a number of families.[96,97]

AIA is associated with a decrease in prostaglandins and an increase in leukotrienes.[98] The possible mechanisms underlying NSAID-induced bronchospasm are believed to directly involve the enhanced generation of autocoid (nonprostanoid) eicosanoid mediators, the sulfidopeptidic leukotrienes LTC4, LTD4, and LTE4, all of which are potent bronchospasmogens. An additional or alternative mechanism may be an increased target organ sensitivity to the leukotrienes, leading to selective receptor upregulation.[99]

NSAIDs precipitate an asthmatic reaction when administered orally, topically (as ophthalmic solutions), intravenously,[100-104] and rectally leading to the development of respiratory failure, and death.[101,105] Another NSAID ketorolac, available for intramuscular and intravenous injection, has been associated with severe, life-threatening anaphylactoid reactions.[106]

Patients with asthma have been reported to respond favourably to indomethacin,[107-109] mefenamic acid,[109,110] ibuprofen,[109] aminophenazone (aminopyrine),[111] dipyrone,[112,113] azelastine,[114] and also to aspirin.[109] Since favourable responses to NSAIDs are infrequent in patients with asthma, occurring in only 1% or less of adult patients with asthma,[89] these medications cannot be recommended for widespread use in such patients in general practice.[115]

Desensitisation to aspirin has been demonstrated in patients with AIA who require the use of NSAIDs for rheumatic diseases.[116] When desensitisation is complete, a decrease in leukotriene E4 levels has been observed in the urine along with a reduced need for corticosteroids. A reduction of nasal symptoms and nasal polyps, less sinus surgery and fewer emergency department visits and hospitalisations have also been observed. However, the procedure is time consuming, often requires hospitalisation and is potentially dangerous.[116]

Under experimental conditions dinoprostone (prostaglandin E_2) and salbutamol at equimolar concentrations of 0.25 μmol, 5 minutes before the aspirin challenge, attenuate aspirin-induced bronchoconstriction.[117] Both prostaglandin E and salbutamol, acting through separate receptors,[118] stimulate production of cyclic AMP by activation of the enzyme adenyl cyclase. By doing so, they inhibit the release of several mediators from the proinflammatory cells. The involved cells can be mast cells,[119] or eosinophils.[117] Eosinophils are present in high amounts in the blood and airways of patients with AIA.[120,121] They represent an abundant source of leukotrienes which are important mediators in AIA.[117]

3.2 Leukotriene Antagonists

The leukotriene antagonists (LA) offer a new approach to the treatment and prophylaxis of asthma. Some respiratory specialists believe that LA may reduce the need for corticosteroids and bronchodilators in patients with asthma.[122] The potent and selective sulfidopeptide LA, SKF-104353, inhibits AIA.[123] Furthermore, the magnitude of the protection achieved by dinoprostone in clinical studies against AIA is similar to that offered by LA[123-125] and better than that provided by sodium cromoglycate[124] or antihistamine drugs.[126,127] However, no formal comparison of these medications has been made.[117]

Selective LA LTD4 antagonists (e.g. pranlukast, zafirlukast, MK-571, and MK-679) as well as zileuton (a direct inhibitor of 5-lipoxygenase), have been developed as antiasthma agents.[128] Clinical and experimental studies have demonstrated the efficacy of these compounds in reducing not only the symptoms of asthma, but also the use of β_2-receptor agonists and the bronchoconstriction induced by exposure to allergens, exercise, aspirin, and cold water.[128,129]

At present, the use of the LA zileuton is somewhat limited because of its 4 times a day administration regimen and the need to monitor biochemical liver function tests. The advantages of the available LA are the once daily (montelukast) or twice daily (zafirlukast) dosage regimens in terms of improved compliance, as well as not needing to routinely mon-

itor liver function.[130] One of the fundamental questions regarding LA use is whether they should be positioned in the guidelines as first-line preventive monotherapy as an alternative to inhaled corticosteroids, or whether their use should be restricted to second-line controller therapy in addition to corticosteroids[130] In a multicentre, randomised, double-blind trial montelukast administered once daily at bedtime significantly improved control of chronic asthma in adult patients (mean age 31 years).[131] In children with asthma aged 6 to 14 years old, montelukast once daily inhibited exercised-induced bronchoconstriction.[132] As is seen with inhaled beclomethasone, oral montelukast has been shown to provide clinical benefit to patients with asthma. This finding is consistent with the use of these agents as controller medications for chronic asthma.[133]

The Churg-Strauss syndrome is a rare allergic granulomatous vasculitis of unknown aetiology characterised by moderate to severe asthma, peripheral blood eosinophilia, mononeuropathy or polyneuropathy, migratory or transient pulmonary infiltrates, paranasal sinus abnormality, and the presence of extravascular eosinophils.[134] Recently, it has been reported that 8 adult patients developed Churg-Strauss syndrome while taking zafirlukast for between 3 days to 4 months, and from 3 days to 3 months after corticosteroid withdrawal.[135] An additional patient developed Churg-Strauss syndrome while he was receiving zafirlukast. This patient had not taken prednisone for approximately 6 months prior to experiencing untoward events.[136] Since an apparent link between LA and Churg-Strauss syndrome is rare, the US Food and Drug Administration has stated that there is no definite proof of a cause and effect relationship between the syndrome and zafirlukast, and because of the rarity of the association it is not recommended that patients discontinue the drug without first consulting their doctor.[122]

3.3 Gold

Gold has been used for the treatment of various disorders, particularly rheumatoid arthritis. The incidence of pulmonary reactions associated with gold therapy appears to be less than 1%.[137] Patients with pulmonary injury secondary to gold salts show findings consistent with a hypersensitivity lung disease or chronic pneumonitis/fibrosis. IP is more commonly observed in patients receiving sodium aurothiomalate than in those taking aurothioglucose, but this may reflect the more common use of the former drug.[138] Pulmonary symptoms may develop from 6 hours to 1 month after receiving the last dose of gold salts.[139] The presentation is rarely acute with fever, wheezing, and cough developing over several hours. More commonly, it is subacute with progressive dyspnoea and nonproductive cough developing over several weeks.[140] A few reports have demonstrated peripheral blood eosinophilia, but this is uncommon. Pleural effusion is not associated with this reaction.

In diffuse IP-fibrosis, the chest x-ray shows a predominantly interstitial process.[138] Bronchoalveolar lavage usually demonstrates a high percentage of lymphocytes, which indicates an immunological reaction.[141] Histologically, the lung demonstrates fibrosis with an interstitial infiltrate of lymphocytes and plasma cells, and focal hyperplasia of type II pneumocytes. Electron microscopic examination demonstrates electron-dense structures which contain gold within lysosomes of endothelial cells of the alveolar capillaries and interstitial macrophages. This suggests a direct toxic effect in the pathogenesis of gold-induced pulmonary reaction.[138]

The treatment may be as simple as withdrawing the drug and allowing the process to resolve spontaneously. However, a number of patients will require corticosteroid therapy.[138]

3.4 Penicillamine

The dimethylcysteine derivative prepared by hydrolytic degradation of penicillin, is an effective chelator of copper, mercury, zinc, and lead.[142] Penicillamine is commonly used to treat lead poisoning, Wilson's disease, cystinuria, rheumatoid arthritis, scleroderma, primary biliary cirrhosis, and other inflammatory diseases.[143] The incidence of penicillamine-induced pulmonary injury is low, occurring in sensitive patients. Diffuse alveolitis,

obliterative alveolitis, hypersensitivity lung disease, systemic lupus erythematosus, and Goodpasture's syndrome are possible complications associated with penicillamine use.[144-146] Fatal bronchiolitis in 2 of 3356 cases treated with penicillamine has also been described.[144] Penicillamine-induced disease appears to be one of the more common causes of drug-induced systemic lupus erythematosus.[145] This condition should always be considered in the patient receiving penicillamine, especially if a pleural effusion is present. A normal concentration of sugar in the effusion eliminates the possibility of a rheumatoid effusion.

The treatment consists of discontinuation of the drug. Corticosteroids have been attempted in patients with bronchiolitis caused by penicillamine with no apparent improvement. Other options include azathioprine,[146] haemodialysis, plasmapheresis, and immunosuppression.[138]

4. Antimicrobial Drugs

4.1 Nitrofurantoin

Acute nitrofurantoin pneumonitis may be one of the most common drug-induced pulmonary diseases. The Swedish Adverse drug Reaction Committee reported 921 patients with adverse reactions to this drug: 43% were acute pulmonary reactions, and another 5% were attributable to chronic IP.[147] The acute presentation occurs within 1 month of institution of therapy, whereas the long term presentation occurs after 2 months to 5 years of continuous therapy.[148] The typical reaction begins a few hours to several days after initiation of therapy.[149,150] It appears to be more common in females, but this is probably because of the increased use of this drug for urinary tract infections in women. Symptoms include dyspnoea (60 to 65% of cases), nonproductive cough (60 to 65%), rash (15 to 20%), fatigue (10%), arthralgias (10 to 15%), chest pain in up to 28% of patients, and fever (80 to 90%). Physical findings include crackles (66% of cases), signs of pleural effusion in up to 26% of patients, cyanosis and hypotension in a small percentage and, rarely, wheezing.[148,151]

Treatment is based on discontinuation and avoidance of the drug. Corticosteroids and antihistamines can provide symptomatic relief.

In chronic reactions, the onset of dyspnoea and cough are usually insidious, beginning 6 months to many years after either continuous or intermittent long term use of nitrofurantoin. Clinically, radiologically, and histologically this condition mimics idiopathic IP and fibrosis with the exception that these patients have ingested nitrofurantoin over a long period of time.[138] Treatment consists of discontinuing the medication and providing supportive measures. A trial of corticosteroids may be given.[138]

4.2 Other Antimicrobial Agents

Isoniazid has been reported to cause a hypersensitivity-like pneumonitis with peripheral eosinophilia. Penicillin also generates a hypersensitivity pneumonitis distinct from systemic anaphylaxis, with peripheral eosinophilia (as high as 80%), alveolar infiltrates, pleural effusion, and positive skin test results. Aminosalicylic acid is estimated to produce a hypersensitivity-like response in approximately 0.3 to 5.0% of patients receiving the drug. Adverse responses include fever, rash, malaise, headache, dry cough, wheezing, angioneurotic oedema with laryngeal oedema, eosinophilia, alveolar infiltrates, lymphadenopathy, pleural effusion and hepatomegaly.[146,152] Sulfasalazine, which is used in the management of inflammatory bowel disease and rheumatoid arthritis, is metabolised to sulfapyridine and mesalazine (5-aminosalicylic acid). Both of these latter agents contribute to the ARDs including cough, dyspnoea, pulmonary infiltrates and eosinophilia, fever, bronchiolitis obliterans and fibrosing alveolitis although these complications are rare.[153-155] Symptoms are generally reversible on withdrawal of sulfasalazine. Death, however, has been reported.[153] Treatment consists of discontinuation of the drug. Corticosteroids may hasten the improvement.[155]

The polymixin and aminoglycoside antibacterials are known to produce respiratory muscle weakness when they reach an excessive concentration in

the blood.[156] These effects, which are rare, may be reversible with physostigmine. The combined administration of granulocytes with amphotericin B may predispose some patients to other rare reactions such as transient deterioration of pulmonary function.[157,158] Furthermore, amphotericin B can be associated with the development of bronchiolitis obliterans in the absence of blood products.[159] Pentamidine, given intravenously or by nebuliser, can cause bronchospasm in some patients.[160,161] Pretreatment with nebulised salbutamol (albuterol) or ipratropium bromide may prevent this adverse effect.

5. Antiasthmatic Medications

5.1 Ipratropium Bromide

Ipratropium bromide, a muscarinic anticholinergic agent, competes with acetylcholine on smooth muscle receptors and inhibits the action of acetylcholine on nicotine receptors only at very high concentrations. It also acts as a bronchodilator and is used when the asthma has resisted other forms of therapy.[162] ARDs associated with this drug are rare. A paradoxical bronchoconstriction is associated with ipratropium bromide therapy in some patients.[163-165] This bronchoconstriction may be attributable to the benzalkonium chloride and edetic acid in the ipratropium bromide nebuliser solution, since both agents are potent bronchoconstrictor agonists when inhaled alone.[164]

5.2 Corticosteroids

Corticosteroids are widely used in the treatment of bronchodilator-resistant bronchial asthma. Although the incidence of ARDs is unknown, it seems that these reactions to corticosteroids are rare. It has been reported that a paradoxical bronchospasm developed with the administration of inhaled and intravenous corticosteroids (hydrocortisone succinate) in a few patients with AIA.[166-170] The mechanism of these reactions is not known, however, results of separate challenges with the active corticosteroid preparation and the diluent suggest that preservatives or stabilisers are not responsible.[171]

Inhaled corticosteroids should be avoided in susceptible individuals. If intravenous therapy is required, it is safer to use corticosteroids other than hydrocortisone succinate in patients with asthma.

5.3 Sodium Cromoglycate

Sodium cromoglycate is an antiallergic agent that mainly acts by inhibiting release of inflammatory mediators. It can be given by inhalation in the prophylactic control of asthma, by nasal insufflation in the treatment and prophylaxis of allergic rhinitis, as eye drops in allergic conjunctivitis, and by mouth in the management of food allergy.[172] Sodium cromoglycate is generally well tolerated and adverse effects are often transient. Adverse respiratory symptoms attributed to this drug include nasal congestion, cough, wheezing, bronchospasm, aggravation of existing asthma, pulmonary oedema, pulmonary infiltrates with eosinophilia,[173-174] anaphylaxis,[175] and death.[176]

Although patients tolerating sodium cromoglycate therapy may demonstrate lymphocyte transformation *in vitro*, only those with clinically apparent adverse reactions produced lymphocyte migration-inhibiting factor or possessed serum-binding activity for the dose administered.[177] It has been reported that adverse reactions to sodium cromoglycate were not based on an immunological mechanism.[178] On the other hand, an immunoglobulin E mechanism has been demonstrated in patients with reactions to sodium cromoglycate by skin prick tests,[179] passive transfer,[180] or detection of serum-specific immunoglobulin E by radioallergosorbent tests.[181]

The rare patient who experiences a hypersensitivity reaction to sodium cromoglycate will require alternative measures for asthma or other allergic condition control.

5.4 Other Components of Inhaled Products

Why do inhaled products cause paradoxical bronchospasm? Is it simply the turbulence of airflow associated with incorrect inhalational technique, the tonicity of the solution,[182-184] or a reflection

of particle size?[185] If it is attributable to the product itself, and not the technique used or the device provided, is it caused by the 'active drug', or is it attributable to other components in the product, that is, propellants,[186-188] emulsifying agents, preservatives, or even contaminants?[185]

Quantitatively, propellants are the major components of any metered dose inhaler, comprising 58 to 99% of the product. In addition, sorbitan, oleic acid, soy lecithin, ascorbic acid, or alcohol may be present in metered dose inhalers, and benzalkonium chloride, edetate disodium, and, until recently, sulfites, have been used in nebulised solutions.[185] There has been speculation that benzalkonium chloride may account for some reports of bronchospasm after the use of nebulised solutions,[164] possibly be releasing mediators from the surface of mast cells.[164] Alcohol, present in inhalers, might also produce bronchospasm.[189] Metabisulfite is well recognised as a bronchoconstrictor agent in patients with asthma, probably as a result of liberating sulfur dioxide which stimulates irritant receptors in the airways,[190,191] and has now been excluded from all nebuliser solutions.[192] Thus, isotonic and preservative-free nebuliser solutions may be more effective in removing the risk of paradoxical bronchoconstriction.[192] Although a paradoxical bronchospasm associated with some other component in the product is rare, the awareness of the possibility of such a reaction is clinically important.

6. Chemotherapeutic Agents

There are 6 predisposing factors for the development of cytotoxic drug-induced pulmonary disease: (i) cumulative dose; (ii) increased age; (iii) concurrent or previous radiotherapy; (iv) oxygen therapy; (v) other cytotoxic drug therapy; and (vi) pre-existing pulmonary disease.[193]

Lung injury occurs in about 10% of all patients who receive bleomycin, with death in 1 to 2%. The changes in the lung are diffusive and include fibrosis of the alveolar septa, and enlargement of the type II alveolar lining cells with bizarre alteration of the nucleus. Clinically, the reaction presents as nonproductive cough, and dyspnoea, often with fever, which develops from days to weeks. The reaction is dose-related, being more likely at total doses over 450 units, although it has occurred at much lower doses, and is more common in elderly patients.[194] Hypersensitivity pneumonitis, which is more amenable to treatment, has also been reported.[195]

Pulmonary damage has been reported in association with an increasing number of other antineoplasic agents as well.[196] Among the alkylating agents cyclophosphamide (as a single agent) has been reported to produce lung injury in less than 1% of cases, although this may be increased if it is a component of combined regimens or where it is combined with radiotherapy.

The incidence of azathioprine related pneumonitis is estimated to be below 1%. Unexplained fatal, noncardiogenic pulmonary oedema has been reported to be associated with cytarabine when used to induce remission in acute leukaemia.[138] Busulfan may produce lung toxicity including insidious pulmonary fibrosis in as many as 4% of patients, usually developing several years after the initiation of therapy, with increased risk the longer the therapy lasts. A few reports exist of IP and fibrosis associated with chlorambucil and melphalan, but these appear to be extremely rare.

The prognosis in patients with alkylating agent–induced fibrosis is often poor, with mortality rates around 50%. The antimetabolite methotrexate can produce symptoms similar to hypersensitivity pneumonitis in up to 7% of patients, sometimes with pleuritis and acute respiratory failure attributable to pulmonary oedema; symptoms are usually reversible even without discontinuing therapy. Other antineoplastic agents known to be associated with pulmonary toxicity include mitomycin (usually in less than 10% of patients although the incidence may be much higher in combined regimens); the vinca alkaloids (generally in combination, and usually producing respiratory failure); chlorozotocin; procarbazine; and possibly teniposide. The nitrosoureas, and particularly carmustine, have also emerged as pulmonary toxins.[197] The onset of symptoms may be very delayed. It has been reported that fibrosis occurred up to 17 years after treatment with car-

mustine.[197] Higher doses of carmustine (above 1500 mg/m^2)[198] seem to be associated with a higher risk of early onset lung fibrosis.[199]

Pulmonary physiological abnormalities related to chemotherapeutic agents are similar regardless of the drug.[193] The most common abnormality is a restrictive ventilatory defect and a reduced diffusing capacity for carbon monoxide (DL_{CO}).[193] An isolated reduction in DL_{CO} has been reported with bleomycin[200] and chlorozotocin, a nitrosourea.[201] This finding has been used to construct screening procedures for patients receiving bleomycin.[202]

Treatment of cytotoxic drug-induced pulmonary disease involves withdrawal of the agent. Corticosteroids may help and probably should be tried.

7. Opioid Agonists

7.1 Diamorphine

As a result of the increased lipid solubility of diamorphine (heroin), it crosses the blood-brain barrier more readily than morphine.[203,204] It is rapidly hydrolysed to monoacetylmorphine and then to morphine. An incidence of chronic lung disease attributable to asthma or chronic bronchitis was observed in 6% and a restrictive defect attributable to interstitial lung disease was seen in 7% of intravenous diamorphine addicts,[205] while pulmonary oedema occurred in 33% of patients admitted with diamorphine overdose.[206] Diamorphine-induced pulmonary oedema is explained by a direct toxic effect on the alveolar capillary membrane, leading to an increased permeability and extravasation of the fluid into alveolar spaces; a neurogenic response to central nervous system injury; an allergic or hypersensitivity reaction; and an acute hypoxic effect on the alveolar capillary membrane in association with secondary increased permeability.[138] Other pulmonary abnormalities include atelectasis, bullous lesions, bronchiectasis, alveolar haemorrhage, and septic emboli from infected thrombophlebitis or tricuspid endocarditis, and necrotising bronchitis.[138,207]

7.2 Cocaine

Cocaine use remains a major problem throughout the world. The number of reports on cocaine addiction are few, reflecting either the low incidence of these complications or the lack of recognition of these phenomena as cocaine-related illnesses. The mechanism by which freebase cocaine can injure the lung is not well defined. Whether an abnormal immunological response to cocaine freebase results in haemorrhage, pneumonitis, or asthma or whether cardiogenic or noncardiogenic factors play a role in the development of pulmonary oedema remain speculative.[208] The abuse of cocaine is related to pulmonary oedema, hypersensitivity pneumonitis, pulmonary haemorrhage, obliterative bronchiolitis, abnormalities of pulmonary function, pneumomediastinum, pneumothorax,[208] lung mass with or without cavitation, bronchiolitis obliterans with organising pneumonia,[209-211] primary pulmonary hypertension,[212] severe or life-threatening exacerbation of asthma,[213] or respiratory failure.[214] The patient tends to respond to corticosteroids.

7.3 Methadone and Dextropropoxyphene

Noncardiogenic pulmonary oedema has been reported in single cases after oral overdoses of methadone and dextropropoxyphene. Dextropropoxyphene is a rapidly absorbed drug, and even after oral ingestion death can occur within 30 minutes from noncardiogenic pulmonary oedema, respiratory depression and arrest.[203]

7.4 Methylphenidate

Another opioid agonist, methylphenidate is an amphetamine like the stimulant indicated for the treatment of narcolepsy and the attention deficit disorder (‘hyperactivity’).[215] The abuse pattern and symptoms of toxicity were similar to those seen with cocaine and amphetamine addiction. In 1 series, all 22 patients (100%) had chest pain and wheezing, abnormal pulmonary function tests were evident in 90%, and haemoptysis occurred in 80%.[216] In another series, severe panlobular emphysema, pulmonary inflammatory infiltrates and occlusive vascu-

Table II. Summary of clinical presentations of drug-induced respiratory disorders[1-10,19-23,27-38,50-61,66-78,85,100-106,137-140,144-161,163-176,185-241,247]

	Cough	Dyspnoea	Asthma	PIE	PLE	BO	IPF	H	ARDS	RF	PE	PVD	DISLE	Death
Cardiovascular drugs														
ACE inhibitors	+	+	+	+										
Amiodarone	+	+			+		+		+	+				+
Anticoagulants	+	+			+			+						
β-Blockers		+	+				+							
Calcium antagonists		+	+											
Dipyridamole			+											
Flecainide							+		+					
Hydralazine					+								+	
Hydrochlorothiazide	+	+	+				+			+	+			
Procainamide					+								+	
Tocainide							+							
Anti-inflammatory drugs														
Aspirin		+	+							+	+			+
Gold	+	+		+		+	+						+	
NSAIDs		+	+	+						+				+
Penicillamine		+		+	+	+	+			+			+	+
Antimicrobial agents														
Amphotericin B		+				+	+			+	+	+		+
Isoniazid				+	+								+	
Nitrofurantoin:														
short term	+	+	+	+	+		+						+	+
long term	+	+		+	+		+						+	+
Aminosalicylic acid	+	+	+	+	+								+	
Penicillin				+	+					+			+	
Pentamidine			+											
Sulfasalazine	+	+	+	+		+	+							+
Sulfonamides	+	+		+	+								+	
Streptomycin					+								+	
Tetracyclines				+	+								+	
Anti-asthmatic drugs														
β-Adrenoceptor agonists		+	+											
Ipratropium bromide		+	+											
Sodium cromoglycate	+	+	+	+						+	+			+
Corticosteroids		+	+											
Leukotriene antagonists				+								+		
Contrast media		+	+							+	+			+
Opioid agonists														
Cocaine		+	+	+		+	+	+		+	+	+		+
Diamorphine		+		+			+	+		+	+	+		+
Dextropropoxyphene		+					+			+	+			+
Methadone		+					+			+	+			
Methylphenidate		+	+	+			+	+		+		+		+
Psychotropic drugs														
Carbamazepine	+	+		+			+							
Benzodiazepines		+									+			
Butyrophenones		+									+			

Table II. Contd

	Cough	Dyspnoea	Asthma	PIE	PLE	BO	IPF	H	ARDS	RF	PE	PVD	DISLE	Death
Phenytoin	+	+		+			+			+			+	
Phenothiazines											+			
Trazodone		+		+						+				
Tricyclics				+					+	+	+			
Miscellaneous														
Anorectics		+										+		
Bromocriptine	+	+			+									
Oral contraceptives/hormone replacement therapy		+		+				+				+	+	+
Inhaled products		+		+										
Propylthiouracil													+	
Pyrimethamine				+										
Methysergide		+			+		+							
Tocolytics	+	+		+	+					+	+	+		

ARDS = adult respiratory distress syndrome; **BO** = bronchiolitis obliterans; **DISLE** = drug-induced systemic lupus erythematosus; **H** = haemorrhage and/or haemoptysis; **HRT** = hormone replacement therapy; **IPF** = interstitial pneumonitis and/or fibrosis; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **PE** = pulmonary oedema; **PIE** = pulmonary infiltrate with or without eosinophilia; **PLE** = pleural effusion; **PVD** = pulmonary vascular disease; **RF** = respiratory failure.

lar lesions were found in all 7 patients who died as a result of profound obstructive lung disease.[217]

8. Psychotropic Medications

ARDs associated with these agents are rare and are described in single patient cases. Acute pulmonary oedema has been reported with overdoses of phenothiazines such as chlorpromazine and perphenazine, and butyrophenones.[218] The most likely pathogenesis of phenothiazine-induced pulmonary oedema is a disturbance of hypothalamic function.[219] About one-third of the pulmonary complications attributed to tricyclic drug overdosage are either noncardiac pulmonary oedema or aspiration. If hypotension results, cardiac pulmonary oedema can occur. Nearly one-half of the patients have an abnormal chest x-ray and in about 10% the adult respiratory distress syndrome develops.[220-222] In addition, tricyclics are associated with Loefler's syndrome.[223] Trazodone overdosage may be attributed to eosinophilic pneumonia and respiratory failure.[152] Acute pulmonary hypersensitivity has been observed during carbamazepine therapy.[224,225] Treatment is supportive and may include mechanical ventilation.

9. Miscellaneous

9.1 Tocolytics

Tocolytics are β-adrenoceptor agonists that have been used in the inhibition of premature uterine contractions. The most commonly used are terbutaline, salbutamol, ritodrine, and other β-adrenergic drugs.[152] Physiological effects associated with the use of these agents are attributable to their effect on β_1- as well as β_2-receptors. These effects include tachycardia, hyperglycaemia, hypokalaemia, and antidiuresis.[226] In addition, β-adrenoceptor agonists increase intracellular cyclic adenosine monophosphate (AMP) levels, thus decreasing muscular contractions.[227] Other predisposing factors include the use of corticosteroids, twin gestation, fluid overload (particularly with saline), and anaemia.[228]

Tocolytics are associated with the development of dyspnoea, bronchospasm, bilateral alveolar infiltrates, acute respiratory distress, thrombotic pulmonary embolus, and pulmonary oedema. The incidence of pulmonary oedema varies from 0 to 4.4% of those receiving these drugs. Treatment includes discontinuation of the drug, oxygen administration, and diuresis.[228]

Table III. Clinical presentation of pulmonary toxicity induced by antineoplastic and immunosuppressant agents[138,194-203,248-259]

	Cough	Dyspnoea	Asthma	HI	PLE	BO	IPF	H	ARDS	RF	PE	PVD	Death
Antilymphocyte immunoglobulin		+											
Azathioprine							+						
Bleomycin	+	+		+	+	+	+			+	+		+
Busulfan	+	+		+	+		+					+	
Chlorambucil	+	+					+						
Cysclophosphamide	+	+	+			+	+				+		
Cytarabine		+		+						+	+		+
Doxorubicin							+						
Interleukin-2			+		+				+	+	+		
Melphalan	+	+					+			+			+
Mercaptopurine							+						
Methotrexate	+	+		+	+	+	+			+	+		+
Mitomycin	+	+	+		+	+	+			+			
Nitrogen mustard (Chlormethine)	+			+	+						+		
Nitrosoureas	+	+					+					+	+
Procarbazine		+		+	+		+			+			
Tumour necrosis factor										+	+		
Vinblastine		+	+				+			+	+		+

ARDS = adult respiratory distress syndrome; **BO** = bronchiolitis obliterans; **H** = haemorrhage and/or haemoptysis; **HI** = hypersensitivity infiltrate; **IPF** = interstitial pneumonitis and/or fibrosis; **PE** = pulmonary oedema; **PLE** = pleural effusion; **PVD** = pulmonary vascular disease; **RF** = respiratory failure.

9.2 Oral Contraceptives

Premenstrual asthma denotes worsening of asthma symptoms shortly before and/or during menstruation. It has been estimated that 30 to 40% of female patients with asthma report worsening of asthma symptoms during the premenstrual period, the menstrual period, or both with a maximum increase in dyspnoea, wheezing, and chest tightness during the premenstrual period.[229,230] In premenopausal women exogenous sex hormones and/or oral contraceptives may similarly produce exacerbation of asthma.[231]

The mechanism of premenstrual asthma has not been established, but it is speculated that hormonal variations during the menstrual cycle may play an important role in its pathogenesis.[232] With regard to the contraceptive pill, exogenous progesterone, but not estrogen, given during the follicular phase, has been shown to decrease β_2-adrenoceptor density and cyclic AMP response in female patients with asthma. This paradoxical effect of progesterone in female patients with asthma suggests an abnormal regulation of β_2-adrenoceptors and might be a possible mechanism for premenstrual asthma when progesterone concentrations are high during this period of the cycle.[232] This hypothesis is supported by the observation that despite an appropriate rise in female sex hormones during the luteal period, β_2-adrenoceptor regulation in female patients with asthma shows a loss of the normal cyclical pattern.[233]

In addition, patients with asthma receiving an oral contraceptive had attenuated cyclical changes in airway reactivity as well as reduced diurnal morning and evening peak expiratory flow rate variability, which was associated with suppression of the normal luteal phase rise in sex hormones.[234] Thus, it is possible that exogenous female sex hormones may be used therapeutically in females with unstable asthma or those with premenstrual asthma,

not controlled by conventional therapy, by smoothing out cyclical changes in airway reactivity.[234]

9.3 Hormone Replacement Therapy

The association of hormone replacement therapy HRT and asthma incidence was evaluated in pre- and postmenopausal women during 582 135 person-years of follow-up in the Nurses' Health Study.[235] In this study, even users of 10 or more years' duration had twice the age-risk of asthma compared with women who never used postmenopausal hormones. Among current users of conjugated estrogens, there was a positive dose-response between daily dose and asthma risk (p for trend = 0.007). The data suggest that estrogen plays a role in the pathophysiology of asthma and that long term use and/or high doses of postmenopausal hormone replacement therapy increase the subsequent risk of asthma.[235]

Table IV. Unusual manifestations of drug-induced pulmonary toxicity[138,152,217,245,248-268]

Presentation	Causative agent(s)
Alveolar cell carcinoma	Busulfan
Alveolar proteinosis	Busulfan
Alveolar haemorrhage	Diamorphine
Atelectasis	Diamorphine
Bronchiectasis, necrotising bronchitis	Diamorphine
Calcification	Antacids, calcium, phosphorus, colecalciferol
Emphysema	Methylphenidate
Extensive bilateral lung opacities	Sulfasalazine, bleomycin, methylphenidate, phenothiazines
Fibrosing alveolitis	Sulfasalazine
Goodpasture's syndrome	Penicillamine
Haemorrhage, haemoptysis	Methylphenidate, cocaine
Lung mass with or without cavitation	Cocaine, amiodarone, bleomycin
Nasal septal perforation	Cocaine
Panlobular emphysema	Methylphenidate
Pneumomediastinum	Cocaine
Pneumothorax	Nitrosoureas, cocaine
Pulmonary hypertension	Anorectics, oral contraceptives
Pulmonary artery medial hypertrophy	Cocaine
Pulmonary ossification	Busulfan
Pulmonary embolism	Intravenous drug abuse, tocolytics, oral contraceptives
Pulmonary alveolar proteinosis	Busulfan

9.4 Methysergide and Bromocriptine

Methysergide is used to treat vascular headache, whereas bromocriptine is used for the treatment of Parkinson's disease. ARDs associated with these drugs are rare and mainly attributed to the development of pleuropulmonary reactions.[236,237] The pleuropulmonary disease produced by both of these agents has an insidious onset. The predominant feature is cough, dyspnoea, pleural thickening and effusion induced by bromocriptine,[236,237] while pleural effusion and fibrosis are related to methysergide therapy.[238] The withdrawal of these medications leads to an improvement in the symptomatology of such patients.[236]

9.5 Anorectic Agents

Primary pulmonary hypertension is a rare, often fatal disease that tends to occur particularly frequently in women during their third or fourth decade.[239,240] The primary incidence of pulmonary hypertension is very low; in the order of 1 case per 500 000 inhabitants.[241] The occurrence of this disease is related to portal hypertension,[242,243] oral contraceptive use,[244,245] infection with HIV,[246] cirrhosis, or use of cocaine or intravenous drugs.[241] Recently, it has been reported that the use of appetite suppressant drugs including derivatives of fenfluramine (dexfenfluramine), and amphetamine-like anorectic agents (amfepramone, clobenzorex, fenproporex, mazindol, and phenmetrazine) was associated with the development of primary pulmonary hypertension.[241] The absolute risk for obese persons who use anorectic agents for more than 3 months would be more than 30 times higher than for non-users. It is not known to what extent the risk continues to increase with longer term use, because the experience with long term use of anorectic agents has been extremely limited.[241]

10. Conclusions

There are many drugs associated with the development of unexplained ARDs (tables II, III and IV). The spectrum of adverse effects ranges from mild to moderate and severe, sometimes leading to death. Many reactions could be avoided if some medications were not administered at all, such as aspirin in AIA, or if the drug administration was stopped in time. Although drug-induced adverse respiratory reactions are unpredictable, they can be reduced to a minimum if knowledge of the possibility of such adverse effects is taken into account for each individual patient.

References

1. McNeill RS. Effect of a beta-adrenergic blocking agent, propranolol, on asthmatics. Lancet 1964; II: 1101-2
2. Tattersfield AE, Harrison RN. Effect of beta-blocker therapy on airway function. Drugs 1983; 25 Suppl. 2: 227-31
3. Lewis RV, Lofthouse C. Adverse reactions with beta-adrenoreceptor blocking drugs: an update [abstract]. Drug Saf 1993; 9: 272
4. Dunn TL, Gerber MJ, Shen AS, et al. The effect of topical ophtalmic instillation of timolol and betaxol on lung function in asthmatic subjects. Am Rev Respir Dis 1986; 133: 264-8
5. Graft D, Fowles J, McCoy CE, et al. Detection of beta-blocker use in people with asthma. Ann Allergy 1992; 69: 449-53
6. Craig TJ. Drugs to be used with caution in patients with asthma. Am Fam Physician 1996; 54: 947-53
7. Odeh M, Oliven A, Bassaan H. Timolol eye-drop-induced fatal bronchospasm in an asthmatic patient. J Fam Pract 1991; 32: 97-8
8. Schoene RB, Abuan T, Ward RL, et al. Effects of topical betaxolol, timolol, and placebo on pulmonary function in asthmatic bronchitis. Am J Ophtalmol 1984; 97: 86-92
9. Harris LS, Grenstein SH, Bloom AF. Respiratory difficulties with betaxolol [letter]. Am J Ophtalmol 1986; 102-274
10. Beta-adrenoreceptor-blocking agents. In: Reynolds JEF, editor. Martindale: the extra pharmacopoeia. 30th ed. London: The Pharmaceutical Press, 1993: 624
11. Perrone MH, Barrett JA. Preclinical pharmacology of celiprolol: a cardioselective β-adrenergic antagonists and mild vasodilator. Am Heart J 1991; 121: 677-83
12. Lamon KD. Clinical safety and efficacy of celiprolol. Am Heart J 1991; 121: 683-7
13. Riddel KG, Shanks RG, Brogden RN. Celiprolol: a preliminary review of its pharmacodynamic and pharmacokinetic properties and its therapeutic use in hypertension and angina pectoris. Drugs 1987; 34: 438-58
14. Doshan HD, Brown R, Applin WJ, et al. Effects of high doses of celiprolol in asthmatic patients. J Cardiovas Pharmacol 1986; 8 Suppl. 4: S109-S11
15. Matthys H, Doshan HD, Ruhle KH. The bronchosparing effects of celiprolol, a new beta-1 alpha-2 receptor antagonist, on pulmonary function of propraolol sensitive asthmatics. J Clin Pharmacol 1985; 25: 354
16. Milne RJ, Buckley MMT. Celiprolol. An updated review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in cardiovascular disease. Drugs; 1991; 41: 941-69
17. Austen KF, Orange RP. Bronchial asthma: the possible role of the chemical mediators of immediate hypersensitivity in the pathogenesis of subacute chronic disease. Am Rev Respir Dis 1975; 112: 423-36
18. Fleckenstein-Grun G, Fleckenstein A. CA dependent changes in coronary smooth muscle tone and the action of Ca compounds with special reference to Adalat. In: Lochner W, Braasch W, Kroberg G, editors. 2nd International Adalat Symposium. New York (NY): Springer Verlag, 1976: 66-75
19. Fish JE, Norman PS. Effects of the calcium channel blocker, verapamil, on the asthmatic airway responses to muscarinic, histaminergic, and allergic stimuli. Am Rev Respir Dis 1986; 133: 73-4
20. Setton I, Hirsh D, Pragier G, editors. Israel Drug Compendium: IDC 1995 Petach-Tikva, Israel: The Pharmaceutical Section Manufacturers Association of Israel, 1995: 387-9
21. Russi E, Danta I, Ahmed T. Comparative modification of antigen-induced bronchoconstriction by the calcium antagonists, nifedipine and verapamil. Chest 1985; 88: 74-8
22. Patel KR, Shama AL, Kerr W. The effects of inhaled verapamil on allergen-induced bronchoconstriction. Clin Allergy 1983; 13: 119-22
23. Ben-Noun L. Acute asthma associated with sustained-release verapamil. Ann Pharmacother 1997; 31: 593-5
24. Williams GH. Converting-enzyme inhibitors in the treatment of hypertension. N Engl J Med 1988; 319: 1517-25
25. Marre M, Hallab M, Billiard A, et al. Small doses of ramipril to reduce micro-albuminuria in diabetic patients with incipient nephropathy independently of blood pressure changes. J Cardiovasc Pharmacol 1991; 18 Suppl. 2: 165-8
26. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. Lancet 1997; 349: 1857-63
27. Cox JP, Duggan J, O'Boyle CA, et al. A double blind evaluation of captopril in elderly hypertensives. J Hypertens 1989; 7: 299-303
28. Lacourciere Y, Poirier L, Provencher P, et al. Once vs twice daily administration of a fixed combination of captopril plus hydrochlorothiaside in essential hypertension: a double-blind crossover study in known responders to a standard combinations. Br J Clin Pharmacol 1991; 32: 115-9
29. Israili ZH, Hall WD. Cough and angioneurotic edema associated with angiotensin converting enzyme inhibitor therapy: a review of literature and pathophysiology. Ann Intern Med 1992; 117: 234-42
30. Visser LE, Stricker BHCH, Van der Velden J, et al. Angiotensin converting inhibitor associated cough: a population based case-control study. J Clin Epidemiol 1995; 48: 851-7
31. Visser LE, Vlug AE, Van der Lei J, et al. Cough due to ACE inhibitors: a case control study using automated general practice data. Eur J Clin Pharmacol 1996; 49: 439-44
32. Charlton V, Dolow S, Fidel J, et al. Reproducibility of angiotensin converting enzyme inhibitor induced cough: a double-blind randomised study. Br J Clin Pharmacol 1995; 39: 125-9
33. Lunde H, Hedner T, Samuelsson O, et al. Dyspnoea, asthma, and bronchospasm in relation to treatment with angiotensin converting enzyme inhibitor. BMJ 1994; 308: 18-21

34. Lefevre J, Poirier L, Lacourciere Y. Prospective trial on captopril-related cough. Ann Pharmacother 1992; 26: 161-4
35. Holzgreve H. Safety profile of the combination of verapamil and trandolapril. J Hypertens 1997; 15 Suppl. 2: S51-S53
36. Dossegger L, Nielsen T, Preston C, et al. Heart failure therapy with cilazapril: an overview. J Cardiovasc Pharmacol 1994; 24 Suppl. 3: S28-S41
37. Rosenthal JR, Osowski U. Tolerability and efficacy of antihypertensive treatment with cilazapril in general practice. Cardiology 1996; 87: 54-9
38. Szucs T, Scheeweiss A. Cilazapril: an overview of its efficacy and safety in hypertension. Cardiology 1992; 80: 34-41
39. Kang PM, Landau AJ, Eberhardt RT, et al. Angiotensin II receptor antagonists: a new approach to blockage of the renin-angiotensin system. Am Heart J 1994; 127: 1388-401
40. Allen TL, Gora-Harper ML. Cromolyn sodium for ACE inhibitor-induced cough. Ann Pharmacother 1997; 31: 773-5
41. McEwan JR, Choudry NB, Fuller RW. The effects of sulindac on the abnormal cough reflex associated with dry cough. J Pharmacol Exp Ther 1990; 255: 161-4
42. Gilchrist NL, Richards AM, March R, et al. Effect of sulindac on ACE inhibitor induced cough: randomised placebo-controlled double blind cross-over study. J Hum Hypertens 1989; 3: 451-5
43. Fogari R, Zoppi A, Tettamanti F, et al. Effects of nifedipine and indomethacine on cough induced by angiotensin-converting enzyme inhibitors. J Cardiovas Pharmacol 1992; 19: 670-3
44. Onson C. Delay in diagnosis and empiric treatment of angiotensin-converting enzyme inhibitor induced cough in office practice. Arch Fam Med 1995; 4: 525-8
45. Pomari C, Turco P, Negro RD. Has theophylline a role in the cure and prevention of ACE-inhibitor related cough? Respiration 1989; 55: 119-21
46. Cazzola M, Matera MG, Licardi G, et al. Theophylline in the inhibition of angiotensin-convertin enzyme inhibitor-induced cough. Respiration 1993; 60: 212-5
47. Aldis WL. Cromolyn for cough due to angiotensin-converting enzyme inhibitor therapy. Chest 1991; 100: 1741-2
48. Jayasuria PH. Sodium cromoglycate for AC inhibitor cough. Med J Aust 1992; 156: 363-4
49. Hargreaves MR, Benson MK. Inhaled sodium cromoglycate in angiotensin converting enzyme inhibitor cough. Lancet 1995; 345: 13-6
50. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity (part 1) Chest 1988; 93: 1067-75
51. Kennedy J Jr I. Clinical aspects of amiodarone pulmonary toxicity. Clin Chest Med 1990; 11: 119-29
52. Dean PJ, Groshart KD, Porterfield JG, et al. Amiodarone associated pulmonary toxicity. A clinical and pathological study of eleven cases. Am J Clin Pathol 1987; 87: 7-13
53. Martin WJ. Mechanisms of amiodarone pulmonary toxicity. Clin Chest Med 1990; 11: 131-8
54. Dimopulou I, Marathias K, Daganou M, et al. Low-dose amiodarone-related complications after cardiac operations. J Thorac Cardiovasc Surg 1997; 114: 31-7
55. Marchlinski FE, Gansler TS, Waxman HL, et al. Amiodarone pulmonary toxicity. Ann Intern Med 1982 1982; 97: 839-45
56. Rakita L, Sobol SM, Mostow N, et al. Amiodarone pulmonary toxicity. Am Heart J 1983; 106: 906-14
57. Greenspon A, Kidwell GA, Hurley W, et al. Amiodarone-related postoperative adult respiratory distress syndrome. Circulation 1991; 84 Suppl. III: S407-S415
58. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity. Recognition and pathogenesis (part 2). Chest 1988; 93: 1242-8
59. Morady, Sauve MJ, Malone P, et al. Long-term efficacy and toxicity of high dose amiodarone therapy for ventricular tachycardia or ventricular fibrillation. Am J Cardiol 1983; 52: 975-9
60. Heger JJ, Prystowsky EN, Jackman WM, et al. Amiodarone. Clinical efficacy and electrophysiology during long-term therapy for recurrent ventricular tachycardia and fibrillation. N Engl J Med 1981; 305: 539-45
61. Totmensch HH, Siron M, Tupliski M, et al. Possible association of pneumonitis with amiodarone therapy. Am Heart J 1980; 100: 412-3
62. VanZadiok N, Darmata JI, Diiren DR, et al. Amiodarone pneumonitis. Eur J Respir Dis 1983; 64: 313-7
63. Heger JJ, Prystowsky EN, Ziper DP. Relationship between amiodarone dosage drug concentrations and adverse side effects. Am Heart J 1983; 106: 931-4
64. Kowey PR, Friehling TD, Marinchak RA, et al. Safety and efficacy of amiodarone. The low-dose perspective. Chest 1988; 93: 54-5
65. Zaher C, Hamer A, Peter I, et al. Low dose steroid therapy for prophylaxis of amiodarone-induced pulmonary infiltrates. N Engl J Med 1983; 308: 779
66. Horn HR, Hadidian Z, Johnson JL, et al. Safety evaluation of tocainide in the American emergency use program. Am Heart J 1980; 100: 1037-40
67. Holmes B, Heel RC. Flecainide: a preliminary report of its pharmacodynamic properties and therapeutic efficacy. Drugs 1985; 29: 1-33
68. Feinberg L, Travis WD, Ferrans V, et al. Pulmonary fibrosis associated with tocainide. Am Rev Respir Dis 1990; 141: 505-8
69. Hanston P, Evrard P, Mahieu P, et al. Flecainide associated interstitial pneumonitis. Lancet 1991: 337: 371-2
70. Akoun G, Cadranel JL, Israel-Biet D, et al. Flecainide-associated pneumonitis. Lancet 1991; 49: 337: 49
71. Ranhovsky A, Kempthorne-Rawson J. The safety of intravenous dipyridamole thallium myocardial perfusion imaging. Circulation 1990; 81: 1205-9
72. Simon RS, Baldwin JL. Drug-induced asthma. In: Bierman CW, Pearlman DS, Shapiro GG, editors. Allergy, Asthma, and Immunology from Infancy to Adulthood. 3rd ed. Philadelphia (PA): WB Saunders, 1996: 549-57
73. Biron P, Dessureault J, Napke E. Acute allergic interstitial pneumonitis induced by hydrochlorothiaside. Can Med Assoc J 1991; 145: 28-34
74. Kavaru MS, Ahmad M, Amirthalingam KN. Hydrochlorothiaside-induced acute pulmonary edema. Cleve Clin J Med 1990; 57: 181-4
75. Bell RT, Lippmann M. Hydrochlorothiazide-induced pulmonary edema. Arch Intern Med 1979; 139: 817-9
76. Steinberg AD. Pulmonary edema following ingestion of hydrochlorothiazide. JAMA 1968; 204: 825-7
77. Dorn MR, Walker BK. Noncardiogenic pulmonary edema associated with hydrochlorothiazide therapy. Chest 1981; 79: 484-3
78. Weddington WW, Mulroy MF, Sandri SR. Pneumonitis and hydrochlorothiaside. Ann Intern Med 1973; 70: 293
79. Bianco S, Vaghi A, Robuschi M, et al. Prevention of exercise-induced bronchoconstriction by inhaled frusemide. Lancet 1988; II : 252-5
80. Bianco S, Pieroni MG, Refini RM, et al. Protective effect of inhaled furosemide on allergen-induced early and late asthmatic reactions. N Engl J Med 1989; 321: 1069-73
81. Anonymous. Inhaled furosemide and asthma. Lancet 1990; 335: 944-6

82. Anderson SD, Wei HE, Temple DM, et al. Inhibition by furosemide of inflammatory mediators from lung fragments. N Engl J Med 1991; 324: 131
83. Lloyd EL. Frusemide and prevention of bronchoconstriction. Lancet 1988; II: 564
84. Chung KF, Barnes PJ. Inhaled frusemide on bronchial responsiveness to methacholine. N Engl J Med 1990; 322: 935-6
85. Flower RF, Moncada S, Vane JR. Drug therapy of inflammation. Analgesic antipyretics and anti-inflammatory agents; drugs employed in the treatment of gout. In: Gilman AG, Goodman LS, Rall TW, et al., editors. The pharmacological basis of therapeutics. 7th ed. New York (NY): MacMillan, 1985: 686-8
86. Falliers CJ. Aspirin and subtypes of asthma: risk factors. J Allergy 1973; 52: 141-7
87. Vedanthan PK, Menon MM, Bell TD, et all. Aspirin and tartrazine oral challenge: incidence of adverse response in chronic childhood asthma. J Allergy Clin Immunol 1977; 60: 8-13
88. Rachelevsky GS, Coulson A, Siegel SC, et al. Aspirin intolerance in chronic asthma detected by oral challenge. Pediatrics 1975; 56: 443-8
89. Szczeklik A, Grylewski RJ. Asthma and antiinflammatory drugs: mechanisms and clinical patterns. Drugs 1983; 25: 533-43
90. VanLeeuwen WS. Pathognomonishe bedeutung der Uebermpfindlichkeit gegen Aspirin bei Asthmatikern. Munch Med Wochenschr 1928; 75: 1588
91. McDonald JR, Mathison DA, Stevenson DD. Aspirin intolerance in asthma. J Allergy Clin Immunol 1972; 50: 198-207
92. Farr RS. The need to re-evaluate acetylsalicylic acid (aspirin). J Allergy 1970; 45: 321-8
93. Stenius BSM, Lemola M. Hypersensitivity to acetylsalicylic acid (ASA) and tartrazine in patients with asthma. Clin Allergy 1976; 6: 119-29
94. Farr RS, Spector SL, Wangaard C. Asthma and non-steroidal antiinflammatory drugs. Ann Intern Med 1978; 89: 577-600
95. Samter M, Beers Jr RF. Intolerance to aspirin: clinical studies and consideration of its pathogenesis. Ann Intern Med 1968; 68: 975-83
96. Lockey RF, Rucknagel DL, Vanselow NA. Familial occurrence of asthma, nasal polyposis and aspirin intolerance. Ann Intern Med 1973; 78: 57-63
97. Settipane GA, Puddupakkam RK. Aspirin intolerance III: subtypes, familial occurrence, and cross-reactivity with tartrazine. J Allergy Clin Immunol 1975; 56: 215-21
98. Dahlen BM, Kumlin DM, Margolskee C, et al. The leukotriene receptor antagonist MK-0679 blocks airway obstruction induced by inhaled lysine aspirin in aspirin-sensitive asthmatics. Eur Respir J 1993; 6: 1018-26
99. Lee TH. Mechanisms of bronchospasm in aspirin-sensitive asthma. Am Rev Respir Dis 1993; 148: 1442-3
100. Szczeklik A, Gryglewski RJ, Czerniavska-Mysik G, et al. Aspirin induced asthma: hypersensitivity to fenoprofen and ibuprofen in relation to their inhibitory action to prostaglandin generation by different microsomal enzymic preparations. J Allergy Clin Immunol 1976; 58: 10-8
101. Santiago Jr SM. Acute respiratory failure secondary to indomethacin in an aspirin intolerant asthmatic patient. Ann Allergy 1976; 37: 138-41
102. Polachek J, Shvartzman P. Acute bronchial asthma associated with the administration of ophtalmic indomethacin Isr J Med Sci 1996; 32: 1107-9
103. Sitenga GL, Yong ER, Van Dellen RG, et al. Asthma caused by topical application of ketorolac. Ophtalmology 1996; 103: 890-2
104. Goldin J, Hayhurst M, Potgieter PD. Severe asthma due to intravenous avapyrazone and dipyrone [letter]. S Afr Med J 1986; 69: 162
105. Timperman JA. A fatal asthmatic attack following administration of an indomethacin suppository. J Forensic Med 1971; 98: 30-2
106. Herbert WG, Scopelitis E. Ketorolac-precipitated asthma. South Med J 1994; 87: 282-4
107. Hume M, Eddy V. Treatment of chronic obstructive airways obstruction with indomethacin. Scan J Respir Dis 1977: 58: 284-6
108. Nishikawa M, Yoshinaga T, Igarashi A, et al. Clinical experience with indomethacin (Indacin). Shiryo- To-Shiyaku 1966; 3: 1917-20
109. Kordansky D, Adkinson F, Norman PS, et al. Asthma improved by nonsteroidal anti-inflammatory drugs. Ann Intern Med 1978; 88: 508-11
110. Jackson RH, Raymer WJ, Etter RL. New therapy in bronchial asthma: an evaluation of Ponstel (mefanic acid) in chronic bronchial asthma and pulmonary emphysema. J Kansas Med Soc 1969; 69: 474-8
111. Herxheimer H, Stresseman E. Anti-asthmatic effect of phenazone and amidopyrine. Nature 1961; 192: 1089-90
112. Hady S. Dipyrone in bronchial asthma [letter]. BMJ 1973; 1: 744
113. Streseman E. Die Wirkung von antipyretischen and analgetischensubstanzen auf das menschliche bronchial asthma und das experimentelle Meerschweiche asthma. Acta Allergologica 1963; 18: 211-34
114. Azelastine- Asthma study group. An evaluation of the efficacy and safety of azelastine in patients with chronic asthma. J Allergy Clin Immunol 1996; 97: 1218-24
115. Ben-Noun L. Drug-related asthma. J Pharm Technol 1998; 14: 116-24
116. Sweet JM, Stevenson DD, Simon RA, et al. Long-term effects of aspirin desensitization- treatment for aspirin-sensitive rhinosinusitis-asthma. J Allergy Clin Immunol 1990; 85 (Pt 1): 59-65
117. Szczeklik A, Mastalerz L, Nizakowska E, et al. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. Am J Respir Crit Care Med 1996; 153: 567-71
118. Seth RV, Clarke VS, Lewis RA, et al. Effect of propranolol on the airway response to prostaglandin E2 in normal man. Br J Clin Pharmacol 1981; 12: 731-5
119. O'Connor BJ, Fuller RW, Barnes PJ. Nonbronchodilator effects of inhaled beta$_2$-agonists : greater protection against adenosine monophosphate than metacholine -induced bronchoconstriction in asthma. Am J Respir Crit Med 1994; 150: 381-7
120. Szczeklik A. Aspirin-induced asthma. In: Vane JR, Botting RM, editors. Aspirin and other salicylates. New York (NY): Chapman & Hall Medical, 1992: 548-75
121. Sladek KR, Dworski J, Soja JR, et al. Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. Am J Respir Crit Care Med 1994; 149: 940-6
122. Josefson D. Asthma linked with Churg-Strauss syndrome [letter]. BMJ 1997; 315: 330
123. Christie PE, Smith CM, Lee TH. The potent and selective sulidopeptide leukotriene antagonists, SK and F 104353, inhibits aspirin-induced asthma. Am Rev Respir Dis 1991; 144: 957-8
124. Dahl R. Oral and inhaled sodium cromoglycate in challenge test with food allergens or acetylsalicylic acid. Allergy 1981; 36: 161-5

125. Israel EA, Fischer MA, Rosenberg CM, et al. The pivotal role of lipoxygenase products in the reaction of aspirin-sensitive asthmatics to aspirin. Am Rev Respir Dis 1993; 148: 1447-51
126. Szczeklik A, Serwonska M. Inhibition of idiosyncratic reactions to aspirin in asthmatic patients by clemastine. Thorax 1979; 34: 654-7
127. Philips GD, Foord R, Holgate ST. Inhaled lysine-aspirin as a bronchoprovocation procedure in aspirin-induced asthma: its repeatability, absence of late-phase reaction and the role of histamine. J Allergy Clin Immunol 1989; 84: 323-41
128. O'Byrne M. Leukotrienes in the pathogenesis of asthma. Chest 1997; 111: S27-S34
129. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in the adult asthmatic patients. J Allergy Clin Immunol 1979; 64: 500-6
130. Lipworth BJ. The emerging role of leukotriene antagonists in asthma therapy. Chest 1999; 115: 313-5
131. Reiss TF, Chervinsky P, Dockhorn RJ, et al. Montelukast, a once-daily leukotriene receptor antagonist in the treatment of chronic asthma. Arch Int Med 1998; 158: 123-20
132. Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year oldchildren with asthma. J Pediatr 1998; 133: 424-8
133. Malmstrom K, Rodriguez-Gomez G, Guerra J, et al. Oral montelukast, inhaled beclomethasone and placebo for chronic asthma. Ann Intern Med 1999; 130: 487-95
134. Masi At, Hunder GG, Lie JT, et al. The American Colledge of Rheumatology 1990 criteria for the classification of the Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum 1990; 33; 1094-100
135. Wechsler ME, Garpestad E, Flier SR, et al. Pulmonary infiltrates, eosinophilia, and cardiomyopathy following corticosteroid withdrawal in patients with asthma receiving zafirlukast. JAMA 1998; 279: 455-7
136. Knoell DL, Lucas J, Allen JN. Churg-Strauss syndrome associated with zafirlukast. Chest 1998; 114: 332-4
137. Flower RJ, Moncada S, Vane JR. Analgetic-antipyretic and anti-inflammatory agents; drugs employed in the treatment of gout. In: Gilman AG, Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. 6th ed. New York (NY): MacMillan, 1980: 682-728
138. Rosenow EC III. Drug-induced pulmonary disease. In: Murray JF, Nadel JA, editors. Textbook of respiratory medicine. Philadelphia (PA): WB Saunders, 1994: 2117-43
139. Smith W, Ball GV. Lung injury due to gold treatment. Arthritis Rheum 1980; 23: 351-4
140. Scott DL, Bradgy GVH, Altman TJ, et al. Relationship of gold and penicillamine therapy to diffuse interstitial lung disease. Ann Rheum Dis 1981; 40: 136-41
141. Ettensohn DB, Roberts NJ, Condemi JJ. Bronchoalveolar lavage in gold lung. Chest 1984; 85: 569-70
142. Klassen CD. Heavy metals and heavy-metal antagonists. In: Gilman AG, Goodman LS, Gilman A, editors. The pharmacological basis of therapeutics. 6th ed. New York (NY): Macmillan, 1980: 1615-37
143. Stein HB, Patterson AC, Offer RC, et al. Adverse effects of d-penicillamine in rheumatoid arthritis. Ann Intern Med 1980; 92: 24-9
144. Lyle WH. D-Penicillamine and fatal obliterative bronchiolitis. BMJ 1977; 1: 105
145. Chalmes A, Thompson D, Stein HB, et al. Systemic lupus erythematosus during penicillamine therapy for rheumatoid arthritis. Ann Intern Med 1982; 97: 659-63
146. Cooper JAD, White DA, Matthay RA. Drug-induced pulmonary disease. Part 2: noncytotoxic drugs. Am Rev Respir Dis 1986; 133: 488-505
147. Holmberg L, Boman G, Bottiger LE, et al. Adverse reactions to nitrofurantoin. Analysis of 921 reports. Am J Med 1980; 69; 733-8
148. Hailey FJ, Glascock HW, Hewitt WF. Pleuropneumonic reactions to nitrofurantoin. N Engl J Med 1969; 282: 1087-90
149. Rosenow EC, Martin WJ. Drug-induced interstitial lung disease. In: Schwarz MI, King Jr TE, editors. Interstitial lung disease. Toronto: BC Decker, 1988: 123-37
150. Prakash UBS. Pulmonary reaction to nitrofurantoin. Semin Respir Dis 1980; 2: 71-5
151. Holmberg L, Boman G. Pulmonary reactions to nitrofurantoin. 447 cases reported to the Swedish Adverse Drug Reaction Committee 1966-1976. Eur J Respir Dis 1981; 62: 180-9
152. Dweik RA. Drug-induced pulmonary disease. In: Baum GL, Crapo JD, Celli BR, et al., editors. Textbook of pulmonary diseases. 6th ed. Philadelphia (PA): Lippincott Raven, 1988: 477-90
153. Wang KK, Bowyer BA, Fleming CR, et al. Pulmonary infiltrates and eosinophilia associated with sulphasalazine. Mayo Clin Proc 1984; 59: 343-6
154. Jordan A, Cowan RE. Reversible pulmonary disease and eosinophilia associated with sulphasalazine. J R Soc Med 1988; 81: 233-5
155. Williams T, Eidus L, Thomas P. Fibrosing alveolitis, bronchiolitis obliterans, and sulfasalazine therapy. Chest 1982; 81: 766-8
156. Warner WA, Sanders E. Neuromuscular blockage associated with gentamicin therapy. JAMA 1971; 215: 1153-4
157. Dutcher JP, Kendall J, Norris D, et al. Granulocyte transfusion therapy and amphotericin B. Am J Hematol 1989; 31: 102-8
158. Levine SJ, Walsh TJ, Martinez A, et al. Cardiopulmonary toxicity after liposomal amphotericin B infusion. Ann Intern Med 1991; 114: 664-6
159. Roncoroni AJ, Corrado C, Besuchio SB, et al. Bronchiolitis obliterans possibly associated with amphotericin [letter]. B J Infect Dis 1990; 161: 589
160. Geahart MO, Bhutani MS. Intravenous pentamidine-induced bronchospasm. Chest 1992; 102: 1891-2
161. Katzman M, Meade W, Iglar K, et al. High incidence of bronchospasm with regular administration of aerolized pentamidine. Chest 1992; 101: 79-81
162. McFadden ER. Obstructive lung disease: anticholinergic agents. In: Branch WT, editor. Office practice of medicine. Philadelphia (PA): WB Saunders, 1987: 315-29
163. Patel KR, Tullet WM. Bronchoconstriction in response to ipratropium bromide. BMJ 1983; 286: 1318
164. Beasley CRW, Rafferty P, Holgate ST. Bronchoconstriction properties of preservatives in ipratropium bromide (Aerovent) nebulised solution. BMJ 1987; 294: 1197-8
165. Connolly CK. Adverse reaction to ipratropium bromide. BMJ 1982; 294: 1197-8
166. Clark RJ. Exacerbation of asthma after nebulised beclamethasone diproprionate. Lancet 1986; I: 74-5
167. McGivern DV, McFarlane JT. Severe bronchoconstriction after inhalation of budenoside. BMJ 1984; 288: 447
168. Shim C, Williams Jr MH. Cough and wheezing from beclamethasone aerosol. Chest 1987; 91: 207-9
169. Kounis NG. Untoward reaction to corticosteroids: intolerance to hydrocortisone. Ann Allergy 1976; 36: 203-6

170. Dajani JC, Sliman NA, Shubar KS, et al. Bronchospasm caused by intravenous hydrocortisone sodium succinate (SoluCortef) in aspirin sensitive asthmatics. J Allergy Clin Immunol 1981; 68: 201-4
171. Partrige MR, Gibson GL. Adverse bronchial reaction to intravenous hydrocortisone in aspirin-sensitive patients. BMJ 1978; 1: 1521-2
172. Prophylactic anti-asthma agents. In: Reynolds JEF, editor. Martindale: the extra pharacopoeia. 30th ed. London: The Pharmaceutical Press, 1993: 1140-6
173. Ibanex MD, Laso T, Irineo MM-S, et al. Anaphylaxis to disodium cromoglycate. Ann Allergy Immunol 1996; 77: 185-6
174. Murphy S, Kelly HW. Cromolyn sodium: a review of mechanisms and clinical use in asthma. Drug Intell Clin Pharm 1987; 21: 22-35
175. Serup J. Severe asthmatic reaction during long-term treatment with disodium cromoglycate powder inhalations. Acta Med Scand 1979; 205: 447-8
176. Leynadier F, Pujade-Lauraine MD, Cornaille G. Death after cromoglycate. Allergy 1985; 40: 540-1
177. Sheffer AL, Rocklin RE, Goetzi EJ. Immunologic component of hypersensitivity reactions to cromolyn-sodium. N Engl J Med 1975; 293: 1220-4
178. Settipane GA, Klein DE, Boyd GK, et al. Adverse reactions to cromolyn. JAMA 1979; 23: 811-3
179. Skarpaas IJK. An unexpected reaction towards disodium chromoglycate. Allergy 1987; 42: 318-9
180. Brown LA, Kaplan RA, Benjamin PA, et al. Immunoglobulin E-mediated anaphylaxis with inhaled cromolyn sodium. J Allergy Immunol 1989; 68: 416-20
181. Wass U, Plaschke P, Bjorkander J, et al. Assay of specific IgE antibodies to disodium cromoglycate in serum from patients with an immediate hypersensitivity reactions. J Allergy Clin Immunol 1988; 81: 752-7
182. Allegra L, Bianco S. Non-specific bronchoreactivity obtained with an ultrasonic aerosol of d stilled water. Eur J Respir Dis 1980; 61 Suppl.: S41-S49
183. Sheppard D, Rizk N, Boushey HA, et al. Mechanism of cough and bronchoconstriction induced by distilled water aerosol. Am Rev Respir Dis 1983; 127: 691-4
184. Schoeffel RE, Anderson SD, Altounyan RE. Bronchial hyperreactivity in response to inhalation of ultrasonically nebulized solutions of distilled water and saline. BMJ 1981; 283: 1285-7
185. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled beta agonists. J Allergy Clin Immunol 1990; 85: 959-64
186. Graff-Lonnevig V. Diurnal expiratory flow after inhalation of Freons and fenoterol in childhood asthma. J Allergy Clin Immunol 1979; 64: 534-8
187. Sterline GM, Batten JC. Effect of aerosol propellants and surfactants on airway resistance. Thorax 1969; 24: 226
188. Valic F, Skuvic Z, Bantic Z, et al. Effects of fluorocarbone propellants on respiratory airflow and ECG. Br J Ind Med 1977; 34: 130
189. Gong Jr H, Tashkin DP, Calvarese BM. Alcohol-induced bronchospasm in an asthmatic patient: pharmacological evaluation of the mechanism. Chest 1981; 80: 167-73
190. Stevenson DD, Simon RA. Sulfites and asthma. J Allergy Clin Immunol 1984; 74: 469-72
191. Schwartz HJ, Chester EH. Bronchospastic responses to aerosolised metabisulphite in asthmatic subjects: potential mechanisms and clinical implications. J Allergy Clin Immunol 1984; 74: 511-3
192. Anonymous. Nebulisers and paradoxical bronchoconstriction [letter]. Lancet 1988; II: 202
193. Cooper JAD, White DA, Matthay RA. State of the art. Drug induced pulmonary disease. Part I: Cytotoxic drugs. Am Rev Resp Dis 1986; 133: 321-40
194. Rosenow EC, Wilson WR, Cockerill FR. Pulmonary disease in the immunocomprised host. Mayo Clin Proc 1985; 60: 473-87
195. Holoye PY, Luna MA, MacKay B, et al. Bleomycin hypersensitivity pneumonitis. Ann Intern Med 1978; 88: 47-9
196. Twohig KL, Mattay RA. Pulmonary effects of cytotoxic agents other than bleomycin. Clin Chest Med 1990; 11: 31-54
197. O'Driscoll BR, Hasleton PS, Taylor PM, et al. Active lung fibrosis up to 17 years after chemotherapy with carmustine (BCNU) in childhood. N Engl J Med 1990; 323: 378-82
198. Selker RG, Jacobs SA, Moore PB, et al. 1,3- Bis (2-chloroethyl) – 1- nitrosourea (BCNU)- induced pulmonary fibrosis. Neurosurgery 1980; 7: 760-5
199. Weiss RB, Poster DS, Penta JS. The nitrosoureas and pulmonary toxicity. Cancer Treat Rev 1981; 8: 111-25
200. Pascual RS, Mosher MB, Sikand RS, et al. Effects of bleomycin on pulmonary function in man. Am Rev Respir Dis 1975; 108: 211-7
201. Ahlgren JD, Smith FP, Kervin DM, et al. Pulmonary disease as a complication of chlorozotocin chemotherapy. Cancer Treat Rep 1981; 65: 223-9
202. Yagoda A, Mukherji B, Young C, et al. Bleomycin: an antitumor antibiotic: clinical experience in 274 patients. Ann Intern Med 1972; 77: 861-70
203. Brashear RE. Effects of heroin, morphine, methadone, and propoxyphene on the lung. Semin Respir Med 1980; 2: 59-69
204. Heffner JE, Harley RA, Schabel SI. Pulmonary reactions from illicit substance abuse. Clin Chest Med 1990; 11: 151-62
205. Overland ES, Nolan AJ, Hopewell PC. Alternation of pulmonary function in intravenous drug abusers: prevalence, severity, and characterization of gas exchange abnormalities. Am J Med 1980; 68: 231-7
206. Smith WR, Wells JD, Glauser FL, et al. Immunologic abnormalities in heroin lungs. Chest 1975; 68: 651-3
207. O'Donnell AE, Pappas LS. Pulmonary complications of intravenous drug abuse. Experience at an inner-city hospital Chest 1988; 94: 251-3
208. Ettinger L, Albin RJ. A review of the respiratory effects of smoking cocaine. Am J Med 1989; 87: 664-8
209. McCarrol KA, Roszler MH. Lung disorders due to drug abuse. J Thorac Imaging 1991; 6: 30-5
210. Kline JN, Hirasuna JD. Pulmonary edema after free-base cocaine smoking not due to an adulterant. Chest 1990; 97: 1009-10
211. Patel RC, Dutta D, Schonfeld SA. Free-base cocaine use associated with bronchiolitis obliterans organizing pneumonia. Ann Intern Med 1987; 107: 186-7
212. Collins E, Hardwick H, Jeffery H. Perinatal cause of cocaine intoxication. Med J Aust 1989; 150: 331-2.
213. Rubin RB, Neugarten J. Cocaine-associated asthma. Am J Med 1990; 88: 438-9
214. Forrester JM, Steele AW, Waldron JA. Crack lung: an acute pulmonary syndrome with a spectrum of clinical and histological findings. Am Rev Respir Dis 1990; 142; 462-7
215. Franz DN. Central nervous system stimulants. In: Gilman AG, Goodman LS, Rall TW, et al., editors. The pharmacological basis of therapeutics. 7th ed. New York (NY): Macmillan, 1985: 586-7
216. Parran Jr TV, Jasinski DR. Intravenous methylphenidate abuse. Arch Intern Med 1991; 151: 781-3

217. Schmidt RA, Glenny RW, Godwin JD, et al. Panlobular emphysema in young intravenous ritalin abusers. Am Rew Respir Dis 1991; 143: 649-56
218. Mahutte CK, Nakasato SK, Light RW. Haloperidol and sudden death due to pulmonary edema. Arch Intern Med 1982; 142: 1951-2
219. Li C, Gefter WB. Acute pulmonary edema induced by overdosage of phenothiazines. Chest 1992; 101: 102-4
220. Roy TM, Ossorio MA, Cipola LM, et al. Pulmonary complications of tricyclic antidepressant overdosage. Chest 1989; 96: 852-6
221. Varnell RM, Godwin JD, Richardson ML, et al. Adult respiratory distress syndrome from overdose of tricyclic antidepressants. Radiology 1989; 170: 667-70
222. Shannon M, Lovejoy Jr FH. Pulmonary consequences of severe tricyclic anti-depressant ingestion. J Toxicol Clin Toxicol 1989; 25: 443-61
223. Wilson IC, Gambill JM, Sandifer MG. Loefler's syndrome occurring during imipramine therapy. Am J Psychiatry 1963; 119: 892-3
224. Cullinan SA, Bower GC. Acute pulmonary hypersensitivity to carbamazepine. Chest 1975; 68: 580-1
225. Stephan WC, Parks RD, Tempest B. Acute hypersensitivity pneumonitis associated with carbamazepine therapy. Chest 1978; 74: 463-4
226. Ingemarsson I, Arulkumaran S, Kottegota SR. Complications of beta-mimetic therapy in preterm labour. Aust N Z J Obstet Gynaecol 1985; 25: 182-9
227. Reed CR, Glauser FL. Drug-induced noncardiogenic pulmonary edema. Chest 1991; 100: 1120-4
228. Pisani RJ, Rosenow EC. Pulmonary edema associated with tocolytic therapy. Ann Intern Med 1989; 110: 714-8
229. Eliasson O, Scherzer HH, DeGraff AC. Morbidity in asthma in relation to menstrual cycle. J Allergy Clin Immunol 1986; 77: 87-94
230. Gibs CJ, Coutts II, Lock R, et al. Premenstrual exacerbation of asthma. Thorax 1984; 39: 833-6
231. Derimanov G, Oppenheimer J. Exacerbation of premenstrual asthma caused by oral contraceptive. Ann Allergy Asthma Immunol 1998; 82: 243-6
232. Tan KS, McFarlane LC, Lipworth BJ. Paradoxical down-regulation and desensitization of beta 2-adrenoreceptors by exogenous progesterone in female asthmatics. Chest 1997; 111: 847-51
233. Tan KS, McFalane LC, Lipworth BJ. Loss of normal cyclical beta 2-adrenoreceptor regulation and increased premenstrual responsiveness to adenosine monophosphate in stable female asthmatic patients. Thorax 1997; 52: 608-11
234. Tan KS, McFarlane LC, Lipworth BJ. Modulation of airway reactivity and peak flow variability in asthmatics receiving the oral contraceptive pill. Am J Respir Crit Care Med 1997; 155: 1273-7
235. Troisi RJ, Speizer FE, Willett WC, et al. Menopause, postmenopausal estrogen preparations, and the risk of adult onset asthma. Am J Respir Crit Care Med 1995; 152: 1183-8
236. Kinnunen E, Viljanen A. Pleuropulmonary involvement during bromocriptine treatment. Chest 1988; 94: 1034-3
237. McElvaney NG, Wilcox PG, Churg A, et al. Pleuropulmonary disease during bromocriptine treatment of Parkinson's disease. Arch Intern Med 1988; 148: 2231-6
238. Hindle W, Posner E, Sweetnam MMT, et al. Pleural effusion and fibrosis during treatment with methysergine. BMJ 1970; 6: 83-102
239. Rubin LJ. Primary pulmonary hypertension. Chest 1993; 104: 236-50
240. Rich S, Danzker DR, Ayrer SM, et al. Primary pulmonary hypertension: a national prospective study. Ann Intern Med 1987; 107: 216-23
241. Abenhaim L, Moride Y, Brenot F, et al. Appetite-suppressant drugs and the risk of primary pulmonary hypertension. N Engl J Med 1996; 335: 609-16
242. Hadengue A, Benhayoun MK, Lebree D, et al. Pulmonary hypertension complicating portal hypertension: prevalence and relation to splanchnic hemodynamics. Gastroenterology 1991; 100: 520-8
243. McDonnell PJ, Toye PA, Hutchins GM. Primary pulmonary hypertension and cirrhosis: are they related? Am Rev Respir Dis 1983; 127: 437-41
244. Kleiger RE, Boxer M, Ingham RE, et al. Pulmonary hypertension in patients using oral contraceptives: a report of six cases. Chest 1976; 69: 143-7
245. Masi AT. Pulmonary hypertension and oral contraceptive usage. Chest 1976; 69: 451-3
246. Legoux B, Piette AM, Boucher PE, et al. Pulmonary hypertension and HIV infection. Am J Med 1990; 89: 122
247. Londino A Jr V, Wolf GL, Calabro JJ, et al. Naproxen and pneumonitis [letter]. JAMA 1984; 252: 1853
248. Antineoplastic agents and immunosuppressants. In: Reynolds JEF, editor. Martindale: the extra pharmacopoeia. 30th edition. London: The Pharmaceutical Press, 1993: 434-507
249. Cherniac RM, Abrams J, Kalica AR. Pulmonary disease associated with breast cancer therapy. J Respir Crit Care Med 1994; 150: 1169-73
250. Cohen MB, Austin JHM, Smith-Vaniz A, et al. Single case reports. Nodular bleomycin toxicity. Am J Clin Pathol 1989; 92: 101-4
251. Santrach PL, Askin FB, Wells RJ, et al. Nodular form of bleomycin-related pulmonary injury in patients with osteogenic sarcoma. Cancer 1989; 64: 806-11
252. Rao SX, Ramaswamy G, Levin M, et al. Fatal acute respiratory failure after vinblastine-mitomycin therapy in lung carcinoma. Arch Intern Med 1985; 145: 1906-7
253. Hoelzer KL, Harrison BR, Luedke SW, et al. Vinblastine-associated pulmonary toxicity in patients receiving combination therapy with mitomycin and cisplatin. Drug Intell Clin Pharm 1986; 20: 287-9
254. Bellamy EA, Husband JE, Blaquiere RM, et al. Bleomycin-related lung damage: CT evidence. Radiology 1985; 156: 155-8
255. Min K-W, Gyorkey FI. Interstitial pulmonary fibrosis, atypical epithelial changes and bronchiolar cell carcinoma following busulfan therapy. Cancer 1968; 22: 1027-32
256. Aymard JP, Gyger M, Lavallee R, et al. A case of pulmonary alveolar proteinosis complicating chronic myelogenous leukemia. A peculiar pathologic aspect of busulfan lung? Cancer 1984; 53: 954-6
257. Sostman HD, Matthay RA, Putman CE. Cytotoxic drug-induced lung disease. Am J Med 1977; 62: 608-15
258. Durant JR, Norgard MJ, Murad TM, et al. Pulmonary toxicity associated with bischloroethyl nitrosourea (BCNU). Ann Intern Med 1979; 90: 191-4
259. Kuplic JB, Higley CS, Niewoehner DE. Pulmonary ossification associated with long-term busulfan therapy in chronic myeloid leukemia. Am Rev Respir Dis 1972; 106: 759-62
260. Stolley PD, Tonascia JA, Tockman MS, et al. Thrombosis with low-estrogen oral contraceptives. Am J Epidemiol 1975; 102: 197-208

261. Wright DG, Robichaud KJ, Pizzo PA, et al. Lethal pulmonary reactions associated with the combined use of amphotericin B and leukocyte transfusions. N Engl J Med 1981; 304: 1185-9
262. Davies D, MacFarlane A. Fibrosing alveolitis and treatment with sulphasalazine. Gut 1974; 15: 185-8
263. Tydd TF, Dyer NH. Sulphasalazine lung. Med J Aust 1976; 1: 570-1
264. Sternlieb I, Bennet B, Scheinberg IH. D-penicillamine induced Goodpasture's syndrome in Wilson's disease. Ann Intern Med 1975; 82: 673-6
265. Shesser R, Davis C, Edeldtein S. Pneumomediastinum and pneumothorax after inhaling alkyloid cocaine. Ann Emerg Med 1982; 10: 213-5
266. Morris JB, Shock JM. Pneumomediastinum in a young male cocaine user. Ann Emerg Med 1985; 14: 264-6
267. Murray JB, Smialek J, Golle M, et al. Pulmonary vascular abnormalities in cocaine users. Am Rev Respir Dis 1988; 137 Suppl. 4 (Pt 22): 459
268. Alfred RJ, Ewer S. Fatal pulmonary edema following intravenous 'freebase' cocaine use. Ann Emerg Med 1981; 10: 441-2

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