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REVIEW

Drug-induced lung disease: 1990 review

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ABSTRACT: Numerous drug-induced pulmonary manifestations have been reported but studies of their pathogenic mechanisms are still rare. These mechanisms should, however, be precisely determined in order to identify subjects at risk and to prevent some of these complications by the proper use of certain drugs in more appropriate conditions. The possibility of an iatrogenic manifestation should always be considered in patients developing pulmonary symptoms. Data from biological investigations, although not specific, contribute to the understanding of lung injury mechanisms.
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Pulmonary side-effects are frequently ascribed to drugs that have recently, or even not so recently, arrived on the market. An exhaustive list of incriminated substances would probably be just as impossible to draw up as it would be to identify precisely the mechanism(s) responsible for the observed symptoms which are often intricate. The diagnosis of iatrogenic lung disease is based on the clinical context, pulmonary and possibly extra-pulmonary signs as well as result from chest roentgenograms, lung function tests and cyto-histological examinations. The attempt to reintroduce the drug is of diagnostic value only if the test is positive. Without formal evidence of its causative role, the drug remains under suspicion and should, therefore, be withheld. We report here on iatrogenic lung manifestations, confining ourselves to those drugs with unquestionable pulmonary side-effects.

Parenchymal manifestations

Mechanisms

Hypersensitivity. The term "drug-induced hypersensitivity pneumonitis" is restricted by certain authors to allergic lung diseases related to inhaled organic antigens. However, lung diseases resembling hypersensitivity pneumonitis are observed in the course of drug reactions. Positive immunological tests are of prime importance in identifying hypersensitivity. No conclusion can be drawn from a negative test. Positive skin tests should be interpreted with caution as a local inflammatory reaction does not automatically mean drug sensitization but sometimes simply reflects the irritating effect of the drug. Skin tests should be carried out with a titrated solution and read at repeated intervals in order to discriminate between early reaction, possibly involving immunoglobulin E (IgE), and 48 h late reaction reflecting genuine delayed hypersensitivity towards the drug. Serum IgE levels in patients with drug-induced hypersensitivity pneumonitis are usually normal. Human basophil degranulation tests in the presence of the suspect drug are rarely carried out [1].

Finding serum antibodies to the drug is of great value, although not always indicative of hypersentivity. Low levels of anti-amiodarone antibodies have been found in patients receiving this drug, but with no adverse effect [2]. Patients with iatrogenic complications from amiodarone presented with high levels of anti-amiodarone serum immunoglobulin G (IgG) [2]. A serum IgG reacting specifically to the patient's pulmonary tissue was seen in one patient with amiodarone-related pulmonary fibrosis [3]. In this case, a humoral reaction was assumed to have taken place against amiodarone with the drug behaving as a hapten linked to pulmonary tissue.

Cell-mediated hypersensitivity testing is based on lymphoblast transformation of blood lymphocytes in the presence of the drug and on the migration inhibition of the more sensitive and more specific leucocytes. The immunological diagnosis of methotrexate pneumonitis for instance is based on these tests [4]. Lymphokine secretion (*e.g.* interleukin$_2$) either by blood lymphocytes or, more conclusively, by alveolar lymphocytes in the

presence of the drug can be taken as evidence of prior drug sensitization of cells, as was described in BCG pneumonitis [5]. Bronchoalveolar lavage examination is important. Results are not specific but provide useful pointers to further investigation. Cytological examination usually shows a lymphocytic alveolitis, 60–80% of recovered cells being lymphocytes, three quarters of which take the CD8 marker [6]. The function of alveolar lymphocytes is not as completely understood here as it is in organic antigen hypersensitivity pneumonitis. Phenotypic studies have shown, however, that activated T cells (HLA-DR markers), are present [7], and that they may be specifically sensitized by the incriminated drug [5]. Whether the lymphocytes have suppressor or cytotoxic functions has not been clearly determined in this condition. By analogy with standard hypersensitivity pneumonitis, one may assume a joint expansion of suppressor and cytotoxic alveolar populations [8, 9]. Moreover, within the cytotoxic population, various populations of natural killers cells, lymphokine-activated killer cells and antigen-specific cytotoxic cells have been reported [10].

In concluding this overview of the immunological investigation of iatrogenic hypersensitivity pneumonitis, two main points should be stressed. Positive results should alert the clinician to the possibility of hypersensitivity without certainty as to the physiopathological role of the suspect drug. A negative test is not sufficient to rule out hypersensitivity; in fact, sensitization can occur only against drug metabolites and not the native product; in addition, only carrier protein binding ensures antigenicity of the molecule, and this should be taken into account when interpreting *in vitro* tests.

Oxidants. The production of free oxygen radicals and alteration of the oxidant-antioxidant balance is one of the mechanisms of iatrogenic pneumonitis. Free radicals can promote lung injury directly through the inflammation they generate. *In vitro* and *in vivo* formation of hydroxyl radicals in the presence of ferrous iron, oxygen and bleomycin suggests oxidants as the cause in bleomycin toxicity [11]. During carmustine and cyclophosphamide treatment, glutathione stocks are reduced, disturbing the oxidant-antioxidant balance [12]. Release of free radicals probably plays an important role in nitrofurantoin-induced pneumonitis. Generation of free radicals by microsomes in the presence of nitrofurantoin has been demonstrated *in vitro* [13]; antioxidants have been shown to prevent nitrofurantoin-induced injury to pulmonary cells in culture [14]. More generally, the inflammation observed in all iatrogenic lung diseases probably contributes to the release of free oxygen radicals from polymorphonuclear neutrophils and alveolar macrophages [15].

Direct cell toxicity. Bleomycin produces lesions in cellular deoxyribonucleic acid (DNA), particularly in type II pneumocytes which are poor in hydrolase (a bleomycin-inactivating enzyme) [16].

Alteration of collagen production. Lung lesions observed in rats after intratracheal administration of bleomycin are accompanied by an increased collagen synthesis [17] and can be prevented by prior intake of a collagen synthesis inhibitor [18]. D-penicillamine alters collagen solubility, thereby delaying repair mechanisms [19]. Gold salts reduce collagen degradation, thus fostering fibrosis [20].

Lipidoses. As a rule, lipidoses are due to drugs containing amphiphilic molecules, *i.e.* molecules with a polar, hydrophilic end and an apolar, hydrophobic end. The hydrophilic end generally contains a basic element. Non-amphiphilic molecules have been incriminated in certain animal studies, including erythromycin, netilmicin, gentamicin [21–23] but there is no evidence of their iatrogenic respiratory effects in humans. The only drugs proved to induce pulmonary lipidosis in man are amiodarone and chlorphentermine [23, 24]; however, many amphiphilic molecules, in particular tricyclic antidepressants, are potential agents of lipidosis. There are indeed experimental data incriminating the role of tricyclic derivatives in animals [25, 26]. Moreover, a minor form of Niemann-Pick's disease induced by chlorpromazine derivatives has been described [27].

Cellular abnormalities are characterized by cytoplasmic inclusions visible on light microscopy, and by concentric lamellar bodies, and/or crystalloid bodies on electron microscopy. Lamellar bodies increase in number and size during the course of treatment, displacing cellular organelles to the periphery: the limiting membrane may disappear and, with it, the distinction between accumulated material and cellular cytoplasm. The accumulated material is composed essentially of phospholipid, thus explaining the lamellar appearance due to accumulated polar lipids. The material is found in cells with high phagocytic potential, namely alveolar macrophages. LULLMAN *et al.* [25] have shown that circulating lymphocytes are the cells most sensitive to the lipidogenic drug effect. The initially extracellular amphiphilic substances pass into the cells as an uncharged element, penetrate the lysosomes where acid pH favours molecular protonization [28], and bind to phospholipids; the complex thus formed accumulates in the lysosomes where phospholipases, inhibited by the complex, are incapable of degrading it. The pulmonary effect is theoretically neither irreversible nor fibrosing. Usually, the drug-phospholipid complex dissociates spontaneously when treatment is discontinued, at a pace dependent on the drug's half-life. Lamellar bodies and the interstitial involvement disappear. It is difficult to predict the development of lipoidosis since, no matter how high the lipoidogenic potential of the amphophilic substance may be, its ability to cause damage varies substantially from one species, and even from one organ, to the next [23]. The lung, where much catabolism of phospholipids takes place, is for that very reason a target organ for this pathology. Usually, however, there is multi-organ injury that can affect the kidneys, spleen, liver, lymph nodes, nerves, or heart. Amiodarone poses a special problem and will be discussed in detail below.

Lipoid pneumonitis. Inhalation pneumonitis induced in children by ingestion of cod liver oil has now disappeared. Adult forms are related to the ingestion of paraffin or vaseline oil as laxatives, or to the instillation of oil-based drugs for nasal problems. Supine position and gastro-oesophageal reflux increase the risk of inhalation. Macrophage activation ensues and results in the secretion of a number of substances, including a neutrophil chemotactic factor. The neutrophils in turn secrete collagenase and a fibroblast growth factor [29].

Lupoid reaction. Several hypotheses have been put forward to explain induced lupus. A number of factors argue against the hypothesis of pre-existing immunological anomalies: the absence of antibodies to single stranded DNA, the regression of signs following cessation of treatment. Personal predisposition is necessary for the induced lupus to develop. Indeed, in subjects at risk, the prevalence of antinuclear antibodies is much greater than the prevalence of clinical signs; genetic features are frequently observed: slow acetylation [30, 31], HLA DR4 phenotype [32]. D-penicillamine causes various immunological diseases (lupus, extra-membranous glomerulonephritis with immune complexes, hyperthyroidism) [33], suggesting an alteration of the immune regulatory system (adjuvant role of drugs) [34]. Isoniazid and hydralazine probably act by altering DNA nucleoproteins thus inducing auto-antibody production. Other drugs, more rarely seen to induce lupus, could act by releasing antigenic nuclear material [35].

Main clinical patterns

The clinical, radiological and functional manifestations of all types of drug-induced pneumonitis are similar. Pulmonary oedema, hypersensitivity pneumonitis or fibrosis are accompanied, depending on various conditions, by similar general signs, increasing dyspnoea, polypnoea, dry cough, and crackles. Diagnosis of iatrogenic pneumonitis must, therefore, be systematically considered. Diffuse reticulonodular infiltrates are the most common abnormal features. Pulmonary function tests may demonstrate a restrictive pattern, a reduced carbon monoxide diffusion capacity (DLCO), and hypoxaemia.

Certain drugs (aspirin, benzotine-benzylpenicillin, ampicillin, erythromycin, methadone, propoxyphone, barbiturates, colchicine, diuretics, thiazides, furantoin) are responsible for clinical and radiological presentations compatible with pulmonary oedema. The haemodynamic pattern is that of oedema due to increased permeability of the pulmonary vascular endothelium. An acute respiratory distress syndrome can be observed in the most severe cases. Before incriminating a drug, however, cardiogenic (haemodynamic) oedema and oedema due to an increased permeability unrelated to drugs (infectious, septic shock, metabolic) must be ruled out. Diagnosis can be a problem in patients under chemotherapy and in immunodepressed subjects, who are likely to develop opportunistic infections as an endothoracic neoplastic localization or a genuine iatrogenic pneumonitis due to cyclophosphamide, methotrexate, busulphan or bleomycin for instance. Anamnesis plays a major role, suggesting for instance, that the total bleomycin dose administered to a patient may have exceeded the recommended threshold, or pointing to the gold salts that the patient might be receiving for chronic rheumatoid polyarthritis in another instance.

Pulmonary oedema

Aspirin. Aspirin-induced pulmonary oedema has probably been the best studied of this type of disorder. In 36 subjects admitted with a salicylate concentration higher than 30 mg per 100 ml [36], pulmonary oedema was present in the oldest eight patients, in all smokers and in patients chronically receiving salicylate derivatives. Neurological abnormalities, proteinuria and a salicylate serum concentration higher than 40 mg per 100 ml were often present. The severity of pulmonary oedema correlated with the salicylate serum concentration, and ranged from discreet to serious forms such as the adult respiratory distress syndrome which required assisted ventilation.

Alveolar-interstitial pneumonitis

Nitrofurantoin. Nitrofurantoin pneumonitis generally occurs within a month of beginning treatment. It is more common in women, particularly if they present with a history of atopy or drug hypersensitivity reactions. Acute forms with haemorrhagic alveolitis have been reported, but symptoms are more generally confined to fever, non-productive cough, dyspnoea, and sometimes chest pain. These signs are often associated with skin rash, facial oedema, arthralgia, nausea, and/or arterial hypotension [37]. Radiological examination shows non-systematized lung infiltrates, predominantly at the bases and associated in 15% of the cases with pleural effusion [38]. In other cases, where the symptoms may be more discreet and the chest roentgenogram normal, only abnormal pulmonary function tests would argue for the diagnosis. Generally, the outcome is favourable when nitrofurantoin is discontinued, with general and respiratory signs subsiding within 48 h, but the radiological and functional abnormalities can last for 2–6 wks. A biopsy of the lungs would show interstitial alveolar infiltrates consisting of mononuclear and polymorphonuclear cells, with occasional eosinophils and sometimes an intra-alveolar haemorrhage. Hypersensitivity is suggested in this case by the lymphoblastic transformation observed in the presence of the drug [39], by the frequent auto-immune abnormalities reported in this disorder [40] and by blood or even pulmonary eosinophilia [41]. The alveolar hyperlymphocytosis together with a CD4/CD8

ratio reduction, is suggestive of a hypersensitivity mechanism [42]. Rarely, when free oxygen radicals released by the drug cause severe tissue injury, the disease becomes chronic, characterized by pulmonary fibrosis [13, 14].

Furazolidone. This drug, chemically close to nitrofurantoin, has been incriminated in extensive acute pneumonitis with fever, headache, blood eosinophilia, and hypoxaemia [43].

Gold salt therapy. The prevalence of gold salt pneumonitis in patients receiving such treatment is lower than 1%. It has been reported that patients with certain groups of HLA haplotypes were at greater risk [44]. The delay before the onset of pneumonitis varies from 1–26 mths [45, 46], with reported cumulative doses ranging from 175–1,060 mg. The onset of the disease is usually acute or subacute, with a non-productive cough, and a progressively more severe dyspnoea, and sometimes chest pain, haemoptysis, weight loss and fever. Chest roentgenograms show dense, bilateral, reticulonodular infiltrates, more often diffuse than localized, and rarely associated with pleural effusion. These clinical and radiological symptoms may be associated with other signs of intolerance, occurring within the first five months of gold salt treatment, such as stomatitis [47, 48], painful dysphagia [47], proteinuria, nephrotic syndrome or thrombopenia. A maculopapular skin rash is found on the chest area and on the lower limbs in nearly one third of the cases [49]. Sedimentation rate is usually elevated with a hyperleucocytosis and a blood hypereosinophilia. Bronchoalveolar lavage typically shows a CD8 alveolar hyperlymphocytosis while pathological examination reveals an alveolar and interstitial infiltration by lymphocytes and plasma cells [46, 50], with occasional areas of fibrosis. Immunofluorescence tests show IgG, IgM and even IgE deposition. On electron microscopy, collagen hyperplasia with lympho-histiocytic septal infiltration, hypertrophy of pneumocytes I and II and frequent alterations of alveolar capillaries are seen [50]. Intracellular inclusions in macrophages and endothelial cells, called aurosomes are rare, and the spectrophotometric search for gold particles is often negative. The outcome is usually favourable when treatment with gold salts is discontinued, all the more so when combined with corticotherapy. Respiratory symptoms subside within a few weeks to a few months. Lung function tests may remain moderately but permanently altered, with a restrictive pattern and a reduced DLCO [51]. The exact mechanism of this pneumonitis has not been elucidated. Because it is so rare and since no definite overdose has been reported, a pure toxic mechanism seems unlikely. Immediate hypersensitivity has been suggested to account for the Loefler-type infiltrates and for the slight hypereosinophilia; IgE, however, has always been found to be normal [48]. On the other hand, several studies suggest delayed hypersensitivity: although the lymphoblastic trans formation is not always positive in the presence of gold salts [50, 52], the lymphocytes specifically cultured with the drug have been shown to secrete appropriate lymphokines.

Salazopyrin. Used in the treatment of haemorrhagic rectocolitis, this drug can occasionally induce pulmonary complication. After several months or even years of treatment, chest roentgenograms show diffuse nonspecific infiltrates and pulmonary function tests show an obstructive more often than a restrictive ventilatory pattern with a reduced DLCO [53]. Blood hypereosinophilia is frequent. Bronchoalveolar lavage shows a hyperlymphocytic alveolitis with a normal CD4/CD8 ratio. The histological aspect may vary from eosinophilic, lymphoplasmocytic infiltrates to fibrosis or bronchiolitis obliterans [54]. Drug withdrawal brings an improvement further promoted by corticotherapy. Findings from bronchoalveolar lavage, lymphoblastic transformation in the presence of the drug, and, above all, the immediate relapse following reintroduction of the drug argue for the immune origin of this pneumonitis [55, 56].

Amiodarone. Pulmonary toxicity of this drug has a reported incidence of 2–15% per year, and a prevalence of 4–6% [57, 58]. Amiodarone pneumonitis is often revealed by dyspnoea on exertion, dry cough, alteration in the general condition of a patient, and only rarely by intense asthenia and/or chest pain [59]. A more insidious form includes fever, shivering and general malaise. Fine bilateral crepitations are heard on examination. The sedimentation rate is often highly increased and the blood count normal. Radiography shows a diffusereticulonodular infiltrate, but confluent alveolar infiltrates can also be observed as well as excavated nodules [60, 61] or uni- or bilateral pleural effusions [62]. Alveolar cellularity is usually increased, mainly through a CD8 hyperlymphocytosis [7]. Basophils, mast cells and eosinophils, normally absent from bronchoalveolar lavage, are found albeit in small quantities. Alveolar macrophages display a vacuolized cytoplasm, which gives them a foamy aspect. Alveolar lymphocytes present with morphological features of activation, with an indented nucleus in a large cytoplasm [7]. Electron microscopy shows large numbers of phospholipidic lamellar inclusions in alveolar macrophages and pneumocytes II. This aspect can also be observed in constitutional dyslipidosis and in thesaurismosis due to amphiphilic drugs [25], as well as in patients taking amiodarone but who did not develop pneumonitis [63].

Due to the lack of specific indications, the clinico-radiological diagnosis is not easy. When, because of its anti-arrhythmic properties, treatment with amiodarone seems to be imperative and when abnormal pulmonary symptoms occur, it might be difficult to decide whether to withdraw or to continue the drug. To assess the degree of inflammation, some authors recommend the use of gallium scintigraphy as a major diagnostic contribution [64]. Furthermore, although a phospholipidic thesaurismosis and a CD8 alveolitis are not specific individually, the combination of both becomes highly indicative of a lung disorder due to amiodarone.

Daily dosage, duration of treatment and total cumulative doses have all been incriminated as triggering factors. It is believed that lower toxicity correlates with a daily dose of less than 400 mg [65] or an amiodarone serum concentration of less than 2.5 $mg \cdot l^{-1}$ [66]. It has also been suggested that a reduced DLCO before the start of amiodarone treatment could predispose for the occurrence of pneumonitis [67]. A fall greater than 20% in DLCO is usually observed in cases of amiodarone pneumonitis, but the predictive value of DLCO alone is poor [58].

Especially if corticotherapy is prescribed, the evolution can be rapidly favourable after discontinuation of the drug. The clinical symptoms improve first, then the radiological and the functional ones. Should amiodarone be continued, an irreversible pulmonary fibrosis could occur. The physiopathogenesis of this development is still being debated. There are two main hypotheses, one favouring a toxic and the other an immunological mediation. The amphiphilic nature of the molecule, its tissue accumulation and the thesaurismosis observed on electron microscopy support the toxic aetiology. On the other hand, the development of pneumonitis at very low cumulative doses, the finding of a bronchoalveolar cell profile similar to that observed in hypersensitivity pneumonitis [7, 68], the usual corticosensitivity, the presence of C_3 and of immunoglobulins on alveolar walls [69] as well as that of circulating immune complexes, strongly argue for an immune mechanism, particularly in view of the fact that lymphocytes from a patient have been shown to secrete lymphokines when cultured *in vitro* with the drug [70].

Finally, serum antibodies specific of his own pulmonary tissues have been found in one patient [3]. It is likely, however, that both mechanisms co-exist. The binding of amiodarone or of its metabolites to pulmonary proteins could elicit an immune reaction towards the drug behaving here as a haptene. Otherwise, toxic injuries of pulmonary tissue could produce neo-antigens then able to trigger an auto-immune response.

Bleomycin. This cytostatic drug may lead to pulmonary fibrosis in 3–4% of patients [71, 72]. Subclinical involvement seems to be more frequent [73]. Fever is rare [71]. Bilateral reticulonodular infiltrates predominate at the bases of the lungs. Decrease in DLCO is an early, yet nonspecific, sign. Early involvement of endothelial cells is associated with interstitial oedema; the disorder then proceeds to necrosis of pneumocytes I and injury of pneumocytes II (loss of lamellar bodies); this precedes the proliferation of pneumocytes II and fibroblasts [74, 75]. There are various predisposing factors to bleomycin-induced pulmonary complications: old age, radiotherapy given simultaneously or sequentially [76], oxygen therapy or concomitant assisted ventilation with high oxygen concentration [77], combination with other drugs toxic to the lung (cyclophosphamide) [78] and kidney failure increasing the drug's half-life [79].

Two precautions can limit toxicity: continuous infusions rather than iterative injection [80, 81], and cumulative doses of bleomycin lower than 400 mg, although irreversible pulmonary lesions have been reported with lower doses [82]. The toxicity can be higher after reintroduction of the drug [83]. Corticotherapy only rarely causes a regression of symptoms, and functional abnormalities can persist permanently. Direct toxicity of the drug through oxidants is likely [11], accounting for the potentiation of the toxic effects of oxygen and radiotherapy [84, 85].

Bleomycin preferentially accumulates in the lung and is inactivated by a hydrolase. The concentration of this enzyme is lower in pulmonary tissue, in particular in pneumocytes II, than in other tissues (liver). Hydrolase-deficient patients may constitute a high risk population [16, 86]. A hypersensitivity-type reaction to bleomycin has also been reported [87].

Mitomycin. The prevalence of mitomycin-induced fibrosis is low (5%) and occurs with total doses of 50–150 $mg \cdot m^{-2}$. Corticotherapy often produces clinical and radiological regression [88].

Alkylating agents. Busulphan, mainly used in chronic myeloid leukaemia, was the first cytotoxic drug to be identified as the cause of pulmonary complications [89]. The incidence of busulphan-induced pulmonary manifestations is about 4% but more than half of reported cases are subclinical. Severe disorders have been reported only when total doses exceeded 500 $mg \cdot m^{-2}$ [90]. Epithelial cells are particularly sensitive to busulphan, but little is known about the mechanism of busulphan-induced injury. Cyclosphosphamide, although rarely, causes pulmonary fibrosis, probably through the release of a toxic metabolite and reduced antioxidant activity. Similarly, chlorambucil and melphalan induced pulmonary fibrosis is rare [91].

Methotrexate. Methotrexate is a folic acid analogue which generates pulmonary complications in about 8% of the patients [92]. The occurrence of pulmonary complications may be chronic, acute or delayed a few weeks after discontinuation of the drug [93]. The usual form is rather subacute with progressive development of malaise, shivers, fever, followed by dry cough and dyspnoea. Skin rash is frequent. Occasionally, chest pain due to pleural effusion is observed. Clinical examination displays fine crepitations, and sometimes cyanosis. Hypereosinophilia is frequent; chest roentgenograms demonstrate diffuse interstitial infiltrates with pleural effusion, which may actually be the only radiological sign [92]. Bronchoalveolar lavage shows an alveolar hyperlymphocytosis with an inverted CD4/CD8 ratio [94]. Histology shows lymphoplasmocytic infiltrates and eosinophils with giganto-cellular granulomas. Prognosis is favourable if the drug is withdrawn at an early stage, and is improved by giving corticosteroids. This disorder is probably due to a hypersensitivity, as evidenced by fever, acute eosinophilia, histological findings, the bronchoalveolar lavage findings [95] and specific lymphocyte activation in the presence of the drug [4]. However, the fact that reintroducing the drug does not always elicit a relapse suggests that this mechanism might not be the only one involved.

Procarbazine. There are clinical (skin rash, fever, eosinophilia) and histological (mononuclear cells and eosinophilic infiltrates) findings, supporting a hypersensitivity mechanism [96]. Clinical signs include dyspnoea and dry cough with a sudden onset shortly after beginning treatment. Pulmonary infiltrates and pleural effusion usually resolve shortly after discontinuation of the drug.

Nitrosoureas. Fibrosis has been reported in 20–30% of patients during carmustine (BCNU) administration [73, 97], usually in a dosage higher than 1,500 $mg \cdot m^{-2}$. Some risk factors are old age, concomitant radiotherapy, and combination with cyclophosphamide [98]. BCNU, by reducing glutathione reserves, might lead to pulmonary injuries through a toxic mechanism (alteration in the oxidant-antioxidant balance).

Azathioprine. Azathioprine-induced lung injury is rare and usually resolves upon discontinuation of the drug and addition of steroids. Bronchoalveolar lavage shows an alveolar hyperlymphocytosis, and inhibition of peripheral blood leucocyte migration in the presence of azathioprine has been reported [99].

Methysergide. In patients taking methysergide, interstitial pneumonitis may develop, sometimes in association with retroperitoneal fibrosis [100].

Bromocriptine. This drug has recently been incriminated in pulmonary, but above all pleural, manifestations [101, 102]. The symptoms are likely to resolve if treatment is discontinued before the development of fibrosis [102].

Acebutolol. Beta-blockers can promote episodes of drug-induced bronchoconstriction. There have also been reports of interstitial pneumonitis developing with these drugs; bronchoalveolar lavage findings argue for a hypersensitivity mechanism [103, 104].

Sodium cromoglycate. Parenchymatous infiltrates have been reported. An immune mechanism has been suggested, based upon lymphocyte proliferation and lymphokine secretion by lymphocytes in the presence of the drug, and upon the finding of serum IgG with an anti-drug specificity in these patients [105].

Post-hypophysia powder. Administered by sniffing in the treatment of diabetes insipidus, the post-hypophysia powder occasionally causes pulmonary miliary infiltrates to be seen on radiography. The discovery of specific serum precipitins argues for an immune mechanism [106].

BCG immunotherapy. Used in vesical neoplasms, this treatment may induce febrile dyspnoea with micro- and macro-nodular images. Symptoms disappear when treatment is discontinued, especially if corticosteroids are given. Bronchoalveolar lavage findings and a study of specific lymphocyte reactivity suggest a hypersensitivity mechanism [5].

Miscellaneous. Hypersensitivity pneumonitis induced by anticonvulsant drugs (diphenylhydantoin) [107, 108] and by antibiotics (PAS) [109], and penicillin [110, 111] has been described. Drug-induced pulmonary pneumonitis has also been reported after the combined use of nilutamide (non-steroid antiandrogen) and an analogue of luteinizing hormone-releasing hormone (LH-RH) in the treatment of prostate carcinoma [112, 113]. Converting enzyme inhibitors have also been reported to induce interstitial pneumonitis [114] of a hypersensitivity type, and pulmonary fibrosis has been associated with use of tocainide an anti-arrhythmic agent [115].

Medicinal oils. Pneumonitis due to the use of such oils is usually latent in adults, unless it produces subacute or chronic symptoms with cough, dyspnoea and mucus expectoration; acute forms are the exception [116]. Systemic signs such as fever or weight loss are seen only in advanced forms. Radiological infiltrates are sometimes diffuse and reticulonodular; more often, a unique pseudo-neoplastic, dense and homogeneous form is observed in the middle lobe, lingula or lower lobes with no associated mediastinal adenopathy; cavitary lesions have also been reported [117]. Pulmonary function tests are often normal. It is only at a later stage that a restrictive pattern will indicate the development of pulmonary fibrosis. Bronchoalveolar lavage recovers a thick, oily fluid containing many vacuolized macrophages laden with lipidic substances. Special stainings (Sudan Black and Oil Red) help to distinguish between mineral, vegetable and animal oils; accurate identification of the oil is based upon thin-layer chromatography of the lipidic extract. Lung biopsy, sometimes performed for diagnostic purposes, shows enlarged alveoli containing free oily substances and/or a great number of lipophages. The granulomatous reaction to oily particles is associated with more or less intense, and sometimes predominant, fibrosis. Progress of lipoid pneumonitis depends on the spread of the lesions. Although prognosis of an isolated pseudo-neoplasic lesion is generally favourable, it is more uncertain for diffuse lesions. Fatal, acute or subacute forms have been reported [116]. Treatment is based upon a total discontinuation of oil intake; corticosteroids have limited impact on evolution. Repeated alveolar lavages for therapeutic purposes, aiming at solubilization and aspiration of oily fluid from alveoli have been proposed [118].

Pseudo-Goodpasture's syndrome. This syndrome is a rare complication of high dose D-penicillamine (750 to 3,500 mg) given for more than 2 yrs [119, 120]. Clinical symptoms have a rapid onset, with dyspnoea on exertion, dry cough, haemoptysis, and haematuria. Respiratory distress rapidly sets in, associated with severe kidney failure [119]. Radiologically, infiltrates predominate at the bases, sometimes asymmetrically [120]. Haemorrhagic pleural effusion is rare. Histological studies reveal intra-alveolar haemorrhage with haemosiderin-laden macrophages, and associated fibrosis [120]. Immunofluorescence studies usually fail to show IgG or C_3 depositions. The absence of circulating anti-basement

membrane antibodies and of immunofluorescent depositions in specimen of kidney biopsy is in contrast with Goodpasture's syndrome. Outcome is often fatal, although plasmapheresis and immunosuppressive treatment improve the prognosis [119].

Airways manifestation

Cough

Converting enzyme inhibitors. Cough induced by converting enzyme inhibitors is increasingly frequent [121, 122]. It may appear 1–3 weeks after treatment has started, and presents as a dry, whooping, diurnal and nocturnal cough. Aggravation of pre-existing asthma has been reported [123] as well as recurrence of asthma in patients on captopril [124]. Chest roentgenograms, rhinological and otological examinations, pulmonary function tests including methacholine challenge tests, are normal [125]. Hypereosinophilia is occasionally present whereas total IgE level is normal. Drug discontinuation leads to cessation of symptoms within a few days. Readministration of the same drug or of a closely related molecule leads to rapid recurrence of cough, which confirms, if needed, the causative role of the drug. The pathogenesis of this condition is still unknown. Converting enzyme inhibitors can generate the release of bronchomotor mediators such as bradykinins and prostaglandins [126, 127]; by stopping cyclic adenosine monophosphate (cAMP) accumulating in the smooth muscle, they can also reduce the bronchodilatory effect of vasoactive intestinal polypeptides (VIPs) or beta-agonists [128], and they can reduce the catabolism of substance P which is a potent bronchoconstrictor [129]. That administration of sulindac (a non-steroidal anti-inflammatory agent) resolves the cough or can prevent it, despite continued intake of converting enzyme inhibitors, supports the above hypothesis [130].

Secretion modifiers. Aerosolized mucolytics (acetylcysteine, dexoribonuclease) cause bronchial oedema associated with a liquefaction of secretions responsible for the bronchial obstruction. Concomitant use of bronchodilators is recommended to prevent aggravation of the respiratory condition [131, 132].

Aerosols. Inhalation of sodium cromoglycate often causes transient irritation of upper airways, associated with cough. More rarely, these symptoms persist and combine with parenchymal signs [105, 133]. Cough and associated bronchospasm have been reported with the use of metered dose inhalers, especially metaproterenol and albuterol metered inhaler [134]. Cough is a common side-effect (40%) of beclomethasone dipropionate aerosols and this may lead to interruption of, or to low compliance with, the treatment (20%). Prior intake of a beta-agonist aerosol helps to greatly reduce these side-effects. Cough is more common when bronchial obstruction is severe, as the aerosol will then deposit in the larger airways and trigger the cough reflex. The causative agent is oleic acid, a dispersant present in beclomethasone. A similar reaction can be observed with a placebo containing only the dispersant and the propulsion gas but not when a different dispersant is used [135, 136]. The lower incidence of side-effects using a beta-agonist metered dose inhaler has been attributed to the presence of the beta-agonist bronchodilator overriding the bronchoconstricting effect of the inert ingredients.

Paradoxical bronchospasm following the use of nebulized bronchodilator solutions may be due to sulphite sensitivity [137]. Nebulized solutions known to contain sulphites include isoetharine, isoproterenol and racemic epinephrine [138]. The original nebulizer solution of ipratropium bromide and its vehicle, both in hypotonic form, produced bronchoconstriction in asthmatic patients. The current preparation of ipratropium bromide is now isotonic and bronchoconstriction in response to this solution is unusual and probably due to an adverse reaction to the inhaled bromide ions [139]. Cough and bronchospasm have frequently been reported as side-effects in patients with the acquired immunodeficiency syndrome treated for *Pneumocystis carinii* pneumonia with aerosolized pentamidine [140]. The mechanism of inhaled pentamidine-induced bronchoconstriction is debated. Proposed mechanisms include nonspecific irritation from the inhaled particles, histamine release [141] and inhibition of cholinesterases by pentamidine, an effect that has been demonstrated *in vitro* [142]. Pretreatment with either a beta-agonist or an anticholinergic agent has controlled symptoms in most cases [143].

Asthma

Aspirin-induced asthma. WIDAL *et al.* [144] were the first to report the association of recurring nasal polyposis, severe asthma and intolerance to aspirin. Asthma may precede the onset of aspirin intolerance; most of the time it is severe and corticodependent [145]. Nasal polyposis, although sometimes absent, is usually preceded by chronic rhinitis associated with bilateral polyps which may cause worsening of asthma if surgically removed [146]. Aspirin causes an asthma attack, flush, rhinorrhoea, even diarrhoea, just a few minutes, and rarely more than an hour, after intake. The severity of asthmatic manifestations differs from patient to patient, but is proportional to the quantity of aspirin absorbed.

Other non-steroidal, anti-inflammatory drugs may induce similar effects, particularly indomethacin, fenamates and phenylbutazone [147]. The stains contained in certain pharmaceutical preparations such as tartrazine may induce asthmatic reactions [145] just as do the preservatives (bisulphites and metasulphites) used in a number of drugs, including corticosteroids [148].

Aspirin intolerance, which should be considered in all asthmatic patients, is more frequently reported by patients than objectively observed after challenge tests [149]. The tests consist in oral administration of gradually increasing

doses of aspirin (10–500 mg), compared with placebo administered under the same conditions. The test is positive if it causes flush, rhinorrhoea, even diarrhoea and bronchial obstruction within an average of 10–40 min, but sometimes up to 24 h following drug intake; bronchial obstruction is usually reversible with administration of beta$_2$-adrenergic drugs.

The pathophysiology of aspirin-induced asthma remains obscure. Successive hypotheses have been considered, including allergy, which could not be documented [150], kinins [145] or complement mediation [151]. In fact, aspirin, as an analgesic and anti-inflammatory agent, acts through inhibition of the cyclo-oxygenase pathway of arachidonic acid metabolism and, therefore, reduces prostaglandin synthesis [152]. So far, the hypothesis that aspirin-induced asthma is due to an imbalance of arachidonic acid metabolism in favour of leukotrienes-lipoxygenase pathway catabolites has not been proved. Autosomal recessive transmission of this condition has been suggested [153], and would explain why it only affects 20% or less of all asthmatic patients [154].

Beta-blocker-induced asthma. The discovery of a beta-receptors antagonist, dichloroisoproterenol (DCI) by POWELL and SLATER [155] and the demonstration that DCI inhibited catecholamine effects led to the examination of the role of beta-blocking drugs in asthma. In animals, pretreatment with a beta-receptor antagonist results in increasing activity of alpha-receptors [156]. Bronchoconstriction caused by beta-receptor antagonists in asthmatic patients is inhibited by atropine but not phentolamine [157]. Inhaled anticholinergic medications are the treatment of choice for beta-blocker-induced bronchoconstriction [158]. The increase in airways resistance by beta-blocking drugs, even cardio-selective beta-blockers, is greater in asthmatic than in non-asthmatic patients [159]. Collyrium timolol also reduces expiratory flows in asthmatic patients [160]. This explains why these drugs may produce symptoms of asthma and why they are contra-indicated.

Other drug-induced asthmas. These reactions are due either to drug hypersensitivity or to mechanical irritation caused by an aerosol's particulate or gaseous phase. Thus penicillin during anaphylactic shock [161, 162], nitrofurantoin [163], pyrazolone derivates (noramidopyrine, amidopyrine) [164], but also adrenocorticotrophic hormone (ACTH) [161], cimetidine [165], aminophylline [166], insulin, trypsin, curare, ketamine, alphamethyldopa, bleomycin, carbamazepine, dyazide, psyllium, vindesine, vitamins K_1 and B_{12} have all been identified as responsible for manifestations of allergic asthma. Antibiotics are more often to blame for occupational asthma, be they phenylglycine chloride used in betalactamine synthesis [167], penicillin and cephalosporins [168] or tetracyclines [169]. Asthma attacks may also be induced by sodium cromoglycate through the action of particles [105, 133] and by bronchodilators through the effect of propulsive gases [170].

Broncholitis obliterans

Drug-induced bronchiolitis obliterans has been described only during administration of D-penicillamine and rarely with gold salts and sulphasalazine [54, 171]. It consistently occurs in women, mostly those who are being treated for rheumatoid polyarthritis [171, 172]. Toxic doses range between 4.5–400 g (daily dosage of 500–1,250 mg) [172, 173]. Complications may appear at an early stage (15 days), but may also be observed within the first 3 yrs of treatment [171]. There is a rapid worsening of clinical signs: dyspnoea, occasionally with wheezing, cough, and rash [171, 172, 174]. Despite the prevailing bronchial involvement, crackles are often heard on auscultation [172, 173].

A chest roentgenogram is often normal, although distension and sometimes transient infiltrates can be noted [171, 172]. The sudden onset of an obstructive breathing pattern is severe and hardly responsive to bronchodilators [172, 173]. The response to corticosteroids is disputed; evolution towards chronic respiratory failure is common [171]. Histologically, obstructive lesions prevail in the small calibre airways (<2 mm). Larger airways are sometimes involved, but alveolar ducts are always spared. The obstruction is due to granulations present in the bronchiolar mucosa and extension may be endobronchial (polypoid aspect) or peribronchial (circumferential fibrosis of the bronchiolus). There is no associated emphysema. The alveoli are normal [54, 172, 173], little is known about the mechanisms involved and the exact role of D-penicillamine. Bronchiolitis obliterans has been described in patients with rheumatoid polyarthritis who were not on D-penicillamine [171]. Moreover, there has been no report of bronchiolitis obliterans when other diseases are treated with D-penicillamine.

Pulmonary vascular diseases

Aminorex-induced pulmonary hypertension

Aminorex, an anorexigen, has been incriminated in the occurrence of pulmonary hypertension (PHT). Many cases of PHT have been reported in countries where the drug has been marketed [175, 176]: 1–2% of aminorex users, more frequently women, were affected within 6–12 mths of the onset of therapy. Symptoms were those of primary PHT: dyspnoea on exertion, and later also at rest, haemoptysis, extreme distress, syncopes [177]. Mortality was about 12–20%, and most patients examined were very disabled during the years following the identification of the disease. A small number of patients recovered.

Histological examination showed hyperplasia of the intima and the media with stenosing fibrosis of the intima, *i.e.* plexogenic pulmonary arteriopathy, both responsible for right heart failure. The vascular lesions were identical to those observed in PHT related to high flow and left-to-right shunts [177]. In several animal species, aminorex administration results in a transient increase of pulmonary arterial pressure and pulmonary

vascular resistance but neither chronic precapillary PHT, nor chronic cor pulmonale could be reproduced.

Extracts of plants from the *Crotalia* family were used for an experimental animal model of PHT. BRAS *et al.* [178] showed that the alkaloids of *Crotalaria fulva* were responsible for a veno-occlusive liver disease. LALICH and MERKOW [179] noted that ingestion of *Crotalaria spectabilis* grains produced pulmonary arteriolar lesions in rats. When administered to rats in a single dose, fulvine, which is found in crotalaria's pyrolysidic alkaloids, causes vasocontriction and hypertrophy of pulmonary artery media, with right ventricular hypertrophy developing progressively a week after ingestion of fulvine. Smooth muscles develop in the arterial adventitia, with associated fibrinoid necrosis and arteritis. Such changes were observed in the pulmonary veins and venulae with walls thickening as a result of constriction, proliferation of muscle fibres and increasing amounts of collagen. All this would lead to luminal occlusion. Fulvine therefore appears to be toxic not only to pulmonary arteries but also to pulmonary veins; this is the reason why this drug was abandoned in experimental studies on PHT.

These animal data were later confirmed by findings in Kenyan children for whom a sorcerer had prescribed uronocrotalin and who presented with pulmonary hypertension (D. Heath, personal data). Accidental perfusion of micro-particles may induce pulmonary arteriolitis with PHT. Such is the case with abuse of drugs by drug addicts [180], as illustrated by reports of PHT induced by intravenous injection of blue velvet (powdered pyribenzamine hydrochloride in solution in blue-coloured paregoric) [181].

Pulmonary thromboembolisms

Most physicians are aware of the precautions or vigilance required in the use of drugs such as oestrogen-progesterone combinations, cortisone and its derivatives, ACTH, neuroleptics, catecholamines or the sudden discontinuation of anticoagulants [182]. Pulmonary thrombosis may also result from heparin: heparin-induced thrombocytopenia can be complicated by pulmonary embolism resulting from peripheral venous thrombosis [183, 184], but also by pulmonary arterial thrombosis through *in situ* aggregation of platelets in pulmonary vessels [185, 186]. This condition calls for discontinuation of heparin therapy, and institution of anti-vitamin K treatment.

Pleural and mediastinal manifestations

Lupoid reaction. Most of the iatrogenic pleural manifestations are due to lupoid reaction. The list of incriminated drugs grows continuously (procainamide, hydralazine, isoniazid, chlorpromazine, D-penicillamine, phenytoin, ethosuximide, carbamazepine, trimethadione, acebutolol, labetalol, pindolol, propanolol *etc.*). The clinical signs are those observed in spontaneous lupus, with a few special characteristics: particularly frequent occurrence of pleuro-pulmonary manifestations (more than 50% of cases) [187] joint and pericardiac involvement, low incidence of skin, kidney, nerve or blood involvement, less frequent occurrence in women, older average age. Biologically, the presence of antinuclear antibodies is frequent [188, 189]. Anti-histone antibodies are specific for lupoid reaction, in contrast to antibodies to single stranded DNA [190]. Other immunological changes may be encountered: hypocomplementaemia [191], circulating anti-coagulant [192]. Clinical signs sometimes occur with very small doses, but most often after several months of treatment (3 mths to 2 yrs). When treatment is discontinued, clinical and biological signs disappear within a few days or months [187].

Other pleural manifestations. Drug-induced pleural manifestations are often associated with parenchymal ones. This is the case with those reported in iatrogenic pulmonary oedema or with intake of certain drugs: nitromycin [193], busulphan [194], procarbazine [96], penicillin, PAS [111], nitrofurantoin and amiodarone [61], bromocriptine [195], gold salts (196). Acute or chronic pleural manifestations have been reported with methysergide. Effusions are uni- or bilateral and resolve upon discontinuation of treatment [197]. Pleural manifestations, whether isolated or associated with adenopathies, are sometimes noted with methotrexate (less than 1%) [198].

Mediastinal fibrosis and lipomatoses. Mediastinal fibrosis, described by GRAHAM *et al.* [100], during methergin treatment, leads to compression signs, and is often associated with retroperitoneal fibrosis. The mechanism is unknown. Most of the time, symptoms resolve after treatment is discontinued, but may sometimes persist [199]. Mediastinal lipomatoses observed in some 15% of iatrogenic Cushing's syndrome. These mediastinal infiltrations by adipose tissue are primarily asymptomatic and require no treatment [200].

Adenopathies. Drug-induced mediastinal adenopathies are very rare and usually concomitant with pleuro-pulmonary manifestations. They can be related to methotrexate, nitromycin [193] and hydantoin [108, 201].

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Maladies pulmaines d'origine médicament: Revue 1990. D. Israel-Biet, S. Labrune, G.J. Huchon.
RÉSUMÉ: Les manifestations pulmonaires consécutives à la prise de nombreux médicaments ont été rapportées, mais les études pathogéniques sont encore rares. Les mécanismes iatrogéniques devraient néanmoins être determinés avec précision, afin d'identifier les sujets chez qui de telles complications peuvent survenir, et d'utiliser de la façon la mieux appropriée certains des médicaments en cause. La possibilité d'une affection iatrogénique devrait toujours être évoquée chez les malades qui présentent des symptômes respiratoires. Les données des examens biologiques, bien que non spécifiques, contribuent à la compréhension des mécanismes lésionnels pulmonaires.
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