

# Drug-induced pulmonary disease

## *Part III. Agents used to treat neoplasms or alter the immune system including a brief review of radiation therapy*

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The most common adverse pulmonary responses produced by anticancer agents are interstitial pneumonitis and interstitial fibrosis. There is no sharp distinction between these two patterns of response and there may be progression from one state to another. In general, the presenting symptoms of interstitial pneumonitis are a more systemic, hypersensitivity response with fever, malaise, and a rapid decline in respiratory function. Although both entities can occur from days to years after medication is started and resolve from hours to months, interstitial pneumonitis is more likely to occur earlier and to resolve more quickly. Also, the pathologic differences are not profound. Interstitial pneumonitis shows evidence of larger numbers of inflammatory cells and less fibrosis than that of interstitial fibrosis. Of the two, interstitial pneumonitis is more likely to resolve upon withdrawal of the drug.

Common symptoms include the insidious onset of dyspnea and cough. The cough is usually dry although a thin, white sputum may be present at times. Malaise, fatigue, and fever occasionally occur. Physical examination generally reveals tachypnea and fine crackles, which are heard best in the bases. An interstitial infiltrate is the most common roentgenographic abnormality. Pulmonary function testing is consistent with a restrictive ventila-

tory defect (low vital capacity or total lung capacity) with a reduced diffusing capacity ( $D_LCO$ ); flow rates are usually preserved. The  $D_LCO$  is the most sensitive parameter and may be used as a predictive test to follow the patient. Hypoxemia is common.

Diagnosis is made by lung biopsy. The list of causes of pulmonary infiltrates in the immunocompromised host always includes infection; appropriate stains and cultures should be done to identify the other causes. Treatment is discontinuance of the agent; steroids may or may not help, but probably should be tried. The response may be followed by serial determinations of the  $PaO_2$ ,  $D_LCO$ , or by the chest roentgen-

ogram; the  $D_LCO$  is the most sensitive.

Occasionally factors such as total cumulative dosage, the patient's age, or prior use of agents, which may act synergistically, e.g., radiation, can be used in anticipating an untoward response. However, individual tolerance and susceptibility appear to play a much larger role in the risk to an individual than any of the factors listed above, even with those agents known to produce cumulative, dose-related toxic damage (*Table 1*). It is, therefore, impossible to predict accurately the risk an individual accepts when treatment programs are begun.

**Table 1.** Anticancer agents with demonstrated adverse pulmonary effects

Chemotherapeutic drugs
Alkylating agents
Mustards
Chlorambucil
Cyclophosphamide
Melfhalan
Nitrogen mustard
Alkyl sulfonates
BCNU
Busulfan
Antimetabolites
Folic acid antagonists
Methotrexate
Purine analogues
Azathioprine
Mercaptopurine
Antibiotics
Bleomycin
Mitamycin
Miscellaneous
Procarbazine
Immunotherapeutic drugs
BCG
Corticosteroids
Corynebacterium parvum
Others
Radioactive iodine
Radiation therapy

BCNU = Bis-chloro-ethyl-nitrosourea;  
BCG = *Bacillus Calmette-Guérin*.

**Neoplastic potential**

In rare instances, these agents have been implicated as causing a pulmonary neoplasm. More commonly they produce dysplastic changes in either the alveolar or bronchiolar lining cells (*Table 2*). The cause of the neoplastic and dysplastic changes is unknown; it is also unknown whether there is an association between the two. It has been suggested that atypical cells proceed from atypia to dysplasia, and finally to carcinoma.<sup>1</sup> The source of these cellular changes may be chromosomal damage caused by the agent discussed in *Part 1* or they may share a common background with "scar carcinomas." The most frequent cell type seen with scar cancers is adenocarcinoma;<sup>2</sup> the dysplastic changes from these agents occur in the bronchial epithelium or the alveolar lining cells. The cell type reported with cancer following busulfan lung has been alveolar cell.<sup>1, 3</sup> Occasionally cytotoxic-induced pulmonary disease can be diagnosed by a combination of sputum cytology and clinical history.<sup>3, 4</sup>

The incidence of second cancers is increased in patients who are receiving chemotherapeutic and immunotherapeutic agents either for neoplasia or to

**Table 2.** Pulmonary cytological changes due to drugs (references)

Drug	Alveolar lining cell atypia	Bronchiolar epithelial cell atypia	Abnormal sputum cytology	Associated with cancer
BCNU	12	...	...	...
Bleomycin	18	15, 18	4, 20	...
Busulfan	1, 22-24, 26	24-26	3, 21, 26	1, 3, 26
Chlorambucil	27	...	...	...
Corticosteroids	30	30	...	...
Cyclophosphamide	32, 33	33	4	...
Melphalan	35	36	...	...
Methotrexate	37	...	...	...
Mitomycin	41	...	...	...
Radiation	46, 49	46, 49	...	...
Mineral oil	50	51	...	50

achieve an immunosuppressed state for transplant acceptance. This may be related to the chromosomal damage discussed above. If so, rapidly regenerating cells, of which the bronchial epithelium and the type II pneumatocyte are examples, would be expected to display the most abnormalities. The increased risk of a nonlymphomatous second malignancy complicating treated Hodgkin's disease expressed as ratio of observed to expected, ranged from 3.3 to 29 depending on the types and aggressiveness of the therapy, according to one review.<sup>5</sup> In a review of the incidence of tumor in renal transplant recipients, Penn and Starzl<sup>6</sup> noted a 4.9% incidence (increased risk ratio, 80); 62% of the tumors were of epithelial origin. Fraumeni<sup>7</sup> reported on the relationship of immunosuppressive states and the development of lung cancer and stated that the kidney transplant recipient is probably at an increased risk for the development of adenocarcinoma of the lung. The incidence of lung adenomas is significantly increased in immunosuppressed mice. Of the 95 tumors in their series, Penn and Starzl<sup>6</sup> found two adenocarcinomas of the lung, one alveolar cell carcinoma of the lung, one undifferentiated cancer involving the lungs, mediastinum, liver, and brain, and eight carcinomas that involved the lung.

The dysplastic/neoplastic changes in the various agents and the references in which these changes were described are listed in *Table 2*. The association between alveolar cell carcinoma and mineral oil abuse is discussed in *Part 2*.

**Azathioprine**

A hypersensitivity reaction has been associated with the use of azathioprine. Diffuse pulmonary infiltrates, fever, dyspnea, and a decreased vital capacity developed in a patient who had taken this medication for the 6 weeks preceding the onset of the infiltrates. The patient had also taken cyclophosphamide, but this had been withdrawn 3½ months prior to the reaction. The fever cleared within 48 hours after the drug was withdrawn and in 9 days the lung function had returned to normal.<sup>8</sup>

***Bacillus Calmette-Guérin (BCG)***

BCG is used as a nonspecific stimulator of the immune system. In immunocompetent patients a flu-like syndrome commonly occurs with repeated injections;<sup>9</sup> a localized hypersensitivity reaction involving primarily the skin is an unusual response. Two rare reactions that occur in the severely immunoincompetent patient may affect the lung. There may be activation of old, dormant, mycobacterial disease or an ac-

quired acid-fast disease; a true BCG infection may develop, which can disseminate widely.<sup>10</sup> Of the two, the BCG infection is the easiest to treat, with 2 to 4 months of isoniazid therapy usually being sufficient.<sup>10</sup>

### **Bis-chloro-ethyl-nitrosourea (BCNU)**

BCNU has recently been reported to cause interstitial pulmonary infiltrates. One report suggested a dose-related phenomenon; a hacking cough developed in 4 of 28 patients (14%). The mean cumulative dose in patients with symptoms was 2030 mg/m<sup>2</sup> body surface area; for those without symptoms, 710 mg/m<sup>2</sup>. Interstitial infiltrates were seen on the chest roentgenograms in three of four patients, but all four had interstitial fibrosis on lung biopsy. Symptoms progressed despite cessation of therapy and one patient died of respiratory failure.<sup>11</sup> Another study found no dose-dependent relationship, but suggested that interstitial infiltrates were more common when BCNU was used concomitantly with cyclophosphamide. Of the ten patients, nine had received other agents capable of causing interstitial fibrosis.<sup>2</sup> In both studies the PFTs commonly showed a decreased DLCO, PaO<sub>2</sub>, and vital capacity. The projected incidence varied from 1.1%<sup>12</sup> to 14%.<sup>11</sup>

### **Bleomycin**

Interstitial fibrosis is the most commonly mentioned adverse pulmonary response to bleomycin. However, an acute response consisting of cough and dyspnea has been reported. These symptoms may occur separately or together and were seen in 6% of 274 patients in one study.<sup>13</sup> The cough may be so severe as to limit the use of the drug. The response usually occurs shortly after in-

jection; in one patient, the response did not develop until the eighth month of treatment.<sup>13</sup> Tracheitis has also been described although infrequently; bleomycin is capable of inducing mucous membrane ulcerations.<sup>13</sup>

Bleomycin is deposited in the skin and lungs. Not unexpectedly, these two organs display the most serious side effects: ulcerations of the skin and interstitial fibrosis.<sup>13</sup> The pulmonary manifestation appears to be a result of toxic accumulation, although cases of hypersensitivity reaction have been reported.<sup>14</sup>

Four patients have been described in whom reversible interstitial pneumonitis developed after receiving total dosages ranging from 133 to 1000 mg.<sup>14, 15</sup> Two of the four had peripheral eosinophilia (12% to 16%) and the biopsy specimen of one showed eosinophilic infiltration of the distal air spaces. Pleural effusions, interstitial infiltrates, and alveolar infiltrates have all been seen on chest roentgenogram. Immunofluorescent studies for immunoglobulins, complement, and fibrinogen were negative.<sup>15</sup> Corticosteroids were used in three of the four patients with reversal of the infiltrates seen on the roentgenogram and symptoms in all four patients.<sup>14, 15</sup>

Interstitial fibrosis occurs in approximately 11% of patients receiving the drug.<sup>16</sup> The incidence is reported to be only 3% to 5% when the total dosage is below 450 mg, but 35.3% when the level of 500 mg is exceeded.<sup>17</sup> These studies, however, employ a triad of roentgenographic, clinical, and histologic findings when assessing the relative risk of a given cumulative dosage to the lung tissue. When pulmonary function testing is done prospectively in large groups, no correlation between PFT changes and daily or total dosage was noted,<sup>13, 17</sup> but for an individual patient, changes

in the  $D_LCO$  or the forced vital capacity (this parameter was used to follow the restrictive defect) were found to decrease with increasing cumulative dosages.<sup>17</sup> In a histologic study of 37 patients (34 specimens were obtained at autopsy), 12 were found to have interstitial pneumonitis at different stages of development. Total dosages ranged from 115 to 800 mg/m<sup>2</sup>. Histologic changes consisted of fibrinous exudate, atypical proliferation of alveolar cells, hyaline membranes, squamous metaplasia, and epithelial dysplasia of distal air spaces, and interstitial and intraalveolar fibrosis. Alveolar septae could be broadened with edema fluid and mononuclear inflammatory cell infiltration or show signs of extensive fibrosis.<sup>18</sup>

Bleomycin pulmonary toxicity may, therefore, include a spectrum of changes. The drug is accumulated in the lungs. There may be an initial, toxic, inflammatory response, which later becomes fibrotic. The earlier the response is identified, the more amenable the damage is to full recovery. The fibrotic states are resistant to reversibility even after the drug and with the use of corticosteroids.<sup>13, 19</sup> The  $D_LCO$  may be the most sensitive parameter for following the patient. Factors that appear to increase the toxic potential include advancing age, total cumulative dose, and prior radiation to the thorax.<sup>16</sup>

The histologic changes of bleomycin-induced interstitial fibrosis resemble busulfan lung as well as desquamative interstitial pneumonitis. The chest roentgenogram shows a nonspecific interstitial pattern. The most severe changes in both the histologic picture and the roentgenographic appearance are in the lung bases and subpleural areas as opposed to busulfan where the roentgenographic abnormalities are more pronounced near the hilum.<sup>18</sup> Symptoms

include dry cough and dyspnea. Physical examination reveals tachypnea, basilar crackles, and concomitant hyperpigmentation of the skin.<sup>16</sup> Diagnosis is by lung biopsy although one report suggested that oral cavity or sputum cytology may have merit.<sup>20</sup> Treatment is withdrawal of the drug. Steroids may or may not help. If the condition is reversible, improvement is shown on the chest roentgenogram and on the PFT.

### Busulfan

Busulfan is considered the prototype drug for cytotoxic drug-induced pulmonary damage. The usual case is one of chronic, toxic damage to the lungs with an insidious onset of symptoms after the patient has taken the drug for 3 to 4 years. No adverse reactions had been identified in a patient who had not taken the drug for at least 8 months until 1978 when a hypersensitivity reaction was reported. Dyspnea and mixed interstitial and alveolar infiltrates developed in a patient who had taken busulfan for 6 weeks. All signs and symptoms receded in 2 months when the use of the drug was discontinued.<sup>21</sup>

Abnormalities in PFTs or chest roentgenogram or other symptoms are present in 2.5% to 11.5% of patients treated with busulfan. Histologic evidence of toxicity can be seen in 12.5% to 42.8% of all patients treated.<sup>19</sup>

Histologic changes include organizing fibrinous edema with bizarre, atypical cells, probably to type II pneumocyte.<sup>22-24</sup> Alveolar lining cells and bronchiolar epithelial cells can both appear abnormal<sup>1, 22, 24, 25</sup> and dysplastic or neoplastic on sputum cytology.<sup>3, 21, 26</sup> There may be evidence of edema or inflammatory cells in the interstitium or,<sup>1, 22-25</sup> more commonly, fibrotic changes.<sup>22-24, 26</sup> Other changes include parenchymal calcification<sup>24, 26</sup> and pro-

liferative endarteritis.<sup>24</sup> The atypical bronchial epithelial cells may be so abnormal as to represent carcinoma in situ<sup>26</sup> and alveolar cell carcinoma may develop in busulfan lung.<sup>2, 3</sup>

The PFTs show hypoxemia, restriction, and a decrease in the diffusing capacity. The  $D_LCO$  may be used to follow the patients. Diffuse interstitial and alveolar infiltrates are usually seen on the chest roentgenogram, but nodular densities, pleural effusions, and normal roentgenograms may also be seen.<sup>19</sup>

Symptoms include cough, dyspnea, and fever. Rosenow<sup>3</sup> stated that fever due to a chronic drug reaction is almost unique to busulfan. Diagnosis is made by sputum cytology or lung biopsy in the appropriate setting. Treatment is withdrawal of the drug and the administration of corticosteroids; histologic changes are not commonly reversible.

### Chlorambucil

Chlorambucil has been implicated as a cause of interstitial fibrosis in a patient who had received a total dose of 4130 mg. Symptoms included the insidious onset of cough and dyspnea; physical examination revealed fine basilar crackles and fever. The  $PaO_2$  was 48 torr; the  $D_LCO$  was also reduced. Histopathologic findings revealed alveolar lining cell dysplasia, interstitial round cell infiltration, and interstitial fibrosis. Signs and symptoms reversed on withdrawal of the drug and the use of corticosteroids.<sup>27</sup>

### Corticosteroids

Patients receiving corticosteroids are prone to opportunistic infections or reactivation of old infections. Rosenow<sup>3</sup> stated that, when given alone, only corticosteroids and cyclophosphamides are capable of precipitating a *Pneumocystis*

*carinii* infection. The incidence of this type of response varies greatly and is dependent on many factors. Corticosteroids may be capable of inducing a vasculitis of the pulmonary vessels (*Part I*).

Mediastinal lipomatosis is an asymptomatic response characterized by increased fat content in the mediastinum.<sup>28</sup> The radiographic appearance is one of a variable degree of mediastinal widening. Other signs include prominence of the epicardial fat pad and fullness in the supraclavicular fossae. The patient with mediastinal lipomatosis is always cushingoid. It is estimated that 15% of patients given enough corticosteroids to produce a cushingoid appearance will have some degree of widening of the mediastinum.<sup>29</sup> This radiographic abnormality can also be seen with Cushing's disease.<sup>29</sup>

Abnormal pulmonary histopathologic changes have also been described. In one series of patients who had taken corticosteroids from one day to 7 years, autopsy findings revealed bronchiolar epithelial hyperplasia and metaplasia in 50%, epithelialization of alveolar spaces in 27%, and atypical bronchiolar epithelium in 7%.<sup>30</sup>

### *Corynebacterium parvum*

*C. parvum* is inactivated by heat and treated with formalin before use as a nonspecific immunopotentiator. The most common and almost universal adverse side effect is a flu-like syndrome. However, in one study of 87 patients, renal and respiratory failure developed in three; renal biopsy findings were compatible with immune complex disease. The chest roentgenogram showed interstitial infiltrates and pleural effusions and physical examination showed anasarca. Other adverse pulmonary reactions include the symptoms of dyspnea and wheezing and peripheral cy-

anosis. These findings are not dose related and are seen infrequently.<sup>31</sup>

### Cyclophosphamide

The pulmonary response to cyclophosphamide is similar to that of busulfan although it is much rarer. The PFTs show hypoxemia, a decreased  $D_LCO$ , and restriction. Interstitial infiltrates are shown on the chest roentgenogram. Symptoms start insidiously and include fever, cough, and dyspnea. These may develop after the patient has received the drug for many months. Diagnosis is by lung biopsy. Histologic study shows proliferation of atypical alveolar lining cells.<sup>3, 19, 32, 33</sup> Signs and symptoms may remit when the drug and corticosteroids are withdrawn.<sup>19, 32</sup>

### Radioactive iodine

An adverse pulmonary reaction to this drug has been seen only in patients with pulmonary metastases from thyroid carcinoma. Of 15 cases reviewed in one study, six patients showed evidence of pulmonary fibrosis on the chest roentgenogram. Four were symptomatic, primarily dyspnea, and two died of respiratory distress, one at 3 months and the other at 8 months after treatment. The cases resembled acute hypersensitivity pneumonitis superimposed on a background of chronic radiation changes. Of the two patients who died, corticosteroids proved to be beneficial in one. The dosage in those patients who became symptomatic ranged from 262 to 657 mCi, with doses of 288 and 300 mCi in the two patients who died.<sup>34</sup> The authors believed that changes in PFTs would be expected when doses of more than 100 mCi were used.<sup>34</sup>

### Melphalan

Interstitial fibrosis developed in a patient who had taken melphalan for 3

months. Other histologic changes included plasma cell interstitial infiltration and proliferation of bronchiolar and alveolar lining cells.<sup>35</sup> Another patient had increasing dyspnea and diffuse interstitial infiltrates after receiving melphalan for 7 months, after displaying a presumed hypersensitivity response to busulfan. Treatment with corticosteroids yielded only partial clearing.<sup>21</sup>

### Mercaptopurine

Acute interstitial pneumonitis was found in a 2-year-old child who had received mercaptopurine for 3 days. Symptoms of respiratory distress developed. The chest roentgenogram showed diffuse, fine nodular infiltrates; histologic study revealed epithelial proliferation and round cell infiltration with no evidence of infection. The signs and symptoms reversed completely when the mercaptopurine was withdrawn.<sup>19</sup>

### Methotrexate

An acute or chronic interstitial response due to methotrexate is one of the more reversible of the cytotoxic drug-induced pulmonary reactions. This response has been described after the oral, intravenous, intramuscular, or intrathecal routes of administration.<sup>36</sup>

In some patients the reaction more closely resembles a hypersensitivity reaction with the acute onset of transient hilar lymphadenopathy, eosinophilia, and defervescence with corticosteroids. In other cases it is more characteristic of a direct toxic action, with fibrosis occurring while the patient is taking corticosteroids, and with lack of eosinophilia, persistence of significant physiologic abnormalities after apparent clinical recovery, and lack of symptoms on rechallenge.<sup>16, 37</sup> Death is caused by respiratory failure.



In one series, the incidence was 7 in 92<sup>37</sup>; in another it was approximately 2.5%.<sup>38</sup> The incidence appears to be related to the frequency of dosage rather than to total dosage (range 40 to 6500 mg; it is rare, however, in patients receiving less than 20 mg/wk); sex, age (range, 3 to 68 years); underlying disease (the response occurs in patients taking methotrexate for skin diseases, connective tissue disease, or leukemia); or duration of therapy (range, 10 days to 5 years; average, 138 days).<sup>37</sup> Leukovorin does not appear to be protective. There may be synergism with cyclophosphamide, especially in adrenalectomized patients, with an increased frequency and severity of response.<sup>39</sup>

The histologic changes resemble desquamative interstitial pneumonitis or busulfan lung, but with fewer abnormal cells. There is alveolar damage with hyaline membranes and prominent, sometimes atypical, alveolar lining cells, interstitial infiltrates with lymphocytes, plasma cells, and eosinophils, and occasionally granulomas and giant cells or interstitial fibrosis.<sup>19, 37</sup>

The PFTs show restriction, hypoxemia, and a decreased  $D_LCO$ . There may be significant residual abnormalities following clinical recovery.<sup>37</sup> The diffusing capacity is the most sensitive parameter and is useful in follow-up of the patient. The chest roentgenogram may be normal or show nodular or reticulonodular infiltrates in the bases and mid-lung zones, diffuse alveolar infiltrates, pleural effusions, or hilar lymphadenopathy. There may be permanent changes of pulmonary fibrosis.<sup>19, 37</sup>

The onset of symptoms is usually 10 days to 4 months after treatment is started. Typically the symptoms include cough, fever, and dyspnea. Headache and malaise are common prodromal symptoms. Cyanosis occurs in 52% of

patients with the  $PaO_2$  ranging from 37 to 80 torr; other signs include tachypnea, crepitant rales in 38%, and skin eruptions in 16%.<sup>37</sup> The differential diagnosis includes leukemic infiltrates, (however, the patient is usually in remission when a methotrexate-induced reaction develops) and opportunistic infection. Diagnosis is by biopsy.

Treatment is withdrawal of the drug. The use of corticosteroids is optional, but may hasten recovery. Interstitial fibrosis develops in approximately 7% of patients and 8% die of respiratory failure.<sup>37</sup>

Methotrexate has also been implicated as causing a pulmonary reaction, which on histologic study resembled bronchiolitis obliterans.<sup>40</sup>

### Mitomycin

Interstitial pathology has been reported in patients taking mitomycin. Total cumulative doses in affected patients range from 50 to 156 mg. Typically symptoms of cough, fatigue, and dyspnea develop insidiously over several months. The chest roentgenogram shows diffuse reticulonodular infiltrates, and physical examination reveals basilar crackles. Fever has not been reported nor has eosinophilia. Three patients demonstrated severe hypoxemia with a  $PaO_2$  ranging from 34 to 51 torr and a  $PaCO_2$  of 23 to 33 torr.<sup>41</sup> Biopsy specimens showed alveolar septal edema and fibrosis, alveolar lining cell hyperplasia, and interstitial infiltration with mononuclear and plasma cells; there was some atypia of the type II pneumocytes.<sup>41, 42</sup> Prednisone therapy can result in prompt clearing of the symptoms and roentgenographic abnormalities.<sup>41</sup>

### Nitrogen mustard

Unilateral pulmonary edema was seen after instillation of nitrogen mus-



tard into the pleural cavity in a patient with breast cancer for control of a recurrent pleural effusion. Other signs and symptoms included fever, cough, and rales. The reaction was self-limited and was believed to represent a local toxic reaction.<sup>43</sup>

### Procarbazine

A hypersensitivity response has been described following the use of procarbazine. It may start within hours after the first dose or may develop after the patient has received the medication for months. Diffuse interstitial infiltrates are seen on the chest roentgenogram. The reaction may result in respiratory failure. Pleural effusions and eosinophilia can occur. The biopsy specimen shows mononuclear and eosinophilic cell infiltrates and interstitial fibrosis. Diagnosis is by biopsy; treatment is withdrawal of the drug and the use of corticosteroids. The abnormalities shown on the chest roentgenogram may resolve over a period of a month.<sup>44, 45</sup>

### Radiation

Three major clinical patterns of radiation-induced pulmonary disease are described: acute radiation pneumonitis, which resembles clinically a hypersensitivity reaction; chronic radiation fibrosis; and steroid withdrawal pneumonitis, which is similar to the acute reaction.

These differences are seen in the clinical presentation only. Pulmonary disease due to radiation is the result of physical damage to the living tissue. Cellular abnormalities are a combination of only two factors: the dose of radiation delivered and the susceptibility of the individual cell to the radiation. Rapidly dividing cells appear to be more susceptible to radiation damage; cells that have no reproductive potential, e.g., neurons, appear radio-resistant.

<sup>46</sup> The cells in the pulmonary system that have the highest mitotic index and, therefore, display the greatest susceptibility to radiation damage are the bronchial epithelial cells, capillary endothelial cells, and the type II pneumocytes.

Thus, radiation-induced cytopathological changes would be expected to develop in any patient given sufficient radiation. It is in the clinical expression of this derangement that there is wide variation. Acute radiation pneumonitis is a clinical entity resembling a hypersensitivity reaction. Presenting symptoms include cough, which is at first dry, but later becomes productive of blood-tinged sputum; dyspnea; fever; and chest pain beginning one to 6 months after radiation. A leukocytosis and elevated erythrocyte sedimentation rate are common, but physical signs are usually absent. The chest roentgenogram is usually abnormal. Typically there is a diffuse haziness with air bronchograms in the irradiated area, although other patterns may be seen including indistinct pulmonary markings, ground glass opacification, signs of parenchymal consolidation, and pleural effusions.<sup>46</sup> Usually this reaction does not occur in less than one month, although radiation bronchitis may occur as soon as one week after delivery.<sup>46</sup>

The steroid-withdrawal response closely resembles the above response in all respects except the timing. Corticosteroids have been shown to be protective when given at the time of irradiation in mice<sup>47</sup> and to suppress the clinical expression of the acute pneumonitis.<sup>46</sup> When high-dose corticosteroids are rapidly withdrawn from a previously irradiated patient, a reaction resembling acute radiation pneumonitis may develop; this response is responsive to resumption of the corticosteroids.<sup>48</sup>

Chronic radiation damage is usually

manifest by 6 to 18 months following irradiation. This is a scarring process, which is manifested physiologically by restriction (decreased lung volumes) and hypoxemia (due to abnormalities in the scarred vessels and alveoli). This may be expressed in its most severe form as chronic respiratory failure. The chest roentgenogram usually shows contraction of lung parenchyma in the irradiated areas; fibrotic streaking, an elevated diaphragm, mediastinal shift, and pleural thickening are typical findings.<sup>46</sup>

Other adverse pulmonary effects include pleural effusion in 5% to 11% of patients, usually when total dosage is over 5000 rads, it is usually small and produces no symptoms and may persist for years; reactivation of preexisting granulomatous disease (rare); spontaneous pneumothorax (rarely due unequivocally to radiation); acute airway obstruction (swelling of tumors located centrally has been reported and can be treated prophylactically with corticosteroids; hyperlucent lung (rare); tracheoesophageal fistula (rare); and carcinogenic effect (speculative).<sup>46</sup>

The incidence of radiation pneumonitis is highly variable and figures ranging from 0% to 100% have been reported.<sup>46</sup> This variability is due to the criteria used in making the diagnosis, i.e., histologic abnormalities, roentgenographic changes, or clinical symptoms. It has been reported that 5% to 15% of patients with acute radiation pneumonitis are symptomatic.<sup>49</sup> Factors known to increase the likelihood of radiation damage include (1) total dosage of radiation delivered and absorbed; this is increased with tissue consolidation, e.g., atelectasis or pneumonia, or with decreased amounts of soft tissue covering the chest wall, e.g., postmastectomy or in a thin patient,<sup>46</sup> (2) total amount of lung irradiated, e.g., poor portal defini-

tion,<sup>46</sup> (3) dose rate; the higher the dose per treatment, the greater the risk,<sup>46</sup> (4) prior radiation therapy,<sup>46</sup> (5) withdrawal of high dose corticosteroids,<sup>48</sup> and (6) the use of some drugs (actinomycin D, cyclophosphamide, and vincristine appeared to enhance the risk of radiation pneumonitis in mice, whereas BCNU and corticosteroids appeared to be protective).<sup>47</sup> Prior lung disease and age did not appear to affect the risk of development or radiation pneumonitis, although both may affect physical impairment due to radiation pneumonitis.<sup>46, 49</sup>

There is probably a progression between the acute radiation pneumonitis and the chronic radiation fibrosis on a cellular level.<sup>49</sup> However, there appears to be no clear-cut relationship in the clinical expression. A patient with symptoms of an acute reaction does not appear to be at higher risk for chronic fibrosis.

The natural history of acute radiation pneumonitis is highly variable. It may persist, subside without sequelae, progress to chronic radiation fibrosis, or decompensate with the patient dying quickly from the adult respiratory distress syndrome.<sup>46</sup> Treatment is with corticosteroids. The PFTs (lung volumes and  $D_LCO$ ) are more sensitive than the roentgenogram in follow-up. Other than supportive therapy, there is no treatment for radiation fibrosis.

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