Cancer Chemother. Pharmacol. 4, 17–27 (1980)

Cancer Chemotherapy and Pharmacology

Lung Damage from Cytotoxic Drugs

C. H. Collis

Institute of Cancer Research and The Royal Marsden Hospital, Clifton Avenue, Sutton, Surrey, England

Summary. *Bleomycin, busulphan, and methotrexate are by far the commonest cytotoxic drugs to cause interstitial pneumonitis. However, many other cytotoxic drugs have been reported to produce similar lung damage. Combined effects of these drugs, and of the drugs with other agents that cause lung damage, such as oxygen and radiation, may result in enhancement of lung damage. Early diagnosis, made possible by awareness of this complication and its correct investigation, may reduce severe morbidity and mortality.*

In some instances, factors that predispose to lung damage are known, and these have been studied in experimental animals.

Introduction

Lung damage following cytotoxic chemotherapy was not described until 1961 [80], and only in the last 12 years have further cytotoxic drugs (shown in chronological order in Table 1) causing lung damage been reported [95, 111, 120]. Most of the drugs had been in use for several years before pulmonary toxicity was reported. The delay in recognizing the association was due not only to the infrequency of lung toxicity, but also to the difficulty of distinguishing it from much commoner conditions with similar clinical features.

The definitive diagnosis of lung damage due to cytotoxic drugs depends on three factors: a history of drug exposure, demonstration of lung damage, and exclusion of other causes of lung damage [16]. To fulfil these criteria it is necessary to have a clear history, a thorough search for micro-organisms, and lung histology. The most common presenting symptoms are dyspnoea, a dry cough, and fever, and there is also frequently malaise, anorexia, and weight loss. At first a common chest infection may be considered, but disproportionate dyspnoea, the presence of bilateral crepitations, and diffuse bilateral shadowing on the chest radiograph suggest a more generalized disorder. Abnormal lung function tests, typically a restrictive ventilatory defect and a diffusion defect, are nonspecific.

The differential diagnosis includes three main alternatives, a generalized infection such as *Pneumocystis carinii* or a viral pneumonia, tumour infiltration, or interstitial pneumonitis (or fibrosing alveolitis), the most common type of lung pathology seen with cytotoxic drugs. Bronchial brushings and transbronchial biopsy via the fibroptic bronchoscope will be diagnostic in the great majority of cases [32]. Occasionally open-lung biopsy may be necessary to obtain adequate histology.

The cytotoxic drugs reported to cause pulmonary damage can be grouped into four categories: antibiotics, alkylating agents, antimetabolites, and others. These are shown in Table 2, which also shows estimates of the frequency of occurrence of lung damage with each drug. It

Table 1. Lung damage from cytotoxic drugs: reports in chronological order

	Date of first report	Date of initial use
Busulphan	1961 [80]	1953
Cyclophosphamide	1967 [6]	1958
Methotrexate	1969 [1]	1948
Bleomycin	1969 [52]	1969
Procarbazine	1971 [60]	1963
Thioguanosine	1971 [36]	1971
6-Mercaptopurine	1972 [64]	1953
Azathioprine	1972 [96]	1961
Melphalan	1972 [21]	1958
Chlorambucil	1972 [97]	1955
BCNU	1976 [53]	1962
Mitomycin C	1978 [35]	1957
Uracil mustard	1978 [44]	1960
Methyl-CCNU	1978 [66]	1971
Neocarcinostatin	1978 [103]	1971

0344-5704/80/0004/0017/$ 02.20

Table 2. Incidence of lung damage from cytotoxic drugs

		Incidence	Number of cases[a]	
Antibiotic Cytotoxics	Bleomycin	10%	>30	
	Mitomycin C		6	
	Neocarcinostatin		1	
Alkylating Agents	Busulphan	2½%	>20	
	Cyclophosphamide		10	(+12)
	Chlorambucil		2	(+6)
	Melphalan		1	(+2)
	Uracil mustard		1	
	BCNU		10	(+15)
	Methyl-CCNU		1	
Antimetabolites	Methotrexate	7½%	>30	
	6-Mercaptopurine		1	(+2)
	Azothioprine		2	
	Thioguanosine		1	
Others	Procarbazine		2	(+3)

[a] The numbers in brackets indicate less clearly defined reports

can be seen that with only three drugs, bleomycin, busulphan, and methotrexate (MTX) does lung toxicity occur sufficiently frequently even to be considered in terms of a 'percentage' incidence. Lung toxicity with the other drugs amounts only to case reports, and many of these case reports are rather poorly substantiated (these numbers are shown in brackets).

These drugs will be described individually below.

Bleomycin

Bleomycin is the most important cytotoxic drug to cause lung damage, since lung toxicity, which occurs relatively frequently, is a major and often dose-limiting side effect [27, 43]. Reports of the incidence of pneumonitis and fibrosis vary from 3% [17] to 40% [27]. Clearly the reported incidence depends on how hard lung damage is searched for, but in reviewing over 1700 patients throughout the world Blum et al. [17] found the overall incidence to be 10%. Progressive fatal pulmonary fibrosis occurred in 1%.

The characteristic symptoms, dyspnoea, sometimes with a dry cough and fever, usually develop over a few weeks, 1–3 months after treatment. Although these features usually regress when the drug is discontinued, they may progress or actually develop after discontinuation of the treatment [27, 52, 111, 122]. Bilateral basal crepitations may be heard in the lower zones. An early chest radiograph may show a fine reticular or reticulomicronodular pattern in the lower zones [27]. Later the changes may become widespread, and patchy linear infiltrates indistinguishable from secondary infection, tumour spread, radiation change, or heart failure may be seen. Neither pleural effusions nor hilar lymphadenopathy have been noted [49, 122]. Gallium-67 scintography has been reported as a sensitive means of assessing lung damage, but is nonspecific [90].

Respiratory function tests are the most sensitive method of detecting early toxicity in clinical practice. There is a restrictive ventilatory defect, as shown by a reduced forced vital capacity (FVC), and a diffusion defect, which can be shown by a reduced 1-min single-breath carbon monoxide diffusion capacity (DL_{CO}) and by arterial hypoxaemia. The reduced DL_{CO} is probably the most sensitive indicator of subclinical toxicity. If the respiratory function is monitored at 2- to 4-weekly intervals lung damage can be minimized by the early withdrawal of bleomycin [23, 42, 56].

Light microscopy shows an interstitial pneumonitis with oedema of the alveolar walls and interstitial tissues, atypical proliferation of the alveolar epithelial cells, collapse of the alveoli, and hyaline membrane formation within the alveoli. There is hyperplasia and migration of Type II (granular) pneumocytes and macrophages into the alveolar lumen. Type I (membranous) pneumocytes are reduced. In more advanced cases there is collagen and reticulin deposition around the basement membranes. Hyperplasia of the bronchiolar muscle fibres and squamous metaplasia of the bronchiolar epithelium are also present [27, 70, 98]. Low-grade dysplasia can be seen on sputum cytology in 37% of bleomycin-treated patients, as against 10% of controls [10].

Electron microscopy confirms interstitial oedema, collagen deposition, accumulation of fibroblasts, lack of Type I pneumocytes, and proliferation of Type II pneumocytes. The abnormalities of Type II cells have been

thought to be consistent with surfactant impairment [11]. Further nuclear, nucleolar, and cytoplasmic abnormalities have been described, but their significance is difficult to interpret [26].

Although interstitial pneumonitis is the usual histopathological finding described, a 'hypersensitivity' pneumonitis has been reported in three patients. A patchy eosinophilic infiltrate surrounded the small airways and distal air spaces, and two cases had peripheral eosinophilia. This variant is particularly notable because of its favourable response to steroid therapy [48].

A number of factors influence the likelihood of pulmonary toxicity occurring. There is a greater incidence of lung toxicity with high doses. A 20% incidence may occur with cumulative doses above 500 mg [4], and a mortality of up to 5% [99]. It is therefore critically important to take into account any previous bleomycin therapy [25]. When the total dose of bleomycin is restricted to less than 300 mg, the incidence falls from 10% to 3%–5%. In general, the lower the total dose of bleomycin, the less the likelihood of lung toxicity [17, 43, 121]. This apparent dose relationship is countered by the fact that even with low total doses, such as 100–150 mg, fatal pulmonary toxicity may occur as an idiosyncratic tissue response [50], and the fact that functional assessment, mostly in asymptomatic individuals, has shown no correlation with dose [82, 122].

The route of administration and schedule may affect the incidence of lung toxicity. In a study of lymphomas there was less toxicity in patients receiving IM injections. It has therefore been suggested that the likelihood of lung toxicity is related to the peak blood levels [43]. Animal studies show that continuous infusion produces less lung damage and more inhibition of growth of the Lewis lung carcinoma than the same total dose given according to an intermittent schedule [106]. In man continuous infusion also produces greater tumour response, and although pulmonary toxicity occurs it may be less frequent than with intermittent administration [63].

Elderly patients (over the age of 70) are more susceptible to pulmonary toxicity [17, 114]. It has also been reported that lung toxicity occurs more frequently in patients with pre-existing poor lung function [114]. However, Yagoda and Krakoff [121] found that the initial pulmonary function studies did not affect the degree of subsequent lung toxicity.

Concurrent or previous irradiation of the lung, in itself insufficient to produce lung damage, leads to increased lung toxicity from bleomycin [31, 77, 99]. Bleomycin lung damage may also be enhanced by concurrent chemotherapy [100]. Severe lung toxicity has been reported many months after bleomycin in patients subjected to over-oxygenation during anaesthesia [38], and oxygen enhancement might also account for the increased lung damage reported when bleomycin 120 mg and local radiotherapy had been given 6 weeks before oesophageal resection [77].

In conclusion, at the present time, there is no reliable way of predicting bleomycin lung toxicity, and therefore no absolute contraindications. Particular care should be taken in the elderly, those with poor lung function, in those receiving more than 300 mg total dose or other pulmonary toxic agents such as radiotherapy, oxygen, particularly during anaesthesia, and concurrent chemotherapy. Patients should be monitored every 2–4 weeks. Signs and symptoms should be sought; chest X-rays and lung function studies with the FVC and the DL_{CO} or equivalent test should be carried out. If, following noninvasive investigation, there remains the possibility of a diagnosis of bleomycin-induced lung damage, histological confirmation, preferably via fibroptic endoscopy, should be sought. In this way, lung toxicity may be identified as early as possible. Bleomycin should be stopped, and avoided in further therapy. Prednisone, 60–100 mg daily, reverses pulmonary damage in some cases [121].

As yet, no agent that prevents bleomycin-induced lung damage has been established, but one report of the use of steroids is encouraging. Although steroids failed to prevent bleomycin lung damage in animal experiments [17] it has recently been reported that concurrent therapy with prednisone prevented side effects, including lung toxicity, in a series of 40 patients receiving a total dose of 420 mg bleomycin [74].

The pathogenesis of bleomycin-induced lung toxicity has been extensively examined in animals. It was initially observed in dogs [37], but most of the subsequent work has been on rodents. Adamson and Bowden [2, 3] have examined the lungs of mice by light and electron microscopy at weekly intervals during and following a 4-week course of twice-weekly bleomycin. They found similar histological changes to those seen in man. The initial site of injury appeared to be the intima of the pulmonary arteries and veins. The endothelial cells became oedematous and were separated from the basement membrane by large blebs. Lymphocytes and plasma cells infiltrated the perivascular spaces. These changes were seen at 2 weeks. At 4 weeks similar changes were seen in the capillaries and there was multifocal necrosis of Type I pneumocytes. There was diffuse interstitial oedema and the air sacs contained numerous vacuolated macrophages. From 4 weeks onwards, there was hypertrophy of the Type II pneumocytes and progressive intra-alveolar and septal fibrosis. Similar changes have been reported by others, not only in mice [8, 59, 88, 105], but also in hamsters, in which the drug was given intratracheally [108, 112], in baboons [71], and in pheasants [12].

These histological changes are due to a direct toxic effect of bleomycin on the lung, and are probably not specific, but represent a general reaction of the lung to injury [12, 58, 59]. Supportive evidence for this mechanism

of action is the finding of relatively high levels of bleomycin in the lungs as well as in the skin [54], and the fact that the occurrence of damage is dose-related in man and the extent of lung damage is dose-related in experimental animals [105].

Methotrexate

Pneumonitis was first reported in 38 out of 93 children with acute lymphocytic leukaemia being treated with twice-weekly oral methotrexate (MTX) [1]. There have subsequently been at least 40 detailed reports, mostly in leukaemic patients on oral maintenance therapy, but also in nonmalignant conditions [20, 72, 119]. Although there have been no prospective studies, and therefore the true incidence is not known, on reviewing the case records of 92 patients treated with MTX Sostman et al [110] found seven (7.5%) with well-documented MTX pneumonitis. However, in many large drug trials pulmonary toxicity has not been reported [120].

Pulmonary toxicity from MTX is difficult to predict. Pneumonitis has occurred after a wide range of doses from 40 mg to 41 g, and from as early as 12 days to as much as 5 years after the start of treatment with the drug [110]. The development of pneumonitis appears to be virtually independent of the dose or duration of treatment, although it has not been reported with doses of less than 20 mg/week [110]. There is also no correlation with age, sex, or underlying disease. It has occurred in patients receiving concurrent steroids and following leucovorin rescue, so that neither of these agents appears to prevent pneumonitis. Pneumonitis has mostly occurred in patients receiving the drug orally, but has also been reported following IM [1, 92], IV [76], and intrathecal administration [40, 65]. It is therefore probably the frequency rather than the route of administration that is important [110]. Other concurrent cytotoxic drugs may increase the likelihood of lung toxicity [15, 113]. However, enhancement of radiation pneumonitis has not been reported.

A dry cough, fever, and dyspnoea are usually the presenting symptoms, although prodromal symptoms of headache and malaise may occur. Cyanosis, tachypnoea and basal crepitations may be found on examination. About half the cases develop eosinophilia [20, 110]. The chest radiograph shows bilateral linear or reticulonodular infiltrates at the bases and midzones in most cases, but a range of appearances from normal to widespread opacification has been reported. Pleural effusions and hilar lymphadenopathy have also been reported [33, 110]. Lung function tests may show a diffusion defect and restrictive ventilatory defect. Although lung function recovers, a residual defect often persists, which does not deteriorate when MTX is given again later [110].

Histological examination of the lungs reveals diffuse alveolar damage, atypical cells, hyaline membranes, and interstitial infiltrates of mononuclear cells and also of plasma cells and eosinophils in some cases. A granulomatous response with multinucleate giant cells is sometimes seen [20, 89]. Interstitial fibrosis, if present is usually mild [33, 110], but in some cases it can be marked [13, 61, 76].

Most patients recover whether or not treated with steroids and whether or not MTX is stopped [110], and once improvement begins resolution is rapid [20, 72]. However, some develop chronic pulmonary changes [76]. This tends to occur in elderly patients and to develop insidiously and progressively; it has been fatal in three out of four cases [13, 61]. Although there is no definite evidence that stopping MTX improves ultimate recovery, there is evidence that by stopping MTX and commencing treatment with corticosteroids recovery time is quartered and mortality may be reduced [110]. At present, this is the recommended management. It has also been reported that daunorubicin may have a beneficial effect. The administration of daunorubicin in three cases of MTX pneumonitis was followed by prompt recovery [83].

A diagnosis is therefore important not only to identify other treatable conditions, such as *pneumocystis carinii*, but also to ensure optimal management of MTX pneumonitis. For a definitive diagnosis, histological confirmation either by an open-lung biopsy or by fibroptic bronchoscopy [32] is required. Once the patient has recovered, MTX can be cautiously reintroduced with apparently no risk of recurrence of pneumonitis [110], unless marked fibrosis is present [13, 61].

The nature of pulmonary toxicity with MTX differs from that seen with bleomycin and the alkylating agents in three principal ways. Firstly, histology shows giant-cell granulomas and seldom shows any fibrosis. Secondly, patients usually show marked or complete resolution. Thirdly, the drug may be reintroduced after recovery from pulmonary toxicity, without causing any apparent further damage. In addition, pulmonary toxicity following MTX appears to be independent of dose.

The pathogenesis of MTX lung damage remains unknown and there are no reports of its being reproduced in experimental animals. An immunological mechanism has been postulated because of the presence of the peripheral eosinophilia and granulomas and the lack of a dose relationship. However, the anti-inflammatory and immunosuppressive properties of MTX, and the lack of a response to a second challenge make this unlikely. A direct toxic effect has been postulated [36, 110] and the moderately high levels of MTX found in the lung [5] also support this theory.

Busulphan

Interstitial pulmonary fibrosis was reported in 1961 [80], which was the first time a cytotoxic drug had been shown

to cause lung damage. Many further reports of lung toxicity have followed, which have been reviewed [95, 111, 120].

The incidence of the true 'busulphan lung syndrome', i.e., symptomatic lung damage, histologically confirmed, is difficult to assess, but is probably not more than about 2.5% [62]. If only post-mortem histology is considered, the incidence may appear as high as 6 out of 14 cases (43%) [46]. On reviewing the post-mortem histology of 81 cases of chronic myeloid leukaemia, only half of whom had received busulphan, Kirschner and Esterly [62] found many characteristic features of interstitial pneumonitis, such as fibrinous oedema, interstitial fibrosis, alveolar epithelialization, and atypism of alveolar cells, occurred equally in both groups. A few features, e.g., hyaline membrane formation and dysplasia of the bronchial epithelium, were predominant in the busulphan-treated group. Extensive honeycombing occurred in both groups. Although distinctive large cells with hyperchromatic nuclei ('busulphan cells') were seen in four patients, all of whom had received busulphan, only one had associated pulmonary fibrosis and respiratory distress. Littler and Ogilvie [67] reported 6 of 21 cases with reduced gas transfer (DL_{CO}), but only one was subsequently confirmed to have interstitial pneumonitis.

The clinical features are similar to those of bleomycin pulmonary toxicity, but the development is usually more insidious. Dyspnoea, sometimes associated with a dry cough and fever, usually develops over several months 3—4 years after the onset of treatment, although it has been reported as early as 9 months and as late as 10 years after [67]. Occasionally the onset may be fulminant, acute, or subacute [41], but such an apparent acute onset may be due to a supervening infection [87]. Cyanosis, basal crepitations, and, rarely, Addisonian signs may be found [45]. Chest radiographs show similar changes to those seen with bleomycin lung damage, with an early reticulonodular pattern, or more often diffuse linear opacities. In addition, pleural effusions and virtually normal radiographs have been reported [107]. Impaired respiratory function is reflected by arterial hypoxaemia and a reduced DL_{CO}. Sometimes a restrictive ventilatory defect is found, although this occurs less often than with bleomycin lung toxicity [111]. The histological appearances found with interstitial pneumonitis have been described above. It is thought that the atypical cells represent a nonspecific response of Type II (granular) pneumocytes to injury [46, 68].

Few factors that influence the development of pulmonary damage have been reported. Although lung damage usually follows prolonged drug administration, no critical total dose has been cited. As with bleomycin, radiation pneumonitis may be enhanced, even when several years have lapsed between drug and irradiation [109].

Following early diagnosis, confirmed at fibroptic bronchoscopy, busulphan should be withdrawn. Despite this the lung damage frequently progresses and the patient dies [95], the median survival from onset of symptoms being 5 months [87]. Steroids are often given, but it is doubtful whether they affect the course of pulmonary disease.

Cyclophosphamide

It is now well established that the commonly used alkylating agent cyclophosphamide can cause pulmonary toxicity [84]. This statement is based upon ten well-substantiated case reports [6, 19, 28, 73, 84, 93, 111, 116, 117], and in addition there are several less well-substantiated reports [84, 95, 111].

Dyspnoea, often associated with a dry cough and fever, has developed from 3 weeks to 3 years [84], and in one case 8 years [117], after commencing cyclophosphamide treatment, and in four cases from 2 months [93] to 6 years [117] after discontinuation of cyclophosphamide [93, 116, 117]. The symptoms develop over a period of a few days to a few weeks. The time course is thus intermediate between that of busulphan and that of bleomycin lung damage [84]. Bilateral basal crepitations may be heard, and the radiological changes are similar to those of bleomycin and busulphan. Similar histological changes, such as bronchoalveolar cell dysplasia, alveolar septal thickening with a mild mononuclear cell infiltrate, and interstitial fibrosis, are found.

On withdrawal of the cytotoxic drug therapy the pulmonary damage resolved in five cases [19, 28, 73, 84, 111], although in one this took several months [73]. Concurrent steroids may aid recovery [84, 111]. In five cases, three of whom were children [93, 117], the pulmonary damage progressed relentlessly.

Cyclophosphamide-induced lung damage has been studied in experimental animals. It was first reported in dogs, which died of pulmonary oedema, but this may have been due to myocardial toxicity, which was also seen [78]. Gould and Miller [39] discovered that sclerosing alveolitis occurred in rats treated with cyclophosphamide. Perivascular oedema, septal thickening, and minute haemorrhages were evident as early as 48 h after drug administration. By 4—7 days after treatment many of the alveoli contained debris and macrophages. Focal hyaline membrane formation was seen and there was alveolar cell hyperplasia with increased septal cellularity and increased interstitial material. Subsequently these changes persisted and septal fibrosis progressed. This pattern of alveolar injury is similar to that seen in man. However, it is not specific, since many cytotoxic drugs, and a variety of other lung-toxic agents produce similar responses in humans and animals [39, 95].

Chlorambucil

Pulmonary fibrosis following chlorambucil and similar to that seen with the other alkylating agents was first briefly reported in four cases by Rubio [97]. Four further cases, including two detailed case histories [22, 57], have since been reported [22, 57, 94].

Dyspnoea, fatigue, weakness, anorexia, and weight loss develop subacutely over a period of 2–3 weeks, usually following a period of prolonged daily oral drug administration. Fever may be present, and the signs, radiographic findings, and lung function defects are similar to those seen with the other alkylating agents. Light and electron microscopy also show similar changes to those seen with busulphan and cyclophosphamide [22].

Although six cases were fatal [57, 94, 97], in one well-documented case resolution followed discontinuation of chlorambucil and institution of steroid therapy [22]. In another case the symptoms improved on withdrawal of the drug, recurred when the drug was reintroduced 20 months later, and again resolved on withdrawal of the drug [94].

Melphalan

Only three cases of melphalan-induced lung damage have been reported [21, 115]. However, atypical epithelial proliferation was found in six out of eleven cases of myeloma treated with melphalan, but in none of a matched control group of myeloma patients [115].

The symptoms developed over 2–10 days, following 3–16 months of oral melphalan. Despite withdrawal of melphalan, and in two cases treatment with steroids, all the patients deteriorated and died within 3 weeks of the onset of symptoms.

BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea)

Eight cases of pulmonary fibrosis in which BCNU was the only drug being given have been reported recently [9, 14, 29, 47, 102]. In another two cases combination chemotherapy that did not include other drugs reported to cause lung toxicity was being given [24, 91]. A further ten cases have been reported in which cyclophosphamide was amongst other cytotoxic drugs given with BCNU [29, 101]. In addition, 'pulmonary infiltrates' have been reported in four children treated with a mean dose of 150 mg/m^2 BCNU daily for 3 days [53].

A dry hacking cough, followed by progressive dyspnoea, may develop from 2 months [53] to 3 years [47] after the onset of treatment. Fever has not been reported. Coarse basal crepitations may be heard, and the chest radiograph shows bilateral diffuse pulmonary shadowing mainly at the bases. Respiratory function tests show a restrictive and diffusion defect, and histological examination reveals interstitial pneumonitis and fibrosis.

Seven of the ten established cases died, one of superimposed pneumonia during steroid therapy, to which she was responding [9], two following open-lung biopsy [14, 47], and four of respiratory failure from 3 months [91] to 2 years [24] after the onset of symptoms. The other cases showed no progression once the BCNU was stopped [102]. Steroids were also reported to produce a response in one case with pulmonary infiltrates, which cleared within 2 weeks [53].

BCNU lung toxicity is probably dose-related, since most of the cases have occurred following prolonged administration resulting in a high total dose. In a series of 28 patients receiving BCNU 80 mg/m^2 for 3 days every 8 weeks, the four patients who developed pulmonary fibrosis had received a mean total dose of 2,030 mg/m^2, whereas the other 24 patients had received only 710 mg/m^2 [102]. Concurrent cyclophosphamide may reduce the total dose of BCNU at which lung toxicity occurs [29, 101]. It has also been suggested that BCNU enhances radiation-induced lung damage [53].

Lung toxicity was reported in the early studies of toxicity of the nitrosoureas, and was found in dogs and rhesus monkeys given BCNU [18], but more detailed animal studies have not been reported.

Mitomycin C

Until recently, pulmonary toxicity was not recognized as a clinical complication of mitomycin C, although lung damage had been recorded in two of 40 dogs tested during early toxicity studies and also in rodents [85]. In 1971 Shimosato et al [104] suggested that mitomycin C might initiate pulmonary toxicity, which is subsequently triggered by bleomycin.

Six histologically proven cases of mitomycin C lung damage have now been reported [7, 35, 81], four of whom had received other chemotherapy that was most unlikely to have been causative. Histology in all these cases showed interstitial pneumonitis with moderate fibrosis. Dyspnoea and cough, in one case associated with chills and sweats, and in another with pleuritic pain, developed after 3–6 months of mitomycin treatment. The patients were afebrile and bilateral basal crepitations were heard. Chest radiographs showed diffuse reticular infiltrates, sometimes with fine nodularity, with a pleural effusion and pulmonary hilar prominence in one case. Three patients improved on stopping the drug and commencing steroids, but ultimately died of their tumours [81]; progression was arrested by stopping the drug in one case [35], and two cases died of pulmonary insufficiency [7].

6-Mercaptopurine (6-MP) and Azathioprine

Sostman [111] reported a case of 6-MP-induced pneumonitis in a 2-year-old child with acute leukaemia in remission following 3 days of treatment with 6-MP. The chest radiograph showed fine nodular infiltrates, and an open-lung biopsy revealed interstitial pneumonitis with no evidence of fibrosis. The patient recovered completely after discontinuing the drug. Two other cases of pulmonary toxicity have been described in the foreign literature [64, 79] and there has been at least one report of 6-MP combined with other therapy resulting in interstitial pneumonitis [15].

There have also been two case reports of similar typical pneumonitis following azathioprine, a drug which is metabolized to 6-MP [96, 118]. In both cases rapid resolution followed cessation of the drug.

Procarbazine

'Hypersensitivity' to procarbazine with pleuropulmonary reactions has been reported in two patients with Hodgkin's disease being treated with mustine, vincristine, procarbazine, and prednisone (MOPP) [30, 60]. Only a few hours after taking the drug, the patients developed nausea, fever, a dry cough, and dyspnoea. There was mild peripheral eosinophilia. The chest radiograph showed bilateral interstitial infiltrates and a right pleural effusion. Within 24 h of the withdrawal of procarbazine, the syndrome resolved. It recurred with the next course of procarbazine and again cleared on stopping the drug. The diagnosis was then confirmed with a specific challenge dose of procarbazine.

In three further patients with Hodgkin's disease receiving MOPP symptoms developed over several weeks, and the histologically proven interstitial pneumonitis resolved following treatment with prednisone [34, 69]. In another histologically proven case, procarbazine may have had an additive effect with other agents, although it was not considered to have been the primary cause of lung damage [28].

Other Drugs

Other drugs with which interstitial pneumonitis and fibrosis have been reported include methyl-CCNU [66], uracil mustard [44], thioguanosine [36], and neocarcinostatin [103]. Pulmonary oedema of unknown cause has been reported with IV vinblastine [55].

Combination Chemotherapy

Many of the reports of pulmonary damage have concerned patients treated with several cytotoxic drugs [21, 28–30, 34, 44, 60, 89, 100, 101, 113]. One principal drug is usually singled out as the most commonly reported drug to cause lung toxicity, and therefore the most likely culprit. However, combined effects probably do occur, particularly when two or more of the agents have been shown to cause lung damage when given individually. As a result, a higher incidence of lung damage than anticipated might be seen [113], or lung damage may occur at lower drug doses than would otherwise have been anticipated, e.g., with BCNU and cyclophosphamide [29, 101] and with

Table 3. The response of the lungs to cytotoxic drugs

Type of response	Characteristics	Drugs
Acute reactive	Rapid development; eosinophilia; granulomas; reversible; responsive to steroids	Procarbazine Methotrexate (Thioguanosine) (Bleomycin) (6-Mercaptopurine) (Azathioprine) (Busulphan)
Subacute	Intermediate	Bleomycin Mitomycin C (Neocarcinostatin) (Uracil mustard)
Chronic fibrotic	Insidious onset; predominant fibrosis; progressive; no response to steroids	(Methotrexate) (Melphalan) Chlorambucil Cyclophosphamide (Methyl-CCNU) BCNU Busulphan

bleomycin and adriamycin, cyclophosphamide, vincristine, and prednisone (BACOP) [100].

This combined effect may occur not only when several drugs are given together or within a short time of each other, but also when one drug is given a considerable time after another drug, such as has been documented with uracil mustard after busulphan [44] and thioguanosine after MTX [36]. If the initial damage is subclinical such combined effects would be difficult to demonstrate, and thus such combined effects may have occurred undetected in many of these reported cases of drug-induced lung damage.

Cytotoxic Drugs with Irradiation or Oxygen Therapy

Of the drugs described above, bleomycin [31, 77, 99] and busulphan [109] have been reported to enhance radiation lung damage. In addition, several other cytotoxic drugs, not in themselves apparently toxic to the lung, may enhance radiation damage, and these have been described elsewhere in detail and will only be briefly discussed here [86]. As with drug-drug combinations, enhancement of radiation damage can occur even when the drugs are given a considerable time from irradiation. This is being studied in experimental animals at this laboratory. In general, maximal lung damage occurs when the cytotoxic drug is given with irradiation; if given a month before irradiation only slight enhancement is seen, but if given a month after irradiation as much lung damage can occur as when the drug is given with irradiation. Although this general rule applies to most drugs, the exact extent of lung damage following combined cytotoxic drugs and irradiation varies with different drugs, the time between drug and irradiation, and the dose and schedule of both drug and irradiation (unpublished data). With a fuller understanding of these relationships, it may be possible to minimize lung damage whilst maintaining antitumour effect.

Oxygen is a further agent that may cause pulmonary toxicity and to which the cancer patient may be exposed. Several cases of lung damage have been described in patients who received oxygen therapy as well as cytotoxic chemotherapy [75]. Pulmonary toxicity has also been reported following routine oxygen exposure during anaesthesia many months after chemotherapy with bleomycin, which itself had had no apparent effect on the lungs [38].

Discussion

Nearly all the cytotoxic drugs discussed in this paper are thought to produce lung damage by a direct toxic effect on the lung parenchyma. Procarbazine is an exception, which can produce a typical allergic pulmonary eosinophilia [30, 60]. The direct toxic effect of these cytotoxic drugs is proposed largely on the basis of lung morphology. The histology of bleomycin-induced lung damage has been carefully examined in man [11, 70, 98] and in experimental animals [2, 8, 12, 59]. There are also extensive reports of busulphan lung histology in man [68, 87] and of cyclophosphamide-induced lung damage in man [84] and in rats [39]. In all these cases, and in most of the case reports of other drug-induced lung damage, there is early pneumonitis with interstitial oedema, degeneration of the Type I cells, hyperplasia of the Type II cells, and vascular damage followed by progressive fibrosis. These changes represent a direct general reaction of the lung to noxious agents, also being seen with radiation damage and oxygen toxicity. The histological features of MTX-induced lung damage, although slightly different, can also be ascribed to direct drug-induced alveolitis [110].

Although a direct toxic action may be the common mechanism of lung damage, the nature of the response varies according to the individual drug. The response of the lung may be graded from acute reactive through subacute to chronic fibrotic reactions, as shown in Table 3. The drugs are listed in order from the hypersensitive allergic response of procarbazine through to the progressive fibrosis of the busulphan lung syndrome. The term acute reactive is used in preference to hypersensitivity since, as has already been discussed with MTX, an allergic mechanism may not be involved [110]. Drugs are shown in brackets in Table 3 if there are only one or two case reports, and to indicate unusual responses that have been reported with bleomycin, MTX, and busulphan [13, 41, 61, 68]. The nature of the response does not appear to depend on dose or schedule, and is therefore presumably related to qualitative differences in the metabolism of the drugs by the lung parenchyma.

The occurrence of lung damage, however, is related to the dose and scheduling in some cases, as has been discussed above with bleomycin and busulphan. However, for other drugs there is little or no evidence of a dose relationship. This apparently sporadic occurrence may be because the human therapeutic doses are so low on the dose effect plot. If higher doses could be tolerated in man a more definite relationship of dose to the development of lung damage might be seen. Further evidence for such dose dependency comes from animal studies. Reproducible and predictable lung damage occurs following administration of bleomycin and cyclophosphamide to rodents [39, 105]. Furthermore, studies in this laboratory (unpublished data) show that the extent of such lung damage is dose-dependent.

Conclusion

Only three drugs, bleomycin, busulphan, and MTX, have been reported to cause lung damage with a measurable

frequency. Even these reported frequencies may be somewhat high, due to the innate tendency of reported data to be selective, to changes in drug schedules currently in use, and even to possible changes in the quality of the drugs used. However, the number of drugs that can cause lung damage is now considerable, and is well substantiated by the continuing reports.

Those regularly using cytotoxic drugs should be fully aware of the possibility of cytotoxic drug-induced lung damage, since if it is promptly and correctly diagnosed and treated severe morbidity and mortality can be reduced. In addition, attention should be given to drug-drug interactions, and particular care taken when there is the possibility of interaction with other potentially lung-toxic agents, such as radiation and oxygen.

Acknowledgements: I should like to thank Mrs. Annabel Thomas for typing the script.

References

1. Acute Leukaemia Group B (1969) Acute lymphocytic leukaemia in children. JAMA 207:923
2. Adamson IYR, Bowden DH (1974) The pathogenesis of bleomycin induced pulmonary fibrosis in mice. Am J Pathol 77:185
3. Adamson IYR, Bowden DH (1977) Origin of ciliated alveolar epithelial cells in bleomycin-induced lung injury. Am J Pathol 87:569
4. Agre K (1974) Bleomycin overview of clinical evaluation in the United States. Read before the New Drug Seminar, Bethesda, Maryland
5. Anderson LL, Collins GJ, Ojima Y, Sullivan RD (1970) A study of the distribution of methotrexate in human tissues and tumours. Cancer Res 30:1344
6. André R, Rochant H, Dreyfus B, Duhamel G, Péchère J-Cl (1967) Fibrose interstitielle diffuse du paumon au cours d'une maladie de Hodgkin traitée par des doses élevées d'endoxan. Bull Soc Med Hop Paris 118:1133
7. Andrews AT, Bowman HS, Patel SB, Anderson WM (1979) Mitomycin and interstitial pneumonitis. Ann Intern Med 90:127
8. Aso Y, Yoneda K, Kikkawa Y (1976) Morphologic and biochemical study of pulmonary changes induced by bleomycin in mice. Lab Invest 35:558
9. Bailey CC, Marsden HB, Morris Jones PH (1978) Fatal pulmonary fibrosis following 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) therapy. Cancer 42:74
10. Bedrossian CWM, Corey BJ (1976) Abnormal sputum cytopathology during chemotherapy with bleomycin. Acta Cytol 20:586
11. Bedrossian CWM, Luna MA, Mackay B, Lichtiger B (1973) Ultrastructure of pulmonary bleomycin toxicity. Cancer 32:44
12. Bedrossian CWM, Greenberg SD, Yawn DH, O'Neal RM (1977) Experimentally induced bleomycin sulfate pulmonary toxicity. Arch Pathol Lab Med 101:248
13. Bedrossian CWM, Miller WC, Luna MA (1979) Methotrexate-induced diffuse interstitial pulmonary fibrosis. South Med J 72:313
14. Bellot PA, Valdisseri RO (1979) Multiple pulmonary lesions in a patient treated with BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) for glioblastoma multiforme. Cancer 43:46
15. Bhat KSS, Anderson KR, Stewart RDH (1974) Lung disease associated with methotrexate therapy. Aust NZ J Med 4:277
16. Blum RH, Carter SK (1973) Pulmonary complications of cancer chemotherapy. N Engl J Med 288:266
17. Blum RH, Carter SK, Agre K (1973) A clinical review of bleomycin – A new antineoplastic agent. Cancer 31:903
18. Carter SK, Newman JW (1968) Nitrosoureas 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) and 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU) – clinical brochure. Cancer Chemother Rep [Pt 3] 1:115
19. Case Records of the Massachusetts General Hospital (1978) Case 12–1978. N Engl J Med 298:729
20. Clarysse AM, Cathey WJ, Cartwright GE, Wintrobe MW (1969) Pulmonary disease complicating intermittent therapy with methotrexate. JAMA 209:1861
21. Codling BW, Chakera TMH (1972) Pulmonary fibrosis following therapy with melphalan for multiple myeloma. J Clin Pathol 25:668
22. Cole SR, Myers TJ, Klatsky AU (1978) Pulmonary disease with chlorambucil therapy. Cancer 41:455
23. Comis RL, Ginsberg SJ, Kuppinger M, Auchincloss JH (1978) Single breath CO diffusion capacity as an indicator of subclinical bleomycin pulmonary toxicity in testicular cancer patients. Proc Am Assoc Cancer Res 19:236
24. Crittenden D, Tranum BL, Haut A (1977) Pulmonary fibrosis after prolonged therapy with 1,3-bis-(2-chloroethyl)-1-nitrosourea. Chest 72:372
25. Crooke ST, Einhorn LH, Comis RC, D'Aoust JC, Prestayko AW (1978) The effects of prior exposure to bleomycin on the incidence of pulmonary toxicities in a group of patients with disseminated testicular carcinomas. Med Pediatr Oncol 5:93
26. Daskal Y, Gyorkey F, Gyorkey P, Busch H (1976) Ultrastructural study of pulmonary bleomycin toxicity. Cancer Res 36:1267
27. De Lena M, Guzzon A, Monfardini S, Bonadonna G (1972) Clinical, radiologic and histopathologic studies on pulmonary toxicity induced by treatment with bleomycin (N.S.C.-125066). Cancer Chemother Rep 56:343
28. Dohner VA, Ward HP, Standord RE (1972) Alveolitis during procarbazine vincristine and cyclophosphamide therapy. Chest 62:636
29. Durant JR, Norgard MJ, Murad TM, Bartolucci AA, Langford KH (1979) Pulmonary toxicity associated with bischloroethylnitrosourea (BCNU). Ann Intern Med 90:191
30. Ecker MD, Jay B, Keohane MF (1978) Procarbazine lung. Am J Roentgenol 131:527
31. Einhorn L, Krause M, Hornback N, Furnas B (1976) Enhanced pulmonary toxicity with bleomycin and radiotherapy in oat cell lung cancer. Cancer 37:2414
32. Ellis JH (1975) Transbronchial lung biopsy via the fibroptic bronchoscope. Chest 68:524
33. Everts CS, Westcott JL, Bragg DG (1973) Methotrexate therapy and pulmonary disease. Radiology 107:539
34. Farney RJ, Morris AH, Armstrong JD, Hammer S (1977) Diffuse pulmonary disease after therapy with nitrogen mustard, vincristine procarbazine and prednisone. Am Rev Respir Dis 115:135
35. Fielding JWL, Stockley RA, Brookes VS (1978) Interstitial lung disease in a patient treated with 5 Fluorouracil and mitomycin C. Br Med J 2:602
36. Filip DJ, Logue GL, Harle TS, Farrar WH (1971) Pulmonary and hepatic complications of methotrexate therapy of psoriasis. JAMA 216:881

37. Fleischman RW, Baker RJ, Thompson GR, Schaeppi UH, Illievski VR, Cooney DA, Davis RD (1971) Bleomycin-induced interstitial pneumonia in dogs. Thorax 26:675
38. Goldiner PL, Carlon GC, Cvitkovic E, Schweizer O, Howland W (1978) Factors influencing postoperational morbidity and mortality in patients treated with bleomycin. Br Med J 1:1664
39. Gould VE, Miller J (1975) Sclerosing alveolitis induced by cyclophosphamide. Am J Pathol 81:513
40. Gutin PH, Green MR, Bleyer WA, Bauer VL, Wiernik PH, Walker MD (1976) Methotrexate pneumonitis induced by intrathecal methotrexate therapy. Cancer 38:1529
41. Gyger M, Legresley L-P, Boulianne P, Lacombe M, Lavallée R, Bonny Y, Boileau J, D'Angelo G (1977) Hétérogénéité clinique de la pneumopathie au myeleran. Union Med Can 106:1522
42. Haas C, Haguet JF, Basset JM, Lebas FX, Choubrac P (1976) Les fibroses pulmonaires de la bléomycine. Thérapie 31:723
43. Haas CD, Coleman CA, Gottlieb JA, Haut A, Luce JK, Talley RW, Samal B, Wilson HE, Hoogstraten B (1976) Phase II evaluation of bleomycin – a Southwest Oncology Group Study. Cancer 38:8
44. Hankins DG, Sanders S, MacDonald FM, Drage CW (1978) Pulmonary toxicity recurring after a six-week course of busulfan therapy and after subsequent therapy with uracil mustard. Chest 73:415
45. Harrold BP (1966) Syndrome resembling Addison's disease following prolonged treatment with busulphan. Br Med J 1:463
46. Heard BE, Cooke RA (1968) Busulphan lung. Thorax 23:187
47. Holoye PY, Jenkins DE, Greenberg SD (1976) Pulmonary toxicity in long-term administration of BCNU. Cancer Treat Rep 60:1691
48. Holoye PY, Luna MA, Mackay B, Bedrossian CWM (1978) Bleomycin hypersensitivity pneumonitis. Ann Intern Med 88:47
49. Horowitz AL, Friedman M, Smith J, Yagoda A, LaMonte C, Watson RC (1973) The pulmonary changes of bleomycin toxicity. Radiology 106:65
50. Iacovino JR, Leitner J, Abbas AK, Lokich JJ, Snider GL (1976) Fatal pulmonary reaction from low doses of bleomycin: An idiosyncratic tissue response. JAMA 235:1253
51. Ichikawa T (1976) Studies of bleomycin: Discovery of its clinical effect, combination treatment with bleomycin and radiotherapy, side effects and long term survival. Gann Monogr Cancer Res 19:99
52. Ichikawa T, Nakano I, Hirokawa I (1969) Bleomycin treatment of the tumours of penis and scrotum. J Urol 102:699
53. Iriarte PV, Hananian J, Cortner JA (1966) Central nervous system leukaemia and solid tumours of childhood: Treatment with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Cancer 19:1187
54. Ishizuka M, Takayama H, Takeuchi T, Umezawa H (1967) Activity and toxicity of bleomycin. J Antiobiot (A) 20:15
55. Israel RH, Olson JP (1978) Pulmonary oedema associated with intravenous vinblastine. JAMA 240:1585
56. Izbicki RM, Baker LH (1977) Prediction of early pulmonary toxicity due to bleomycin (BLEO) in cancer patients treated with combination therapy. Proc Am Soc Clin Oncol 18:345
57. Jacobs S (1975) The Hamman Rich Syndrome following treatment of lymphoma with chlorambucil. J La State Med Soc 127:311
58. Jones AW (1978) Bleomycin lung damage: the pathology and nature of the lesion. Br J Dis Chest 72:321
59. Jones AW, Reeve NL (1978) Ultrastructural study of bleomycin-induced pulmonary changes in mice. J Pathol 124:227
60. Jones SE, Moore M, Blank N, Castellino RA (1972) Hypersensitivity to procarbazine (Matulane) manifested by fever and pleuropulmonary reaction. Cancer 29:498
61. Kaplan RL, Waite DH (1978) Progressive interstitial lung disease from prolonged methotrexate therapy. Arch Dermatol 114:1800
62. Kirschner RH, Esterly JR (1971) Pulmonary lesions associated with busulfan therapy of chronic myelogenous leukaemia. Cancer 27:1074
63. Krakoff IH, Cvitkovic E, Currie V, Yeh S, LaMonte C (1977) Clinical and pharmacologic and therapeutic studies of bleomycin given by continuous infusion. Cancer 40:2027
64. Lampert F (1978) Lungenveränderungen bei der akuten lymphoblastischen Leukämie. Radiologe 8:308
65. Lascari AD, Strano AJ, Johnson WW, Collins GP (1977) Methotrexate-induced sudden fatal pulmonary reaction. Cancer 40:1393
66. Lee W, Moore RP, Wampler GL (1978) Interstitial pulmonary fibrosis as a complication of prolonged methyl-CCNU therapy. Cancer Treat Rep 62:1355
67. Littler WA, Ogilvie C (1970) Lung function in patients receiving busulphan. Br Med J 4:530
68. Littler WA, Kay JM, Hasleton PS, Heath D (1969) Busulphan lung. Thorax 24:639
69. Lokich JJ, Moloney WC (1972) Allergic reaction to procarbazine. Clin Pharmacol Ther 13:573
70. Luna MA, Bedrossian CWM, Lichtiger B, Salem PA (1972) Interstitial pneumonitis associated with bleomycin therapy. Am J Clin Pathol 58:501
71. McCullough B, Collins JF, Johanson WG, Grover FL (1978) Bleomycin-induced diffuse interstitial pulmonary fibrosis in baboons. J Clin Invest 61:79
72. Manni JJ, Van den Broek P (1977) Pulmonary complications of methotrexate therapy. Clin Otolaryngol 2:131
73. Mark GJ, Lehimgar-Zadeh A, Ragsdale BD (1978) Cyclophosphamide pneumonitis. Thorax 33:89
74. Merrin CE (1978) Prevention of bleomycin-induced lung fibrosis with simultaneous administration of prednisone. Proc Am Soc Clin Oncol 19:382
75. Meschan I, DeArmas CR, Scharyj M (1969) Adult bronchopulmonary dysplasia: The similarity in roentgen and histologic appearance between some cases of oxygen toxicity, radiation pneumonitis and postcytotoxic non-specific bronchopneumonia. Radiology 92:612
76. Nesbit M, Krivit W, Heyn R, Sharp H (1976) Acute and chronic effects of methotrexate on hepatic, pulmonary and skeletal systems. Cancer 37:1048
77. Nygard K, Smith-Erichsen N, Hatlevoll R, Refsum SB (1978) Pulmonary complications after bleomycin, irradiation and surgery for oesophageal cancer. Cancer 41:17
78. O'Connell TX, Berenbaum MC (1974) Cardiac and pulmonary effects of high doses of cyclophosphamide and isophosphamide. Cancer Res 34:1586
79. Okita H, Ito K, Taketomi Y, Fujimura K, Kuramoto A, Uchino H (1974) Four patients with leukaemia who showed especially atypical type of interstitial pneumonia, probably caused following the administration of anti-leukaemic drugs. Jp J Clin Hematol 15:764
80. Oliner H, Schwartz R, Rubio F, Dameshek W (1961) Interstitial pulmonary fibrosis following busulfan therapy. Am J Med 31:134
81. Orwoll ES, Kiessling PJ, Patterson JR (1978) Interstitial pneumonia from mitomycin. Ann Intern Med 89:352

82. Pascual RS, Mosher MB, Sikand RS, De Conti RC, Bouhuys A (1973) Effects of bleomycin on pulmonary function in man. Am Rev Respir Dis 108:211
83. Pasquinucci G, Ferrara P, Costellari R (1971) Daunorubicin treatment of methotrexate pneumonia. JAMA 216:2017
84. Patel AR, Shah PC, Rhee HL, Sassoon H, Rao KP (1976) Cyclophosphamide therapy and interstitial pulmonary fibrosis. Cancer 38:1542
85. Philips FS, Schwartz HS, Sternberg SS (1960) Pharmacology of mitomycin C. I: Toxicity and pathological effects. Cancer Res 20:1354
86. Phillips TL, Fu KK (1976) Quantification of combined radiation therapy and chemotherapy effects on critical normal tissues. Cancer 37:1186
87. Podoll LN, Winkler SS (1974) Busulfan lung: Report of two cases and review of the literature. Am J Roentgenol 120:151
88. Pozzi E, Zanon P (1978) On the pathogenesis of bleomycin lung toxicity. Int J Clin Pharmacol Biopharm 16:575
89. Rawbone RG, Shaw MT, Jackson JG, Bagshawe KD (1971) Complications of methotrexate-maintained remission in lymphoblastic leukaemia. Br Med J 4:467
90. Richman SD, Levenson SM, Bunn PA, Flinn GS, Johnston GS, DeVita VT (1975) ^{67}Ga accumulation in pulmonary lesions associated with bleomycin toxicity. Cancer 36:1966
91. Richter JE, Hastedt R, Dalton JF, Marshall D, Raymond LW (1979) Pulmonary toxicity of bischloronitrosourea. Cancer 43:1607
92. Robertson JH (1970) Pneumonia and methotrexate. Br Med J 2:156
93. Rodin AE, Haggard ME, Travis LB (1970) Lung changes and chemotherapeutic agents in childhood. Am J Dis Child 120:337
94. Rose MS (1975) Busulphan toxicity syndrome caused by chlorambucil. Br Med J 2:123
95. Rosenow EC (1972) The spectrum of drug-induced pulmonary disease. Ann Intern Med 77:977
96. Rubin G, Baume P, Vandenberg R (1972) Azathioprine and acute restrictive lung disease. Aust NZ J Med 3:272
97. Rubio FA (1972) Possible pulmonary effects of alkylating agents. N Engl J Med 287:1150
98. Rudders RA, Hensley GT (1973) Bleomycin pulmonary toxicity. Chest 63:626
99. Samuels ML, Johnson DE, Holoye PY, Lanzotti VJ (1976) Large-dose bleomycin therapy and pulmonary toxicity: a possible role of prior radiotherapy. JAMA 235:1117
100. Schein PS, De Vita VT, Hubbard S, Chabner BA, Canellos GP, Berard S, Young RC (1976) Bleomycin, adriamycin, cyclophosphamide, vincristine and prednisone (BACOP) combination chemotherapy in the treatment of advanced diffuse histiocytic lymphoma. Ann Intern Med 85:417
101. Schreml W, Bargon G, Anger B, Kubanek B, Heimpel H (1978) Progrediente Lungenfibrose unter Kombinationstherapie mit BCNU. Blut 36:353
102. Selker RG, Jacobs SA, Moore P (1978) Interstitial pulmonary fibrosis as a complication of 1,3-bis-(2-chloroethyl)-1-nitrosourea (BCNU) therapy. Proc Am Soc Cancer Res 19:333
103. Seltzer SE, Griffin T, D'Orsi C, Tryka F, Herman PJ (1978) Pulmonary reaction associated with neocarcinostatin therapy. Cancer Treat Rep 62:1271
104. Shimosato Y, Baba K, Watanabe S (1971) Pulmonary lesions produced by antitumour drugs: Studies on autopsy cases [in Japanese]. Gan no Rinsho (Cancer Clinic) 17:21
105. Sikic BI, Young DM, Mimnaugh EG, Gram TE (1978) Quantifications of bleomycin pulmonary toxicity in mice by changes in lung hydroxyproline content and morphometric histopathology. Cancer Res 38:787
106. Sikic BI, Collins JM, Mimnaugh EG, Gram TE (1978) Improved therapeutic index of bleomycin when administered by continuous infusion in mice. Cancer Treat Rep 62:2011
107. Smalley RV, Wall RL (1966) Two cases of busulfan toxicity. Ann Intern Med 64:154
108. Snider GL, Hayes JA, Korthy AL (1978) Chronic interstitial pulmonary fibrosis produced in hamsters by endotracheal bleomycin: Pathology and stereology. Am Rev Respir Dis 117:1099
109. Soble AR, Perry H (1977) Fatal radiation pneumonia following sub-clinical busulfan injury. Am J Roentgenol 128:15
110. Sostman HD, Matthay RA, Putman CE, Walker Smith GJ (1976) Methotrexate-induced pneumonitis. Medicine 55:371
111. Sostman HD, Matthay RA, Putman CE (1977) Cytotoxic drug-induced lung disease. Am J Med 62:608
112. Starcher BC, Kuhn C, Overton JE (1978) Increased elastic and collagen content in the lungs of hamsters receiving intratracheal injection of bleomycin. Am Rev Respir Dis 117:299
113. Stutz FH, Tormey DC, Blom J (1973) Nonbacterial pneumonitis with multidrug antineoplastic therapy in breast carcinoma. Can Med Assoc J 108:710
114. Svanberg LE (1976) Bleomycin and lung cancer. Gann Monogr Cancer Res 19:193
115. Taetle R, Dickman PS, Feldman PS (1978) Pulmonary histophathologic changes associated with melphalan therapy. Cancer 42:1239
116. Topilow AA, Rothenberg SP, Cottrell TS (1973) Interstitial pneumonia after prolonged treatment with cyclophosphamide. Am Rev Respir Dis 108:114
117. Tucker AS, Newman AJ, Alvorado C (1977) Pulmonary pleural and thoracic changes complicating chemotherapy. Radiology 125:805
118. Weisenburger DD (1978) Interstitial pneumonitis associated with azathioprine therapy. Am J Clin Pathol 62:181
119. Whitcomb ME, Schwarz MI, Tormey DC (1972) Methotrexate pneumonitis: case report and review of the literature. Thorax 27:636
120. Willson JKV (1978) Pulmonary toxicity of antineoplastic drugs. Cancer Treat Rep 62:2003
121. Yagoda A, Krakoff IH (1976) Observations on the use of bleomycin in the treatment of malignant lymphoma in the USA. Gann Monogr Cancer Res 19:255
122. Yagoda A, Mukherji B, Young C, Etcubanas E, LaMonte C, Smith JR, Tan CTC, Krakoff IH (1972) Bleomycin, an antitumour antibiotic: Clinical experience in 274 patients. Ann Intern Med 77:861

Received November 21, 1979