PULMONARY MANIFESTATIONS OF DRUG TOXICITY

INTERNAL MEDICINE GRAND ROUNDS

UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER
DALLAS, TEXAS

W. DOUGLAS PITCHER, M.D.

AUGUST 29, 1991

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INTRODUCTION

Adverse reactions to therapeutic agents may involve the respiratory system in a number of ways. In some circumstances the mechanism is an exaggerated pharmacologic response to the drug. Central nervous system depression may lead to respiratory failure from narcotics or sedatives. The respiratory airways may be affected through the pharmacologic actions of beta-blocking agents and drugs which affect prostaglandin balances such as aspirin or non-steroidal anti-inflammatory agents. Oxygen, radiation therapy, and many of the cancer chemotherapy drugs produce a direct, toxic injury to the lung which is often mediated by oxygen-radical formation and which may then incite non-specific inflammation and fibrosis. There is also growing evidence of an important role for the immune system in drug-related reactions, either through direct immune-mediated injury (e.g. autoimmune disease, pulmonary infiltrates with eosinophilia, or hypersensitivity pneumonitis) or through alterations in immunologic modulation of injury, inflammation, and repair.

MAJOR MECHANISMS OF DRUG-RELATED RESPIRATORY COMPLICATIONS

Pharmacologic
Direct toxic injury
Inflammatory responses
Immunologic injury
Immunologic modulation

In reviewing this subject, it was not difficult to identify over 80 drugs or therapeutic agents which can affect the respiratory system; this number will surely continue to increase. There have been recent reports, for example, which have shown that captopril and other angiotensin-converting enzyme inhibitors may cause persistent cough (Stoller, 1988; Gibson, 1989), bronchial hyper-reactivity (Bucknall, 1988; Kaufman, 1989; Lindgren, 1989), and overt asthma (Popa, 1987; Lipworth, 1989). Bromocriptine has also been recently added to the list of drugs which may cause pleuropulmonary complications (McElvaney, 1988; Kinnunen, 1988). Aerosolized pentamadine has been implicated in the induction of bronchospasm, "spontaneous pneumothorax," and the development of atypical infiltrative patterns with recurrence of Pneumocystis carinii pneumonia The subject of drug-related pulmonary disease has become too broad to be covered comprehensively in this discussion, and has been dealt with in prior Grand Rounds (Pierce, 1972; Goldings, 1983). A number of excellent reviews have appeared in the literature which may be useful to the clinician (Rosenow, 1988; Cooper, 1986; White, 1985; Rosenow, 1972), including an entire issue of Clinics in Chest Medicine (Cooper, editor, 1990).

Many of the drugs which cause pulmonary toxicity result in common injury patterns and clinical presentations; the mechanisms involved are also shared by a number of different drugs. Further, any one drug may produce a number of different clinical syndromes and may have a variety of simultaneous (and interrelated) pathophysiologic mechanisms. This discussion will attempt to focus upon three drugs for which a reasonable amount of information is available and which serve to illustrate the more common clinical presentations

and pathophysiologic mechanisms of drug-induced pulmonary disease: amiodarone, bleomycin, and procainamide.

AMIODARONE: DIRECT TOXICITY AND HYPERSENSITIVITY

Clinical use of amiodarone was begun in 1967 in Europe where it was initially used for its antianginal properties. However, its potent suppressive effect on both supraventricular and ventricular dysrhythmias led to its expanded use as a class III antiarrhythmic agent. Unfortunately, significant side effects were noted in over 50% of patients treated (Waxman, 1982; Raeder, 1985; Harris, 1983). Toxic effects of amiodarone have included grey-blue skin discoloration, photosensitivity, corneal micro-deposits, neurologic and muscle disturbances, clinical and chemical thyroid abnormalities, as well as hepatic and gastrointestinal dysfunction (Smith, 1986; Harris, 1983; Wilson BD, 1991). Pulmonary toxicity was first reported in 1980 (Rotmensch, 1980) and has developed as one of the most significant and potentially lethal side-effects of amiodarone. As a consequence, when the drug was released in the United States in 1985, it was approved solely for use with severe, life-threatening, refractory ventricular arrhythmias (Mason, 1987).

TOXIC EFFECTS OF AMIODARONE

Gray-blue skin color
Photosensitivity
Corneal deposits
Neuromuscular weakness
Thyroid abnormalities
Hepatic dysfunction
GI dysfunction
Pulmonary toxicity

Amiodarone is an iodinated benzofurane derivative which is amphophilic. It binds avidly to plasma proteins and in tissue so that it has a volume of distribution near 5000L (Kennedy, 1990). Bioavailability is variable while uptake and distribution display a biphasic pattern; consequently the drug has a delayed onset of action and requires initial high loading doses (Haffajee, 1983). The drug is accumulated to remarkable levels (up to 1000 fold) in adipose tissue, liver, and lung and to a lesser extent in skin and myocardium (Mason, 1987). The terminal elimination half-life is therefore both long and variable, averaging 52 days (Holt, 1983).

Serum drug levels have not proven useful in predicting efficacy or toxicity (Kannan, 1987). Amiodarone resembles triiodothyronine, T3, and is associated with frequent alterations in thyroid function studies (especially reverse T3, rT3) as well as clinical hyper- or hypothyroidism. Although this led to speculation that measurement of serum rT3 levels might be predictive of efficacy and/or toxicity (Kerin, 1986), this has not proved to be the case. Thus, the pharmacologic properties of amiodarone make it a difficult drug to monitor and its toxic effects may persist for considerable periods even after drug cessation.

REPORTED INCIDENCE OF SYMPTOMATIC PULMONARY TOXICITY
IN PATIENTS TAKING AMIODARONE

Study	Patients (n)	Pulmonary Toxicity (%)
Marchlinski, 1982	70	5.7
McGovern, 1983	59	6.8
Morady, 1983	154	3.9
Kudenchuk, 1984	72	6.9
Raeder, 1985	217	3.7
Kennedy, 1987	154	9.7
Dean, 1987	171	6.4
Total	897	5.9%

The reported incidence of pulmonary toxicity due to amiodarone has varied considerably, in large part owing to imprecise definitions of clinical toxicity and the lack of a specific diagnostic test. If one accepts only reports of patients who are symptomatic, have new or worsening radiographic infiltrate(s), and for whom other causes have been reasonably excluded, then the incidence of pulmonary toxicity is approximately 6% (see table). The mortality associated with amiodarone pulmonary toxicity is more difficult to quantify as most patients treated are at high risk for sudden death and as the elimination time is so long following discontinuation. However, a mortality of 5-10% appears to be a reasonable estimate (Martin, 1988).

Pathophysiology

The pathogenesis and mechanism(s) of amiodarone pulmonary toxicity remain controversial. There are data to support both direct toxic effects of the drug and hypersensitivity immunologic mechanisms (Martin, 1990).

Amiodarone causes inhibition of lysosomal phospholipase A and C (Heath, 1985; Kodavanti, 1991). This results in the accumulation of a variety of different phospholipids within the lysosomes of affected cells in experimental models (Kodavanti, 1991; Wilson JS, 1991) and in humans (Martin, 1988). In the lung, this intracellular phospholipidosis occurs predominately in alveolar macrophages. Similar phospholipid accumulation has been demonstrated in other tissues in which amiodarone concentrates including myocardium, liver, and skin (Arbustini, 1991). Perhaps through a similar mechanism, serum lipoprotein levels are also be increased by amiodarone (Albert, 1991) and this effect is independent of alterations in thyroid function (Wiersinga, 1991).

The intracellular phospholipidosis leads to the characteristic finding of "foamy" alveolar macrophages in histologic sections; in patients with pulmonary toxicity, these foamy macrophages are found in abundance in association with interstitial inflammation, fibrosis, and hyperplasia of type II pneumocytes (Myers, 1987). These characteristic appearing macrophages can also be found in cytologic preparations from the bronchoalveolar lavage of

patients with pulmonary toxicity (Martin, 1985; Israel-Biet, 1987). The bronchoalveolar lavage of amiodarone patients contains significantly increased amounts of phospholipids (Martin, 1988) which is confined to the cellular fraction (Martin, 1988; Nicolet-Chatelain, 1991). Isolated endothelial cells can be induced to develop intracellular phospholipidosis in vitro and this is associated with evidence of cell damage (Martin, 1985). In animal studies there is evidence of dose-related pulmonary accumulation of amiodarone and phospholipids (Wilson BD, 1991) which correlates as well with pulmonary inflammation (Wilson BD, 1990; Wilson BD, 1991).

These observations suggest that amiodarone may thus cause direct cellular toxicity through the intracellular accumulation of phospholipids. The major metabolite of amiodarone is desethylamiodarone (DEA) and it also possesses potent antiarrhythmic activity. Unfortunately DEA is not a clinically relevant alternative as it causes cytotoxic effects which are similar to (or greater than) the parent compound (Kodavanti, 1991; Wilson BD, 1990; Wilson BD, 1991; Daniels, 1989).

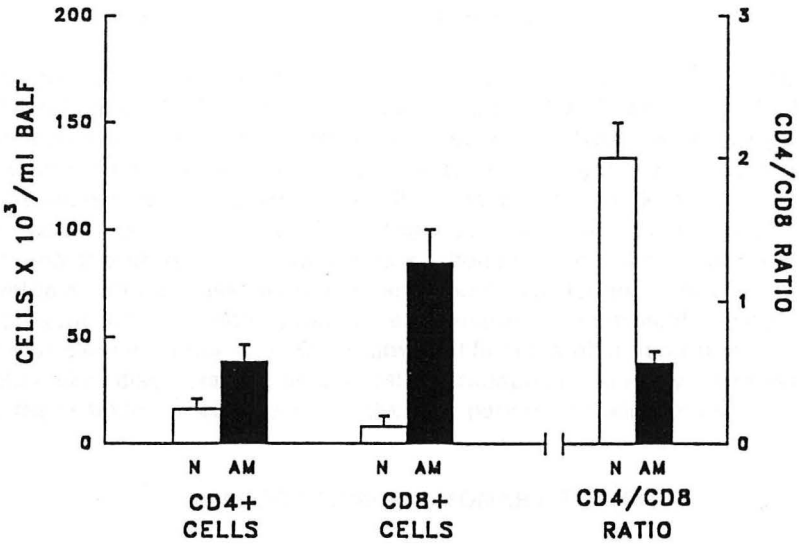
Although intracellular phospholipid accumulation is associated with toxicity, it is not entirely clear how injury actually occurs. In vitro studies have provided evidence that amiodarone may cause oxidant lung injury (Hasan, 1984; Li, 1987; Kennedy, 1988). The possibility that the iodine content of the drug is somehow important cannot be discounted as well. Patients receiving amiodarone tend to have high attenuation coefficients in the lung parenchyma on chest CT scan (Kuhlman, 1990) which has been attributed to the iodine content serving as a contrast agent. The significance of this finding is not clear, but there have been 3 reports of the rapid development of a fatal ARDS-like syndrome immediately following intravenous administration of radiographic contrast media to patients with amiodarone pulmonary toxicity (Wood, 1985; Kuhlman, 1990).

While both amiodarone and DEA cause direct toxicity, it is unlikely that this completely explains the pathogenesis of pulmonary toxicity. A dose-response relationship in human subjects is suggested by the observation that pulmonary toxicity was rarely recognized in Europe when first introduced, but became common when used in the United States. In Europe smaller doses were typically used for antianginal and supraventricular arrhythmias, while in the United States higher doses were used to treat refractory ventricular arrhythmias. However, pulmonary toxicity has been reported in patients receiving relatively small doses (less than 200 mg/day) for brief periods and many patients receive very high cumulative doses without toxicity.

Macrophage phospholipidosis is highly characteristic for amiodarone toxicity; however, similar changes can be demonstrated in other conditions and in response to other cationic amphophilic drugs, not all of which are associated with clinically significant pulmonary toxicity (Reasor, 1981). Further, macrophages obtained from patients receiving amiodarone who are without evidence of clinical toxicity also demonstrate similar degrees of macrophage phospholipidosis (Liu, 1986) and have similar bronchoalveolar and biopsy findings (Liu, 1986; Kennedy, 1987; Myers, 1987). These findings therefore suggest that intracellular phospholipidosis is not specific for amiodarone toxicity and imply that other or additional pathophysiologic mechanisms may be important.

Recent studies have suggested an immunologic role in the development or amplification of amiodarone pulmonary toxicity. Although a lung autoantibody has been described in a patient with amiodarone toxicity (Fan, 1987), the predominance of data suggest that cell-mediated mechanisms are more important. Bronchoalveolar lavage from approximately 70% of patients with amiodarone toxicity demonstrate an absolute and relative lymphocytic alveolitis (Israel-Biet, 1987; Akoun, 1991; Martin, 1990). Phenotypically the lymphocytes are virtually all T-lymphocytes, with a CD8 + predominance (giving a reduced CD4 + /CD8 + ratio). Thus, many patients have a significant increase in alveolar suppressor/cytotoxic (CD8 +) lymphocytes. This type of CD8 + lymphocytic alveolitis is similar to the pattern seen in hypersensitivity pneumonitis due to inhaled allergens (Leatherman, 1984; Semenzato, 1986). With clinical resolution of the pulmonary toxicity following withdrawal of amiodarone (with or without steroids), this lymphocytic alveolitis tends to resolve (Israel-Biet, 1987). Lung natural killer cell activity has been shown to be increased in animal studies (Karpel, 1991).

BRONCHOALVEOLAR LAVAGE LYMPHOCYTES IN NORMALS (N) AND AMIODARONE PATIENTS (AM)



COMPILED FROM ISRAEL-BIET, 1987 AND AKOUN, 1991

While these observations strongly suggest a cell-mediated immunologic mechanism in the development of amiodarone pulmonary toxicity, at least 30% of patients with symptomatic disease do not show this CD8 + lymphocytic alveolitis (Akoun, 1991; Israel-Biet, 1987). Asymptomatic pigeon breeders, with no evidence of clinical hypersensitivity pneumonitis, typically demonstrate a lymphocytic alveolitis on bronchoalveolar lavage which is similar to that seen in patients with overt disease (Johnson, 1989). The same is true for asymptomatic farmers (Cormier, 1986). Bronchoalveolar lavage has been reported in a small number of asymptomatic patients taking amiodarone who had no evidence of toxicity; lavage data paralleled that of normal volunteers except that the CD4+/CD8+ ratio is decreased (Israel-Biet, 1987). It is also interesting that in a report of two patients who had amiodarone pneumonitis who were inadvertently re-challenged, symptoms did not recur immediately, but were delayed by 6 and 12 months (Chrysanthopoulos,1988).

Thus, the findings suggestive of a hypersensitivity response are not universally present and may not be specific. While it is possible that cell-mediated immunity plays a role, a direct causal relationship has not yet been established. The cellular responses described may represent events which are secondary to byproducts of direct drug toxicity; such events might thus serve to amplify the injury rather than being the direct cause. Strain differences in animal models of amiodarone toxicity (Wilson BD, 1990; Wilson BD, 1991) as well as the wide variation in dose-responsiveness in humans suggest a genetic susceptibility to amiodarone and/or secondary immune responses.

Clinical Findings

The clinical features of amiodarone pulmonary toxicity are characteristic, but not specific (Marchlinski, 1982; Kennedy, 1987; Martin, 1988; Kennedy, 1990). Virtually all patients complain of dyspnea, especially with exertion. Non-productive cough is common. Constitutional symptoms include fever, malaise, and weight loss. Chest pain, usually of a pleuritic nature, is present in many cases. Proximal muscle weakness and myalgias have also been reported (Marchlinski, 1982). Symptoms usually do not occur until after the patient has been receiving the drug for several months, though onset can occur earlier. Patients will either develop an abrupt onset with fever and cough which mimics pneumonia or have a more insidious presentation in which dyspnea predominates. The physical findings include rales and (occasionally) pleural friction rub. Other physical findings of amiodarone may be present such as grey-blue skin discoloration or corneal microdeposits (usually seen only by slit-lamp); however, these finding merely confirm that the patient is taking the drug.

AMIODARONE PULMONARY TOXICITY

Dyspnea
Non-productive cough
Fever
Malaise
Weight loss
Chest pain

Laboratory studies are entirely non-specific and include leukocytosis, elevation of the erythrocytes sedimentation rate (ESR), and an increase in serum lactate dehydrogenase (Martin, 1988). The abnormalities of thyroid function mentioned earlier are not specific for pulmonary toxicity, including the elevation of reverse T3.

RADIOGRAPHIC FINDINGS OF AMIODARONE TOXICITY

Diffuse infiltrates
Localized infiltrates
Nodular or mass lesions
Pleural effusions
Enhanced CT attenuation

The typical radiographic pattern is one of diffuse, bilateral infiltrates. These may be either interstitial or alveolar in nature (Marchlinski, 1982; Kennedy, 1987). A third of patients may have well-localized infiltrates, which may be lobar (Kennedy, 1987). Nodular (Patel, 1987; Arnon, 1988), mass-like (Piccione, 1989), and cavitary (Pollak, 1984) densities have been described in some patients. Small pleural effusions may also occur (Kennedy, 1987).

Pulmonary function tests of patients with symptomatic amiodarone pulmonary toxicity will typically demonstrate a restrictive pattern with reduced diffusion capacity (DLCO) and arterial hypoxemia (Kudenchuk, 1984; Gleadhill, 1989; Magro, 1988). The diagnosis of pulmonary toxicity should be questioned if pulmonary function tests (especially the DLCO) are normal (Gleadhill, 1989). However, while these abnormalities are present in most cases of overt toxicity they are highly non-specific and would be expected in most conditions in the differential diagnosis. Further, interpretation of changes in the DLCO for individual patients over time must take into account the large variability inherent in this test; the minimum coefficient of variation for the DLCO in clinical laboratories is 10% and variations of from 15-20% can be found in stable patients with repeated testing (Crapo, 1986).

Although earlier reports suggested that the pulmonary functions of some asymptomatic patients taking the drug might detect "subclinical disease" or predict which patients might developed toxicity prior to actually starting therapy (Kudenchuk, 1984; Adams, 1986), prospective studies have not substantiated this view (Adams, 1988; Magro, 1988; Gleadhill, 1989). Indeed, no pre-existing abnormality of pulmonary function testing, chest X-ray finding, or drug-dose relationship has been shown to be useful in predicting drug toxicity in individual patients. In patients who were being followed prospectively with serial pulmonary function testing, there was no premonitory decline in any variable (including DLCO) which heralded the onset of toxicity in those who developed overt disease (Gleadhill, 1989; Magro, 1988). Some have questioned the wisdom of serial pulmonary function testing in patients receiving amiodarone as they are not useful in predicting toxicity and might inappropriately lead to withdrawal of therapy in some patients (Horowitz, 1988; Mason, 1989). Based upon these considerations, pulmonary function testing (including DLCO and arterial blood gas testing) should be obtained prior to (and perhaps once or twice shortly after) institution of therapy for purposes of establishing the patient's baseline; subsequent testing should be reserved for those patients who develop new pulmonary symptoms or radiographic infiltrates.

Diagnosis

The clinical findings of amiodarone pulmonary toxicity are highly non-specific and the differential diagnosis is necessarily quite broad. The most commonly encountered entities in this setting, however, include congestive heart failure (CHF), infection, pulmonary embolism/infarction, and malignancy. Patients receiving amiodarone have a very high prevalence of impaired left ventricular function and thus CHF is ultimately diagnosed in more than a third of cases. The symptoms, chest X-ray, and pulmonary function changes (restrictive pattern with reduced diffusion capacity, DLCO) of amiodarone toxicity are virtually indistinguishable from CHF. Thus, an empiric trial of diuresis or even right heart catheterization may be justified, especially given the problematic nature of treating amiodarone toxicity (see below).

FINAL DIAGNOSIS IN PATIENTS SUSPECTED OF HAVING AMIODARONE PULMONARY TOXICITY (n=47)

Amiodarone pulmonary toxicity	55%
Congestive heart failure	36
Pneumonia	6
Pulmonary embolism/infarction	2
Other	1

Gleadhill IC. Am J Med 86: 4, 1989.
Zhu YY. Chest 93: 1126, 1988.

Fever, lung infiltrate, and leukocytosis may suggest infection, and thus appropriate cultures and treatment with antibiotics may be instituted. The presence of any of these findings, especially with pleural pain/effusions would also be compatible with pulmonary thromboembolic disease. The diagnosis of pulmonary embolism should be pursued when indicated on clinical grounds. In this regard, however, the clinician should be aware that there have been reports of fatal onset of ARDS in patients receiving amiodarone after administration of intravenous contrast material for pulmonary angiography (Wood, 1985; Kuhlman, 1990). Especially when the presentation is one of insidious onset of dyspnea with diffuse infiltrates, malignancy must also be excluded before rendering a diagnosis of amiodarone toxicity. In this regard, lymphangitic spread of carcinoma, lymphoid malignancy, and primary bronchoalveolar cell carcinoma should be considered.

Chest computed tomography often demonstrates that the radiographic abnormalities observed on plain films have a high attenuation, presumably owing to the high iodine content of the drug (Standertskjold, 1988; Kuhlman, 1990). Although this has been suggested to be useful in diagnosis, it likely represents drug accumulation in the lung and is not necessarily specific for toxicity; similar findings have been described in asymptomatic patients taking the drug who have normal plain films of the chest (Nicholson, 1989).

As with other interstitial diseases, gallium-67 scanning has been advocated for the diagnosis of amiodarone pneumonitis (Dake, 1985; van Rooij, 1984; Moinuddin, 1986; Lecklitner, 1988). It is thought to be especially useful in distinguishing CHF (which should not have uptake) from other causes. However, analogous to other interstitial diseases, the clinical utility of this test is questionable for it is difficult to interpret, requires 24 to 72 hours to perform (Martin, 1990) and is neither entirely sensitive nor specific. False positive (Zhu, 1988; Xaubet, 1987) and false negative (Fraioli, 1990; Zhu, 1988) results can occur in the setting of suspected amiodarone pulmonary toxicity. A newer study involving Tc-99 labeled diethylene triamine penta-acetic acid (DTPA) has been described which appears to discriminate between amiodarone pneumonitis and asymptomatic patients taking the drug (Terra-Filho, 1990). The study is said to detect abnormal permeability of the alveolar-capillary membrane and as such might be useful in distinguishing CHF from drug-toxicity; a greater experience with the study is needed before its wide-spread use can be recommended.

Bronchoscopy with bronchoalveolar lavage has played an important role in furthering our understanding of the pathogenesis of amiodarone toxicity as described in detail earlier. While the findings of foamy alveolar macrophages and lamellar lysosomal inclusions are characteristic of amiodarone, these histo/cytologic and ultrastructural changes are not specific for the drug and do not distinguish between toxic and non-toxic patients (Kennedy, 1987; Kennedy, 1990). Thus, these findings merely confirm exposure to the drug and in themselves add little to the clinical history. As noted earlier, phenotypic characterization of bronchoalveolar lavage lymphocytes may prove of some use when a reduced CD4+/CD8+ ratio is found in the appropriate clinical setting. However, the overall utility of this finding remains limited as 30% of patients with clinical toxicity lack the finding, as limited data exist with respect to asymptomatic patients receiving the drug, and as this methodology is not yet widely available for clinical purposes (see above). Thus, the principle utility of bronchoscopy in patients with suspected amiodarone pulmonary toxicity is for the exclusion of other conditions, especially infection and malignancy.

DIAGNOSIS OF AMIODARONE PULMONARY TOXICITY

Compatible clinical symptoms
Radiographic infiltrate(s)
Exclusion of other conditions

Given the lack of specific markers for amiodarone pulmonary toxicity, the diagnosis remains clinical and is based upon the exclusion of other possible causes of the patient's findings. The diagnosis should be made when: (1) the patient has been taking amiodarone, (2) the patient has new, compatible symptoms, (3) there are new or changing radiographic infiltrates, and (4) other diagnostic considerations have been reasonably excluded (especially CHF, infection, thromboembolism, and malignancy). The work-up might thus include appropriate cultures, bronchoscopy, evaluation for pulmonary embolism, and especially tests or empiric therapy for congestive heart failure.

Therapy

The treatment of amiodarone pulmonary toxicity would appear to be deceptively simple: discontinuation of the drug. Indeed, most patients who develop toxicity will have complete or near resolution of symptoms and other findings with drug elimination (Kennedy, 1990). The time course of this response may be somewhat prolonged (weeks to months) given the long half-life of the drug, but is nearly complete in the majority of cases. Unfortunately this apparently favorable outcome must be tempered by other findings. The mortality of amiodarone lung toxicity is reasonably estimated to be 5-10% (Martin, 1988). However, the mortality associated with drug discontinuation (within one month) may be as high as 45% (Dean, 1987). This is not entirely surprising as most patients who die shortly after discontinuation do so as a consequence of sudden cardiac death, to which virtually all are predisposed by definition. However, it is in sharp contrast to the usual prognosis of patients who are maintained on the drug and have an expected one year mortality of 14-19% (Peter, 1983; CASCADE Study, 1991). Obviously, if the patient can receive alternative treatment, then this should be undertaken. However, assuming that the patient was initially started on amiodarone only after being found to have truly refractory, life-threatening ventricular dysrhythmias, the decision to withdraw the drug in response to toxicity cannot be made lightly. Despite the only weak dose-response relationship between amiodarone therapy and toxicity, there are well-documented reports of clinical improvement following reduction in amiodarone doses alone (Leech, 1984; Martin, 1988).

TREATMENT OPTIONS FOR AMIODARONE PULMONARY TOXICITY

Stop Amiodarone
Lower dose ($\pm$ steroids)
Same dose with steroids

The role of steroids in the management of amiodarone lung toxicity is controversial. The available data suggesting a role for hypersensitivity immune responses in the pathogenesis of the disorder might suggest a role for immunosuppressive therapy. However, most reports of improvement following cessation of drug differ little from those in which concomitant steroid therapy was employed. Not surprisingly, controlled trials are lacking, and not likely to be forthcoming. There are reports of patients who have developed toxicity and who were maintained on the same or lower doses of amiodarone who improved with the addition of steroids (Zaher, 1983; Myers, 1987). Thus, in patients who are severely symptomatic or in whom continuation of amiodarone is felt to be necessary, the addition of therapeutic doses of corticosteroids may be indicated.

BLEOMYCIN: OXIDANT INJURY AND FIBROSIS

Bleomycin is a cancer chemotherapeutic antibiotic agent which is derived from bacterial glycoprotein products (Jules-Elysee, 1990). While it is effective as a single agent, it is used primarily in combination regimens for malignant lymphomas, germ cell neoplasms, and some squamous cell carcinomas (Yagoda, 1972; Blum, 1973; Bennett, 1979). The drug is particularly useful in combination therapy because of it's lack of marrow suppression and as it tends to "synchronize" tumor cells, enhancing susceptibility to other cytotoxic agents. Bleomycin's antitumor effects are largely mediated through disruption of DNA, probably via iron-dependent oxygen free-radical formation (Bennett, 1979). The drug is rapidly excreted except when renal function is significantly impaired, i.e. at creatinine clearances of less than 25 ml/min.

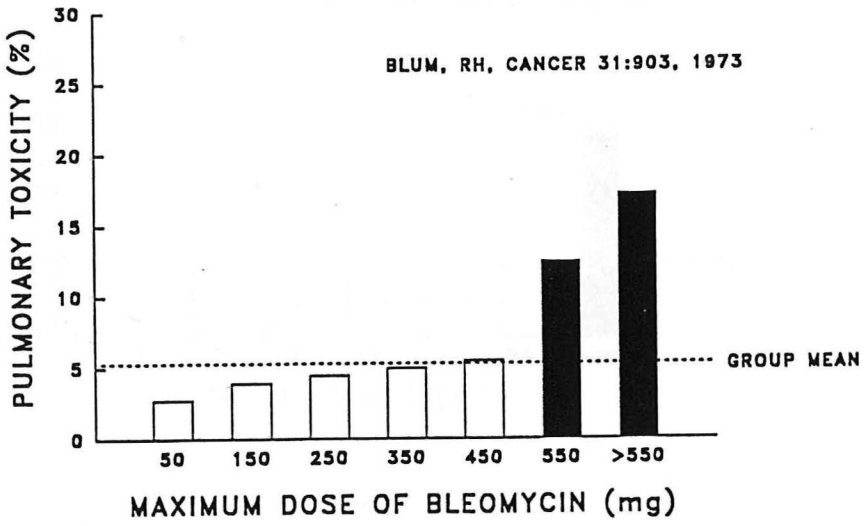
The principle toxicity limiting the use of bleomycin is pulmonary. This usually takes the form of an acute oxidant lung injury followed by progressive pulmonary fibrosis (Yagoda, 1972; Blum, 1973). However, a syndrome of pulmonary eosinophilic pneumonia has also been reported in a small number of patients (Holoye, 1978; Yousem, 1985). The overall incidence of pulmonary toxicity is 11-13% (Blum, 1973; Scheulen, 1987). The development of lung disease carries a 10% mortality, usually from respiratory insufficiency developing over a period of months (Scheulen, 1987); rapidly progressive fatal cases have been reported as well (Dee, 1987). If the patient survives the initial injury period, then recovery is usually complete (Van Barneveld, 1987).

RISK FACTORS FOR BLEOMYCIN PULMONARY TOXICITY

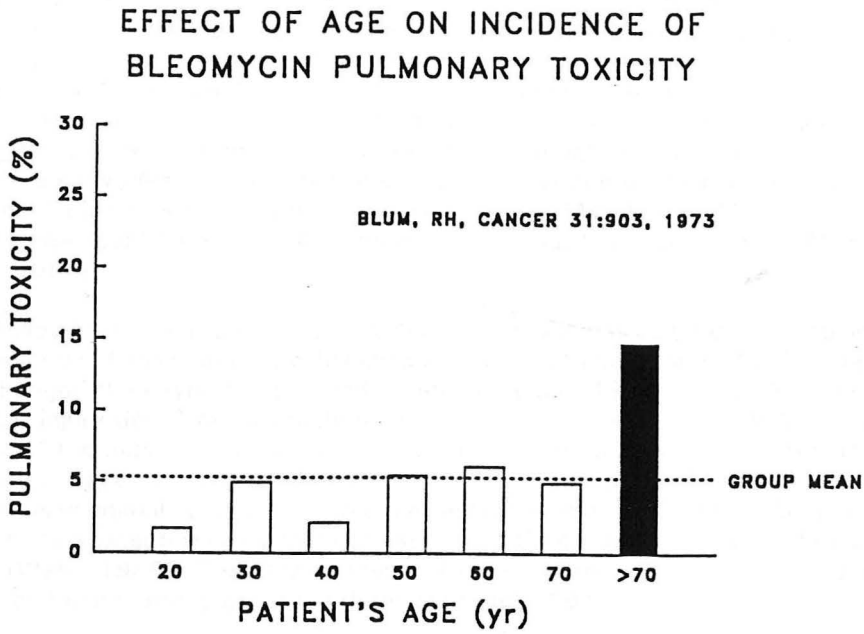
Definite	Possible
Cumulative dose	Age over 70 years
Supplemental oxygen	Renal insufficiency
Chest radiotherapy	Route of administration
	Other cytotoxic agents

The development of bleomycin lung injury is influenced by several risk factors, some of which are well established and others which are somewhat speculative. The cumulative dose of bleomycin which the patient has received influences the incidence of toxicity in a non-linear fashion. Up to total doses of approximately 450 mg the incidence remains fairly constant at 3-5%, and toxicity has been seen after as little as 20 mg (Bechard, 1987). However, above doses of 450 mg the incidence jumps to 13-17% (Blum, 1973). Lung injury and the resulting inflammatory response is dose-dependent in animal models of bleomycin pulmonary toxicity (Moseley, 1984).

EFFECT OF CUMULATIVE DOSE OF BLEOMYCIN
ON THE INCIDENCE OF PULMONARY TOXICITY



Chest radiotherapy appears to have a synergistic effect with bleomycin in producing lung injury in animal experiments (Collis, 1983) and this enhanced toxicity has been observed in humans as well (Jules-Elysee, 1990). A considerable body of evidence from animal models clearly establishes that supplemental oxygen, which is itself toxic, predisposes to bleomycin induced injury. Clinical reports have substantiated the contributory role of oxygen as well (see below). There is likely a higher incidence of toxicity in patients over the age of 70 years, though this is based upon a small number of patients (Blum, 1973). Renal insufficiency is also said to enhance toxicity, but this likely only occurs at extremely low levels of renal function (Van Barneveld, 1984; Jules-Elysee, 1990). The route and/or method of drug administration (Krakoff, 1977) and the concomitant use of other toxic agents (Rabinowits, 1990) have also been reported to increase the frequency of pulmonary toxicity, though this is less well established.



Pathophysiology

Animal models of bleomycin-induced lung disease have contributed greatly to our knowledge of this disorder and to a better understanding of lung injury and fibrosis in general (Chandler, 1990). Bleomycin induces an acute injury pattern which, though generalized, tends to predominate in subpleural locations. The histopathologic changes, though characteristic, are not specific and can be seen with other cytotoxic agents and with oxygen toxicity. The primary injury appears to cause a loss of type I pneumocytes and the hyperplastic proliferation of type II alveolar epithelial cells. These type II pneumocytes are very prominent and have bizarre shapes, abundant cytoplasm, prominent nucleoli, and marked variation in size (Jules-Elysee, 1990). There is frequently accumulation of alveolar proteinaceous material. These hyperplastic changes are accompanied by an interstitial pleomorphic cellular infiltration; polymorphonuclear leukocytes predominate early, followed by mononuclear cellular infiltration, and culminating in fibrosis.

The acute injury appears to be mediated in large part by the production of oxygen-derived free-radicals. Hyperoxic conditions potentiate bleomycin injury and mortality in animals (Rinaldo, 1982; Tryka, 1982; Coursin, 1988), while hypoxia may actually be protective. Supplemental oxygen has also been reported to worsen bleomycin injury in humans as well (Bauer, 1983; Ingrassia, 1991). Pre-treatment of animals with antioxidants attenuates the toxicity of bleomycin (Wang, 1989). The oxidative injury appears to be dependent upon iron. Iron chelation with desferoxamine ameliorates bleomycin injury in vitro (Martin, 1987) and in vivo (Chandler, 1988). Iron deficiency produces reduced fibrosis in an animal model as well (Chandler, 1988).

At the molecular level, this early phase of injury is accompanied by alterations in the interstitial extracellular matrix (Lazo, 1990) with accumulation of hyaluronic acid (Nettelbladt, 1989; Bray, 1991) followed by collagen deposition (Chandler, 1990). There are concomitant changes in alveolar phospholipids, including alterations in surfactant which are associated with increased lung elastic recoil (Thrall, 1987; Low, 1988; Horiuchi, 1990). The early injury also leads to the local production of chemotaxins for polymorphonuclear leukocytes (PMNs); this leads to the early PMN alveolitis which is detectable with bronchoalveolar lavage and which resembles the findings in idiopathic pulmonary fibrosis (Moseley, 1984; White, 1987). While the PMNs may contribute to lung injury in this setting, the exact role of PMNs is not clear (Osanai, 1988).

Following the acute injury and PMN alveolitis, there is influx of mononuclear cells and local activation of coagulation mechanisms which leads to fibrin deposition. In animal studies, these changes then typically proceed to fibrosis (Idell, 1987). It is clear, however, that bleomycin injury does not inevitably lead to fibrosis (Van Barneveld, 1987). Although the intensity of the initial injury appears to be a prime determinant of ultimate fibrosis (Shen, 1988), other factors may modulate the process. Prostaglandin synthesis inhibition alters fibrogenesis in animal models, though the effect is variable (Giri, 1987). Genetic factors also contribute to susceptibility as there are species differences in animal models of bleomycin toxicity (Ward, 1988). This heterogeneity of responsiveness would appear to include both immune and non-immune genetic differences (Rossi, 1987).

Clinical Findings

Patients usually have a subacute presentation with onset of symptoms 4 to 10 weeks (rarely up to 6 months) after bleomycin treatment. Symptoms almost invariably include exertional dyspnea; non-productive cough is also common. Fever, usually low grade, is frequent, but highly variable in its incidence. Chest pain is uncommon, but has been described. The physical exam is usually only remarkable for basilar rales, though this finding may be absent. Laboratory exam is unrevealing except that the patient may be hypoxemic (Jules-Elysee, 1990).

The chest X-ray of patients with bleomycin toxicity demonstrates bilateral infiltrates. These tend to be diffuse, but may be very patchy, especially with early disease. The process is said to typically begin in subpleural locations; new nodular infiltrates in the costophrenic angles are a characteristic early finding (Jules-Elysee, 1990). While the infiltrates are typically diffuse, they may be localized. Lobar consolidation simulating bacterial pneumonia can be seen. Of particular concern is that, while uncommon, patients with pulmonary toxicity have been described with multiple nodules or masses resembling metastatic disease; this has been most often reported in patients with germ cell neoplasms (Zucker, 1987; Trump, 1988; Cohen, 1989) or with osteogenic sarcoma (Scharstein, 1987; Santrach, 1989). These lesions can (rarely) cavitate (Talcott, 1987). Although CT scan determination of parenchymal density has been reported to correlate with bleomycin toxicity (Bellamy, 1987), this finding is highly non-specific and of questionable clinical utility.

Pulmonary function tests will generally demonstrate a restrictive pattern with reduced DLCO and hypoxemia. Although much has been written about the components of the DLCO which may change with "early" disease (the pulmonary capillary volume, Vc, tends to be

abnormal in many patients receiving the drug), the routine use of serial pulmonary function testing in these patients is of doubtful clinical utility (Luursema, 1983; Van Barneveld, 1984). Indeed, these changes are not specific and many falsely abnormal results are obtained, especially due to patient weakness, pain, narcotic use, anemia, and inherent test variability (Lewis, 1980). As such, pulmonary function testing should be performed at baseline and thereafter only when the patient develops new signs or symptoms. Changes in pulmonary function should not be used to define bleomycin toxicity in clinical settings, but used merely in a supportive diagnostic context or to quantify impairment.

Diagnosis

The most important differential diagnostic considerations in patients with findings suggestive of bleomycin pulmonary toxicity includes recurrent or metastatic malignancy and infection, especially with opportunistic organisms when the patient is immunocompromised as a consequence of the primary malignancy or other chemotherapeutic agents. Although the histologic findings with bleomycin toxicity are characteristic, they are not specific. Bronchoalveolar lavage also is non-specific and will usually demonstrate an increased number and percentage of polymorphonuclear leukocytes (see above). Thus, the role of bronchoscopy or even thoracotomy, in patients with suspected bleomycin toxicity is to evaluate for malignant and infectious etiologies. The diagnosis of bleomycin should be made when the patient has compatible clinical signs and symptoms, new or changing radiographic infiltrates, and other etiologies have been reasonably excluded.

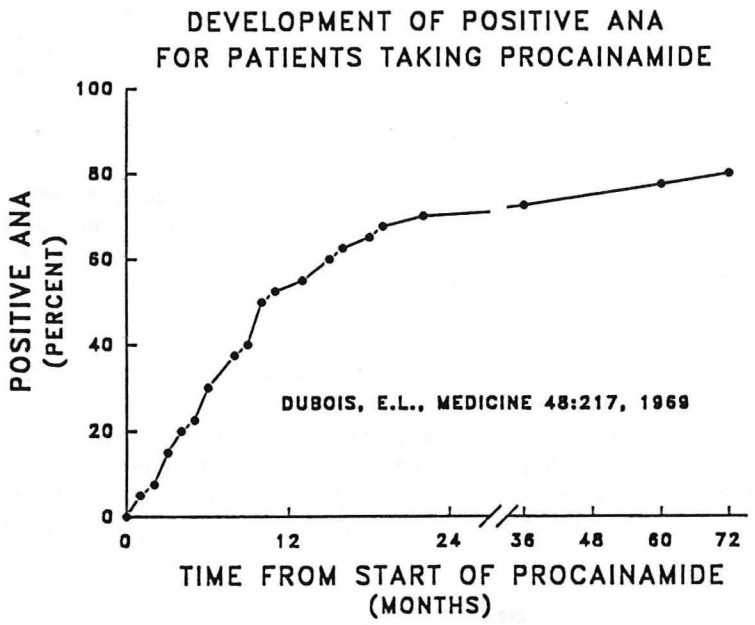
Therapy

The treatment for bleomycin toxicity is cessation of drug therapy. In the majority of cases this will lead to symptomatic, radiographic, and pulmonary function improvement in weeks to months. In the majority who survive the initial illness, recovery can be expected to be complete (Van Barneveld, 1987). As the ultimate outcome is most likely dependent upon the severity of the initial injury (Shen, 1988) and as experimental studies have shown little significant modulation of the pulmonary response with steroid administration (Grunze, 1988), routine use of steroids in these patients cannot be recommended. When given, steroids should likely be used only during the initial phase of severe bleomycin reactions. Given the abundance of data suggesting a pivotal role for oxygen in bleomycin toxicity (see above), supplemental oxygen should be used with extreme caution in patients receiving the drug and should be maintained at minimum levels (e.g. to maintain arterial saturation near 90%).

PROCAINAMIDE: AUTOIMMUNITY

More than 50 different drugs and chemicals have been reported to have caused a clinical syndrome resembling systemic lupus erythematosus (SLE); of these, drug-induced lupus (DIL) has been most common and best described for hydralazine and procainamide (Solinger, 1988). Drug-specific differences exist in patients who develop DIL (e.g. anti-nuclear antibody specificity). However, the clinical features are strikingly similar, so that procainamide associated DIL may serve as a prototype.

Patients taking procainamide for prolonged periods will commonly develop anti-nuclear antibodies (ANA); as many as 50-80% of patients will be found to have a positive ANA (Dubois, 1969; Blomgren, 1969). The development of a positive ANA marks the development of serologic autoimmunity and will be present in virtually all patients with DIL. However, only 12-29% of patients taking procainamide will actually have any of the clinical features of DIL (Goldings, 1983).



Clinical Findings

The clinical features of DIL closely resemble idiopathic SLE, especially with respect to signs of polyserositis. The commonest findings in DIL are pleuritis, pleural effusion(s), pulmonary infiltrates, and pericarditis. Arthralgias, myalgias, and fever are also common. However, in contrast to idiopathic SLE, renal and CNS involvement are exceptionally rare (Solinger, 1988). It is postulated that these clinical differences might in part be due to the absence of anti-nuclear antibodies specific for native (or double-stranded) DNA and/or the absence of significant complement activation in patients with DIL (Blomgren,1972). Leukopenia and anemia are less common in DIL than in idiopathic SLE; positive tests for rheumatoid factor and LE preparations can be found in both.

CLINICAL FEATURES OF IDIOPATHIC AND DRUG-INDUCED LUPUS SYNDROME

	Idiopathic SLE	Procainamide DIL
Pleuritis	+	+
Pleural effusion	+	+
Pulmonary infiltrates	+	+
Pericarditis	+	+
Arthralgias	+	+
Myalgias	+	+
Fever	+	+
Rash	+	±
Renal	+	0
CNS	+	0
Lymphadenopathy	+	0
Hypocomplementemia	+	0
Leukopenia	+	0
Anemia	+	0

The demographic profile is shifted considerably in patients with procainamide DIL. The predilection of idiopathic SLE for young black women is lost so that the typical patient with DIL is middle aged, white and may be equally likely to be a man or woman (Goldings,1983). This shift is clearly related in part to the population which is usually treated with procainamide, but may also suggest important genetic differences with respect to susceptibility to disease in the presence of autoantibodies.

Diagnosis

The diagnosis of DIL should be made when the patient has: (1) no prior history of idiopathic SLE prior to taking procainamide, (2) a positive ANA, (3) clinical features of lupus, and (4) other possible causes of the clinical findings have been excluded. The diagnosis can be considered firm if clinical findings and serology revert to normal after discontinuation of procainamide. Most patients will fulfill at least 4 of the standard criteria for the diagnosis of lupus, though a single compatible clinical finding (e.g. pleural effusion) may be sufficient if the other features listed above are satisfied (Goldings, 1983).

DIAGNOSIS OF DRUG-INDUCED LUPUS

No prior history of SLE
Positive ANA
Clinical feature(s) of lupus
Exclusion of other conditions

When a patient taking procainamide has a positive ANA and the typical presentation of fever, myalgias, arthralgias and pleuropericarditis, the principle differential diagnostic consideration is viral infection. When there is isolated pleural or parenchymal pulmonary disease, then bacterial (or mycobacterial) infections, thromboembolic disease, and malignancy must be considered. While the ANA will be positive in all cases, a positive test is not specific and thus is not sufficient to make the diagnosis; other diseases must be independently and reasonable excluded. Bronchoscopy in these patients has a limited role, as the pathology is highly non-specific and bronchoalveolar lavage demonstrates increased numbers of PMNs (Goldberg, 1984), which is also non-specific given the usual differential diagnosis. The principle utility of bronchoscopy in patients with suspected DIL is to exclude malignancy.

Therapy

Treatment of patients with procainamide-induced lupus consists of discontinuing the drug. This is usually not difficult as effective alternative treatments usually exist and as the drug is rapidly cleared. In the majority of cases drug withdrawal results in prompt resolution of symptoms over a period of days to weeks. Serum ANAs will also resolve, though more slowly. Although complete resolution can be expected in most cases, symptoms may persist in a small minority (Byrd, 1969). Aspirin or non-steroidal anti-inflammatory agents may be helpful, especially for the symptoms of polyserositis (Solinger, 1988). Prednisone may be needed on occasion, especially in refractory or life-threatening cases such as pericardial effusion with tamponade (Greenberg, 1972).

Anti-Nuclear Antibodies

Virtually all patients with either idiopathic SLE or DIL will have a positive ANA. The titers do not offer significant discrimination in individual patients. The antinuclear antibody profile differs when comparing idiopathic SLE and DIL (see table), as do the nuclear antigenic specificity of the antibodies (Solinger, 1988). Patients with both SLE and DIL will frequently have antibodies to denatured, or single-stranded, DNA (ssDNA); antibodies to native, or double-stranded, DNA (dsDNA) are found in patients with SLE but not those with DIL (Winfield, 1974). Similarly, antibodies to the Smith antigen (Sm), one of the extractable nuclear antigens (ENA) are unique to idiopathic SLE, though only about 20-30% of patients with SLE have these antibodies (Tan, 1982). Antibodies directed to the histone proteins of the deoxyribonucleoprotein complex are characteristic of DIL and are found in the vast majority (Rubin, 1985; Totoritis, 1988). While as many as 90% of DIL patients have anti-histone antibodies, 30% of patients with SLE will also have histone antibodies (Gohill, 1985). The specificity of the anti-histone antibodies in patients with idiopathic SLE may be directed to any of the five different classes of histones, while those with procainamide DIL are restricted primarily to H2A-H2B histone complexes (Gohill, 1985; Rubin, 1985; Portanova, 1987; Totoritis, 1988). Interestingly, other drugs causing DIL will also lead to anti-histone antibodies, but they tend to be restricted to different classes of histone proteins. Hydralazine induces histone antibodies to the H3 and H4 classes (Portanova, 1987; Craft, 1987). However, the restricted nature of these antibodies may not be as definite as earlier reports have suggested (Pauls, 1990).

ANTI-NUCLEAR ANTIBODY PROFILES

	Idiopathic SLE	Procainamide DIL	Procainamide Asymptomatic
ANA	+ + +	+ + +	+ +
Diffuse	+ +	+ +	+ +
Peripheral	+	+	+
Speckled	+ +	0	0
Anti - ss DNA	+ + +	+ + +	+ +
Anti - ds DNA	+ +	0	0
Anti - Sm (ENA)	+	0	0
Anti-histone	+ +	+ + +	+
Epitopes	All five	H2A, H2B	H2A, H2B

Solinger AM, Rheum Dis Clin N Am 14: 187, 1988.

These observations regarding the patterns and antigenic specificities of anti-nuclear antibodies are important in helping to understand the mechanisms underlying the development of lupus and may provide clues regarding the different clinical spectrum seen in DIL as compared to SLE (e.g. the lack of renal disease). However, for clinical purposes these differences in ANAs are not as useful. Distinguishing a new case of idiopathic SLE in a patient who is taking procainamide from a case of DIL has little operational significance; in either case one would likely stop the drug and consider using anti-inflammatory agents. The distinction may become important prognostically, and in this regard the presence of renal or CNS involvement, positive antibodies to native DNA (dsDNA) or to ENAs such as the Smith antigen, hypocomplementemia, or failure to resolve promptly would suggest idiopathic SLE (Solinger, 1988). However, in clinical settings this argument is somewhat circular and would appear to contribute little to patient management.

For clinical purposes it would be more important to be able to distinguish between DIL and a "false-positive" ANA in a patient with another cause for their clinical findings (e.g. pulmonary embolism or post-primary pleural tuberculosis). There have been reports which showed that asymptomatic individuals taking procainamide who have a positive ANA tend (as a group) to have a lower frequency of antibodies to denatured DNA (Winfield, 1974) and to the H2A-H2B histone complex epitopes (Rubin, 1985; Totoritis, 1988). Unfortunately neither of these is entirely discriminatory and is of no use in individual patients (see table). The diagnosis of procainamide DIL requires the presence of positive ANAs which may have a

characteristic, but not sufficiently specific, profile to be pathognomonic. As with most forms of drug-induced lung disease, the diagnosis ultimately hinges upon the exclusion of other causes for the patient's ailments.

Pathophysiology

The actual pathogenesis of procainamide DIL is not known. Procainamide is capable of binding to DNA and DNA complexes (Tomura, 1988). The drug can cause structural (Tomura,19880) as well as conformational changes (Zacharias, 1990). The antibodies to deoxyribonuclear proteins have binding specificities for exposed regions of the histone proteins (Gohill, 1987), suggesting that drug-chromatin interactions might lead to the development of autoantigen (Bigazzi, 1988). This might explain how procainamide causes serologic autoimmunity (i.e. a positive ANA), but it does not explain why the majority of patients with positive ANA do not develop disease.

INFLUENCE OF ACETYLATION STATUS IN PATIENTS TAKING PROCAINAMIDE

	Average Time from Start of Therapy (months)	
	Positive ANA	Disease Onset
Slow Acetylators	3	12
Rapid Acetylators	7	48

Woosley RL. N Engl J Med 298: 1157, 1978.

The different demographic profile of patients with DIL as compared to idiopathic SLE suggests that genetically-determined idiosyncratic differences might determine susceptibility (see above). Procainamide is metabolized in the liver by the N-acetyltransferase enzyme system to N-acetylprocainamide (NAPA). This metabolite has significantly less propensity to induce either anti-nuclear antibodies (Woosley, 1978; Lahita, 1979; Sonnhag, 1979) or clinical disease (Stec, 1979). The enzyme system's functional capacity is genetically determined following a recessive Mendelian pattern; the homozygous recessive phenotype is referred to as the "slow acetylator". It has been well-documented that individuals with the slow acetylator phenotype tend to develop antinuclear antibodies and DIL more quickly than their rapid acetylator counterparts (Woosley, 1978; Lahita, 1979). However, rapid acetylators whose drug levels are maintained at similar levels as slow acetylators are not protected from the development of positive ANAs or of active DIL (Sonnhag, 1979). This suggests that acetylation status is a genetically determined feature which is important in the process, but it likely serves to modulate the time course for developing serologic autoimmunity and does

not explain differences in susceptibility to disease in those with positive ANAs. Other genetic factors are likely to be important and higher prevalances of certain HLA phenotypes have been demonstrated for other drugs causing DIL (Russell, 1987); however, similar HLA associations have not been formally reported for procainamide induced disease. It has also been postulated that regulation of collagen might also be involved and that this too might be altered by the drug with genetically-determined influences (Solinger, 1988).

PROCAINAMIDE LUPUS: IMMUNE REGULATION

Anti-lymphocyte antibodies
Circulating activated B-lymphocytes
Inhibition of suppressor/cytotoxic T-cells
Enhancement of helper T-cell function

There is growing evidence that idiopathic SLE may be governed by genetically determined immunoregulatory mechanisms; this is beyond the scope of this discussion, however. With respect to DIL, there is also evidence suggesting alterations in immune function. Antilymphocyte antibodies have been found on the surface of circulating lymphocytes from patients taking procainamide (Bluestein, 1981). Patients with active procainamide DIL have been shown to have circulating activated B-lymphocytes; this was not seen in asymptomatic individuals taking the drug (Forrester, 1988). While no alteration in CD4 or CD8 subsets has been identified (Forrester, 1988), there is also evidence for procainamide induced T-lymphocyte functional alterations (Bigazzi, 1988). Work done at this institution has shown that procainamide can inhibit suppressor T-cell effects on immunoglobulin secreting cells (Ochi, 1983), suggesting that it might thus augment autoantibody production. Similarly, others have shown enhanced helper T-cell function with respect to immunoglobulin production (Miller, 1982). More recent data suggest that these effects are in part dose-dependent in vitro; net enhancement of immunoglobulin production is observed at lower doses, while higher doses produce suppression (Adams, 1989). Inherited alterations in the complement system may be important in the development of both idiopathic and drug-induced lupus; this has been demonstrated with respect to susceptibility to hydralazine DIL (Speirs, 1989).

Although the exact significance of these findings remains to be shown, it would appear likely that alterations in both humoral and cellular immune regulation may play an important role in this disorder and that genetic differences might determine an individual's ultimate response to the presence of the drug and ultimately to the development of autoimmunity and susceptibility to active disease.

CONCLUSIONS

It is hoped that the foregoing discussion will be useful to the clinician faced with a patient with new respiratory symptoms. Given the ever expanding list of drugs which may potentially lead to pulmonary complications, a very high index of suspicion in such circumstances is in order. This should equally be the case when patients taking medications

commonly associated with respiratory side-effects present with new symptoms or when patients fail to respond to conventional therapy for common disorders. In diagnosing drug-related illnesses, there are certain laboratory or histopathologic features which are characteristic for certain drugs or classes of drugs; unfortunately, however, these changes are in general more indicative of drug exposure or effect than they are specific for drug-induced disease. Our understanding of drug-induced pulmonary injury has given us an opportunity to better understand lung injury in more broad circumstances and has taught us that many mechanisms may be operant in a given case. These include drug-specific and genetically-determined effects such as: direct pharmacologic effects, primary toxicity, non-specific inflammatory responses, direct immune-mediated injury, and immunologic modulation of normal or drug-induced pulmonary function.

APPENDIX A: DRUGS ASSOCIATED WITH RESPIRATORY TOXICITY

Cardiovascular

Amiodarone
Atenolol
Betaxolol
Calcium Channel Blockers
Captopril
Enalapril
Esmolol
Hydralazine
Labetalol
Methyldopa
Metoprolol
Minoxidil
Procainamide
Propranolol
Quinidine
Reserpine
Tocainide

Cancer Chemotherapy

Bleomycin
Busulfan
Carmustine (BCNU)
Chlorambucil
Cytosine Arabinoside
Etopside (VP-16)
Lomustine (CCNU)
Melphalan
Mitomycin
Procarbazine
Semustine (Methyl-CCNU)
Teniposide (VM-26)
Vincristine
Zinostatin

Antibiotics

Colistin
Gentamicin
Grisefulvin
Isoniazid
Kanamycin
Neomycin
Nitrofurantoin
PAS
Penicillin
Pentamidine (Aerosol)
Polymyxin B (Aerosol)
Streptomycin
Sulfonamides
Tetracycline

Rheumatologic

Allopurinol
Aspirin
Colchicine
Gold Salts
Non-steroidal Anti-inflammatory Agents
Penicillamine

Immunosuppresives

Azathioprine (Imuran)
Cyclophosphamide
Methotrexate
Sulfasalazine

Neuro-Psychiatric

Carbamazepine (Tegretol)
Chlorpromazine
Cholinesterase Inhibitors
Diphenylhydantoin
Imipramine
Lithium
L-Dopa
Methylsergide

Endocrine

Bromocriptine
Chlorpropamide
Estrogens
Pituitary Snuff
Propylthiouracil

Illicit Drugs

Heroin
Methadone
Propoxyphene

Other Agents

Acetylcysteine
Aminorex
Cromolyn
Dantrolene
Iodinated Contrast Media
Metrizamide
Mineral Oil
Neuromuscular Blocking Agents
Oxygen
Radiation

APPENDIX B: DRUGS ASSOCIATED WITH DIFFUSE PULMONARY INFILTRATES

Amiodarone
Aspirin (ASA)
Azathioprine (Imuran)
Bleomycin
Bromocriptine
Busulfan
Carmustine (BCNU)
Chlorambucil
Cromolyn
Cyclophosphamide
Cytosine Arabinoside
Diphenylhydantoin
Etopside (VP-16)
Gold Salts
Heroin
Hydralazine
Iodinated Contrast Media
Lomustine (CCNU)
Melphalan
Methadone
Methotrexate
Methylsergide
Mineral Oil
Mitomycin
Nitrofurantoin
Oxygen
Penicillamine
Pituitary Snuff
Procainamide
Procarbazine
Propoxyphene
Propylthiouracil
Radiation
Semustine (Methyl-CCNU)
Sulfasalazine
Tocainide
Vincristine
Zinostatin
Other Drugs Causing P.I.E.
Other Drugs Causing S.L.E.

APPENDIX C: DRUGS ASSOCIATED WITH DRUG-INDUCED LUPUS

Procainamide
Hydralazine
Isoniazid
Methyldopa
Chlorpromazine
Atenolol
Captopril
Carbamazepine (Tegretol)
Diphenylhydantoin
Labetalol
Lithium
L-Dopa
Metoprolol
Nitrofurantoin
Penicillamine
Propylthiouracil
Quinidine
Allopurinol
Estrogens
Gold Salts
Griseofulvin
Methylsergide
Metrizamide
Minoxidil
PAS
Penicillin
Reserpine
Streptomycin
Sulfasalazine
Sulfonamide antibiotics
Tetracycline

APPENDIX D: DRUGS ASSOCIATED WITH HYPERSENSITIVITY PNEUMONITIS

Amiodarone
Gold Salts
Methotrexate
Penicillamine
Atenolol
Azathioprine (Imuran)
Cromolyn
Diphenylhydantoin
Pituitary Snuff
Procarbazine
Propranolol
Propylthiouracil
Radiation
Vincristine

APPENDIX E: DRUGS ASSOCIATED WITH ASTHMA OR COUGH

ACE Inhibitors
Acetylcysteine
Aspirin (ASA)
Beta-blocker Agents
Cholinesterase Inhibitors
Cromolyn
Iodinated Contrast Media
Neuromuscular Blocking Agents
Non-steroidal Anti-inflammatory Agents
Pentamidine (Aerosol)
Pituitary Snuff
Polymyxin B (Aerosol)

APPENDIX F: DRUGS ASSOCIATED WITH PULMONARY INFILTRATES AND EOSINOPHILIA

Nitrofurantoin
Diphenylhydantoin
Aspirin (ASA)
Bleomycin
Captopril
Chlorpropamide
Gold Salts
Hydralazine
Imipramine
Methotrexate
PAS
Penicillamine
Penicillin
Sulfasalazine
Sulfonamide antibiotics
Tetracycline

APPENDIX G: DRUGS ASSOCIATED WITH PLEURAL DISEASE

Amiodarone
Bromocriptine
Diphenylhydantoin
Hydralazine
Methylsergide
Nitrofurantoin
Penicillamine
Procainamide
Other Drugs Causing P.I.E.
Other Drugs Causing S.L.E.

APPENDIX H: DRUGS ASSOCIATED WITH NON-CARDIOGENIC PULMONARY EDEMA

Aspirin (ASA)
Cyclophosphamide
Cytosine Arabinoside
Heroin
Iodinated Contrast Media
Methadone
Methotrexate
Non-steroidal Anti-inflammatory Agents
Propoxyphene
Teniposide (VM-26)

APPENDIX I: DRUGS ASSOCIATED WITH RESPIRATORY NEUROMUSCULAR DYSFUNCTION

Beta-Blocker Agents
Calcium Channel Blockers
Cholinesterase Inhibitors
Colchicine
Colistin
Dantrolene
Gentamicin
Isoniazid
Kanamycin
Lithium
Neomycin
Neuromuscular Blocking Agents
Penicillamine
Procainamide
Quinidine
Streptomycin
Tetracycline

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