9 The diagnosis of pneumoconiosis and novel therapies

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DEFINITION OF PNEUMOCONIOSIS

Pneumoconioses are lung diseases which result from mineral dust deposition in the lung and the subsequent host response. This term is derived from the Greek language (*pneumo*, the Greek root for lung and *konis*, the root for dust) and has been applied in clinical medicine since the early 19th century (Meiklejohn, 1951). These are illnesses rooted in antiquity, which have had their highest human toll during the industrial age, yet it remains a tragedy of our time that these preventable diseases have not disappeared.

A number of respiratory manifestations associated with the inhalation, retention and tissue reaction to mineral dusts have been described and reflect the different effects of these dusts on the lung (Balaan *et al.*, 1993). Although a wide variety of mineral dusts are implicated in disease, all share common diagnostic criteria. The focus of this report is the description of diagnostic criteria for the most frequently occurring disorders. These are illnesses attributable to coal dust inhalation [coal workers' pneumoconiosis (CWP)], inhalation of dusts containing crystalline silica (silicosis), and inhalation exposure to asbestos fibers (asbestosis and other asbestos-related pulmonary disorders). Novel, but unproven, therapeutic approaches which may alter the natural history of pneumoconioses will also be considered.

There are three major criteria for the diagnosis of pneumoconiosis. The first is a sufficient exposure to a mineral dust known to cause pneumoconiosis with an appropriate latency period. Exposures to silica, coal or asbestos occur most commonly in an occupational setting. The second criteria is the recognition of a characteristic chest radiograph which meets published standards for the diagnosis of pneumoconiosis. Although respiratory symptoms and impairment in lung function commonly occur in workers diagnosed to have pneumoconiosis, neither is requisite for the diagnosis. The third is the absence of an illness which might mimic pneumoconiosis. Disseminated mycobacterial or fungal disease might mimic CWP or silicosis, as may sarcoidosis. Asbestosis is not infrequently confused with idiopathic pulmonary fibrosis, bronchiolitis obliterans with organizing pneumonia, or interstitial lung disease associated with collagen vascular disease (Banks *et al.*, 1993; Wilt and Banks, 1995). The diagnosis of pneumoconiosis, therefore, is a clinical one and only in the very unusual situation is a lung biopsy indicated to make the diagnosis.

A HISTORY OF EXPOSURE TO MINERAL DUST

The important issues when considering the diagnosis of pneumoconiosis are listed in Table 9.1 and relate to the suspected occupational exposures, the use of

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Table 9.1 Important concerns in the history of a worker with suspected pneumoconiosis

1. Are the suspected and recognized occupational exposures, as well as the respiratory protective devices, noted?
2. Is this an epidemic?
3. Are all of the jobs listed?
4. Are there important non-occupational exposures?

respiratory protective devices, and the consideration of whether dust exposure was sufficient to induce respiratory disease. Because the diagnosis of pneumoconiosis is a clinical diagnosis, answers to these concerns serve to strengthen or weaken the attribution of disease to work place exposure for a patient and determine whether additional invasive investigations are needed.

In the context of reporting a worker's exposure, the physician may be obliged to include a specific job description of each place of employment, as well as the nature and duration of exposure to the suspected offending agents. Perhaps the most effective approach is to begin with the individual's first job and proceed on a year-by-year, job-by-job basis. It is not enough, for example, to understand that the worker served in the Navy, when such a term of duty could range from land-based clerk, to shipbuilder with clinically important asbestos exposure, to sandblaster with sufficient silica exposure to induce pneumoconiosis.

The first criterion which must be addressed by the physician, determining whether the worker's occupational exposure is sufficient to cause pneumoconiosis, requires knowledge of the work environment and the worker's exposures. The most important data which aid in determining whether the exposures were sufficient to cause disease include knowledge regarding the daily job activities, a description of the nature of the exposure associated with that activity, the years when employed and the length of employment, exposure measurements (if available), and whether the worker was provided effective respiratory protection, and if it was used or not.

As an example, a reasonable starting point would be the understanding that silicosis occurs in association with industrial processes where the silica particle is made respirable size. Without manipulation of the silica particle, the particle generally remains large and is trapped in the upper airway defenses. Making the particle respirable size is the common thread among occupations where silicosis is a clearly recognized risk (Table 9.2). Furthermore, underground coal mining jobs often require drilling. Roof bolters, in particular, are at increased for silicosis, because the drilling needed to erect supports to hold up the roof is done beyond the coal seam and exposure is not just to coal dust, but to hard rock or sandstone which borders the seam. In this instance, it may be silicosis, rather than CWP which develops in the underground miner.

Why some workers develop pneumoconiosis (or greater or lesser extents of this illness) while employed in the same general work area may be related to the adequacy of respiratory protection. Pneumoconiosis can certainly occur in workers even though personal respiratory protection is used. To begin with, since each respirator has a limit beyond which the dust level exceeds the protective capacity (expressed as a multiple of the permissible exposure limit), the worker may be using a respiratory protective device which is inadequate for the amount of dust present (Glindmeyer and Hammad, 1988). Second, the worker may be using the wrong type of respirator. Respiratory protective devices are designed to protect for specific exposures. If a respirator designed to block solvent fumes from entering the lung were to be used for dust protection, the effectiveness would be compromised. Third, the respirator may be ill-fitting. Finally, and probably most importantly, protective devices increase the work of breathing. They are hot, they make it impossible for the worker to speak to co-workers, and they must be removed to smoke cigarettes. These features are relevant to the worker's decision as to whether or not they will wear these protective devices. Overall, protection by respirator is much less likely to be successful as compared with properly constructed engineering controls.

Information regarding dust levels in the work place can also provide important information. However, this approach cannot be guaranteed to represent the complete picture. For example, acute silicosis in surface coal mine drillers has been reported where the measured dust levels were within normal limits (Banks, *et al.*, 1983). The measurements were not representative of the overwhelming dust exposures which induced very aggressive silicosis, nor were there measurements of the percentage of free crystalline silica in the dust. Although fraud has been reported in coal mine sampling in US underground mines (Hearl and Hewitt 1993; Weeks, 1993), perhaps the US surface coal mines are the most notorious in their approach to collecting dust samples. Not only were dust exposures during active drilling infrequently measured, but when they were measured, they were not always representative of work place exposures. On the days of sampling, the worker might be away from the drill when personal sampling was performed, alter the amount of dust generated by changing the drill parameters, or use a wet drilling process. Because of

these potential abuses and inconsistencies, laws mandating sampling at surface mines have been changed and now, if the drills are generating plumes of dust, the mine is considered to be out of compliance and a citation issued (Code of Federal Regulations, 1994).

Therefore, although dust measurements can be helpful, understanding the conditions under which the samples were collected and having confidence that these measurements accurately represent the work place environment is essential. Sometimes this can only be understood by visiting the work place to see how work is undertaken.

COAL WORKERS' PNEUMOCONIOSIS

In order to diagnose CWP, a history of exposure to coal mine dust must be obtained. Underground coal mine employment is an important risk factor for the development of CWP. Miners who work near the face of the coal seam underground are generally exposed to the highest dust levels and are at greatest risk for developing the disease. Coal may also be found close to the surface and can be mined after removing the soil and hard rock overburden. Respirable dust levels at surface mines are generally lower than in underground mines, although silica dust levels can be excessive (Amandus and Piacitelli, 1987; Lapp and Parker, 1992).

The time from initial exposure to coal mine dust and the subsequent development of CWP is variable and depends in part on the intensity of exposure. The recognition of CWP is uncommon in the first 10–15 years after initial dust exposures.

SILICOSIS

Millions of workers world-wide are exposed to silica dust and are believed to be at risk for silicosis (Wilt and Banks, 1995). Again, an occupational history is of paramount importance in diagnosing this form of pneumoconiosis. Occupations when silicosis occurs include mining (metal, coal, and non-metallic minerals) as well as working with clay, stone and glass. Hazardous exposures also occur in other workplaces such as in sandblasting, pottery making, stone masonry and foundry work (Table 9.2). Virtually every ore or mineral is embedded in silica-containing rock and thus the mining and quarrying industry, in general, have had a long association with the disease. Both acute and chronic silicosis has been reported in surface coal miners (Banks *et al.*, 1983, 1993) (Figures 9.1a, b). Workers exposed to finely ground silica seem to be at especially high risk (Banks *et al.*, 1981). The rate of progression of dyspnea and the decline in lung function appears to depend on the amount of dust exposure (Hughes *et al.*, 1982). The clinical characterization of silicosis is often related to the duration of exposure in relation to clinical presentation (Chapter 13).

Table 9.2 Major industries with silica exposure

Occupation	*Exposure*
Sandblasting	Shipbuilding, oil rig maintenance, preparing steel for painting
Mining	Surface coal mining, roof bolting, shot firing, underground mining
Milling	Silica flour workers
Glassmaking	Polishing with sand and enameling
Pottery	Crushing flint and fettling
Foundry worker	Mold making and mold cleaning
Quarrying and stone work	Cutting of slate, sandstone and granite
Abrasive workers	Inhaling fine particles during grinding

ASBESTOSIS

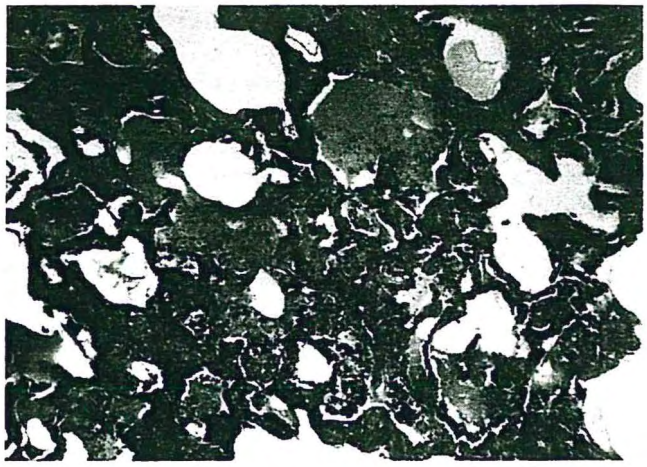
Asbestos has been used in many work sites with numerous applications throughout the world. Unlike silicosis, it is a disease which was first recognized in this century (Murray, 1907; Pancoast *et al.*, 1917; Oliver, 1927). Although the use of asbestos has decreased in many of the developed countries of the world, cases are still reported. The long latency period from the inhalation exposure of asbestos fibers to the development of adverse health effects is well known and a search for a history of exposure in individuals with interstitial lung disease is an important part of their clinical investigation. Because of its widespread use, it has been estimated that over 25 million workers in North America alone are at risk for developing asbestos-related disease (Murphy *et al.*, 1986).

Asbestos is still commonly used in the developing world, and many more workers remain at risk to develop asbestosis and asbestos-related disease. Asbestos has been used in automotive brakes, in boiler rooms and furnaces, in shipbuilding, in spray paints, in the construction of houses and buildings, and in asbestos cement products.

Asbestos fiber inhalation induces distinct clinical scenarios, some of which have never been adequately



(a)



(b)

Figure 9.1 A 34-year-old man was hospitalized with a 6-month history of progressive shortness of breath, a dry cough, weight loss of 30 pounds (13 kg), and Raynaud's phenomenon. He had worked as a surface coal mine driller for the previous 5 years but 2 years previously had had a normal physical examination and chest radiograph. Physical examination revealed a cachectic man who was tachypneic at rest. There were coarse crackles at the bases, stellate scars on the fingertips, and sclerodactyly. Laboratory information showed microscopic hematuria and proteinuria with mildly impaired renal function, a decreased serum albumin, a normal level of complement, and circulating immune complexes. Lung function showed moderate restriction and a diffusing capacity only 18% of predicted. The radiograph (a) showed an alveolar filling pattern in both lower lung zones, a presentation consistent with acute silicosis. An open-lung biopsy was performed, from which the lung tissue showed features described as acute silicosis (b). The alveolar spaces are filled with a relatively acellular proteinaceous material, there are inflammatory cells in the interstitium with thickening of the interstitium, but negligible development of silicotic nodules within the interstitium. Because of elevated serum levels of circulating immune complexes, the worker received daily oral cyclophosphamide at doses of 2 mg/kg. Despite 8 months of therapy, he became more dyspneic and his FVC and FEV_1 declined to approximately half of the initially measured values. He was unable to perform a diffusing capacity maneuver due to dyspnea. A chest radiograph taken 14 months after the initial film showed conglomerate mass lesions in both lungs and loss of volume in the right upper lobe with tracheal distortion, blunting of both costophrenic angles and bilateral pleural thickening. The patient died of respiratory failure 26 months after his initial evaluation. (Reproduced with permission from Banks, D.E., Bauer, M.A., Castellan, R.M. and Lapp, N.L. (1983) Silicosis in surface coal mine drillers, *Thorax*, **38**, 275–78.)

explained. The first is a pleural effusion that is usually exudative and benign. This has the shortest latency, usually 10–15 years. Subsequent thickening or calcification of the pleura is probably the most commonly encountered asbestos-related clinical syndrome and is the result of inflammation and fibrosis as a sequelae of these effusions. Asbestos-related primary lung cancer and mesothelioma generally typically have latencies of greater than 20 years. Asbestosis occurs predominantly in the lower zones (Figure 9.2). This is frequently described by an exaggerated profusion of lower zone irregular opacities. Historically, caution has been recommended if 1/1 International Labour Office (ILO) profusion category, or greater, is not present. The American Thoracic Society has developed criteria for a non-invasive (i.e. without pathologic specimen examination) diagnosis (Murphy *et al.*, 1986). It is important to note that asbestos-related pleural disease may occur independently from the parenchymal scarring as well as to point out that the latency period for asbestosis, as well as the manifestations of other illness, is variable, but generally develops 10 or more years after initial exposure (Figure 9.3). In those with clinical or radiographic features suggestive of asbestosis, but with no obvious exposure history, it is important to ask questions regarding any unsuspected exposure. For example, spouses of asbestos workers have been known to present with asbestos-related pulmonary disease.



Figure 9.2 This chest radiograph from an asbestos-exposed worker shows extensive bilateral interstitial abnormalities in lower and mid-zones, classified as ILO profusion category 3/2 and opacity size and shape s/t. Blunting of the left costophrenic angle consistent with diffuse pleural thickening and a likely pleural plaque on the medical aspect of the right hemidiaphragm is apparent. Underlying emphysema is also noted.

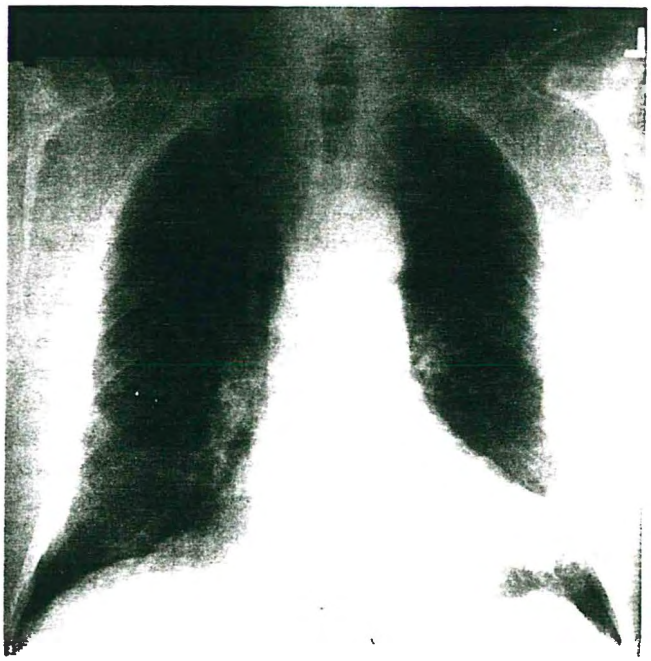


Figure 9.3 This radiograph demonstrates bilateral chest wall pleural plaques with sparing of the costophrenic angles. This is referred to as 'circumscribed pleural thickening'. If the costophrenic angles were blunted and these changes contiguous with chest wall pleural thickening, a finding such as this would be described as 'diffuse pleural thickening'. In addition, there is a discrete plaque on the left hemidiaphragm and obliteration of the right cardiophrenic angle by pleural thickening. The lateral aspect of the left heart border is obscured by a face-on pleural plaque. There is also parenchymal fibrosis manifest by an increase in irregular interstitial markings in the mid- and lower-lung zones bilaterally. The right hilum, in particular, is prominent, raising concerns regarding pulmonary hypertension and neoplasm. When extensive pleural disease including face-on plaques are present, the precision of profusion classification of parenchymal fibrosis is difficult and can be improved by the use of other imaging techniques such as high-resolution chest tomography.

CHEST RADIOGRAPHIC EVALUATION OF PNEUMOCONIOSIS

Radiography showing evidence of dust-induced disease is paramount in making the diagnosis of pneumoconiosis. The current standard method was last updated in 1980 by the ILO (International Labour Office, 1980). This system describes radiographic changes seen on the chest radiograph of exposed individuals. The classification calls for recognizing and grading of both parenchymal and pleural abnormalities, and allows for the detection and recording of abnormalities that are possibly unrelated to occupational exposure. In addition, the technical quality of the radiograph is also scored. The standard films published by the ILO are required for comparison with films being read or classified and this side-by-side method of observation is integral for determining small opacity profusion.

The parenchymal abnormalities are classified by the presence (or absence) of opacities, the size and shape of these abnormalities, as well as their anatomic location. In addition, the profusion level is characterized. Parenchymal opacities less than 1 cm in diameter are defined as small lesions and are subdivided into two distinct categories – rounded or irregular. On the basis of opacity diameter, they are labeled *p* (<1.5 mm), *q* (1.5–3 mm) and *r* (3–10 mm). The irregular-shaped opacities are also defined by their width and are labeled *s* (fine linear opacities up to 1.5 mm width), *t* (fine linear opacities from 1.5–3 mm width) and *u* (fine linear opacities from 3–10 mm width). Both round and irregular opacities may be seen and described on the same film.

The profusion of opacities denotes the relative number of abnormalities (i.e. either rounded or irregular), per unit area of lung. The four major profusion categories (0, 1, 2 or 3) are determined by comparing the radiograph to known ILO standards. These major categories can be subdivided into 12 minor categories, utilizing two numbers of the major categories, much like when grading the size of opacities. The first

number is the category felt by the reader to be most representative of the standard ILO film. The second number is the major category which was considered to be similar to the film being read, but not eventually chosen. For example, a film will be read as 1/1 if it most resembles a standard ILO film of category 1. A film will be read as 3/2 if it mostly resembles standard film category 3, but a similarity to a standard film of category 2 was seriously considered.

A large opacity is a parenchymal abnormality greater than 1 cm diameter in size. These are labeled as A, B or C, once again denoting size of the abnormality. Large opacities considered to be A size are each greater than 1 cm in diameter, with the sum of their diameters not exceeding 5 cm. Large opacities considered to be B size are greater than 5 cm in diameter, but their combined area is less than the volume encompassed by the right upper lobe. Large opacities considered to be C size represent lesions whose combined area exceeds the volume encompassed by the right upper lobe (Figure 9.4).

Pleural abnormalities are similarly described by the type of lesion, the anatomic location and the approximate size of the lesion. Pleural disease encompassed by the ILO classification system includes a pleural effusion, pleural calcification, diffuse pleural thickening and pleural plaques or circumscribed pleural thickening (Figure 9.5). A scheme for recording the types of pleural abnormality (i.e. in profile and en-face), as well as its site, width, extent and presence or absence of calcification, is part of the ILO classification.



Figure 9.4 This radiograph, taken from a 44-year-old surface coal mine driller with accelerated silicosis, demonstrates upper and mid-zone large opacities on a background of small rounded opacities of ILO category 2/3. Note also the dramatic compensatory basilar emphysema, retraction of the hilum, and distortion of the mediastinal structures. He died of respiratory failure approximately 2 years after this radiograph was made.

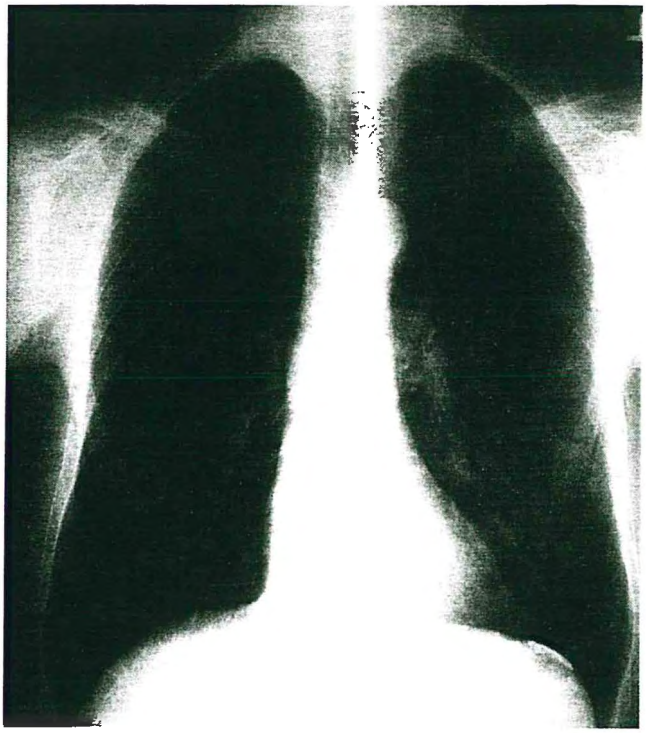


Figure 9.5 This radiograph demonstrates a calcified pleural plaque on the dome of the left hemidiaphragm. Underlying emphysema is present. The pleural change is a not infrequent finding of asbestos exposed workers who have a considerable latency period. This pleural change serves as a useful marker of asbestos exposure.

The ILO classification scheme has proved to be a very useful method to describe and to classify chest radiographs. It has improved and standardized epidemiologic research, fostered the identification of health hazards, and served as an important aid in establishing exposure–response relationships in the work place. It has frequently been useful for screening and surveillance programs in industry, as it helps to help identify early radiographic abnormalities as well as to monitor health trends.

HIGH-RESOLUTION CHEST TOMOGRAPHY AND OTHER IMAGING TECHNIQUES
(with special emphasis on asbestos-related diseases)

The non-invasive assessment of the lungs of dust-exposed workers was the near exclusive purview of the traditional chest radiograph for over 75 years. More recently, advanced imaging techniques have provided

new opportunities for enhanced visualization of lung and chest wall structures. These techniques, conventional computed chest tomography (CT), high-resolution CT (HRCT) and magnetic resonance imaging (MRI), have expanded the array of options for clinicians and researchers to evaluate chest diseases, including those diseases resulting from silica, coal and asbestos dust exposures (Staples *et al.*, 1989). Most importantly, chest CT and HRCT are recognized to be sensitive and specific tools in separating the pleural and parenchymal abnormalities resulting from asbestos exposure from normal lung structures such as extrapleural fat or competing parenchymal shadows (Begin *et al.*, 1989).

Although there is a relatively good correlation between lung pathology findings and the chest radiographic interpretation for dust-exposed workers (particularly at higher profusion levels), traditional radiographs are insensitive to early changes resulting from dust exposure (Epler *et al.*, 1978). For example, nearly 20% of asbestos-exposed workers with fibrotic changes on pathologic examination have no detectable radiographic abnormalities (Kipen *et al.*, 1987). The radiograph may be normal in some cases of asbestosis confirmed by functional abnormality and histopathology. Importantly, imaging techniques such as CT or HRCT provide better views of the pleural surface and more detail of the pulmonary parenchyma than traditional chest films, though reports do exist of even normal HRCT scans with histologic evidence of fibrosis (Gamsu *et al.*, 1995). Both HRCT and ILO classification of plain films are excellent predictors of clinical abestosis (Harkin *et al.*, 1996).

CT of the chest plays an important role in detecting pleural plaques, as well as defining the extent of malignant disease. HRCT images detail the pulmonary parenchyma and are useful in supplementing, but not replacing, the traditional chest radiograph when detection of the earliest changes of fibrosis is desirable. For example, asbestos-related pulmonary parenchymal fibrosis is considered to be present when the previously described radiographic findings are apparent, in the context of a consistent exposure history. A chest CT along with a few HRCT cuts may confirm the findings on plain film, as well as identify pleural or parenchymal abnormalities which might not have been appreciated on the plain film. When seen together, pleural and parenchymal abnormalities strengthen the accuracy of the diagnosis of asbestos-related disease.

MRI currently plays little role in studying asbestos-related diseases of the chest, although it is a particularly helpful technique in helping to answer neurologic and orthopedic concerns. Gallium scanning can detect inflammation, infection and tumors, but is not currently an important modality in the evaluation of asbestos-related chest diseases. The same is true of other nuclear medicine studies such as ventilation or profusion scans. The role of position emission tomography (PET) scans also requires more study and evaluation.

Chest CT has improved sensitivity for detecting diffuse lung disease, such as asbestosis, by eliminating superimposition of structures and enhancing attenuation discrimination. HRCT provides even greater detailed images of pulmonary architecture by thin collimation (1 to 1.5 mm-thick sections) (Naidich, 1989; Remy-Jardin *et al.*, 1992). Detection of basilar parenchymal abnormalities in the prone position is of particular value (Aberle *et al.*, 1988). Additional clinical and research utilization of HRCT has led to the delineation of several important findings (Akira *et al.*, 1991; Webb *et al.*, 1993; Gamsu *et al.*, 1995):

- Centrilobular thickening, or radiating fine lines within 1–2 cm of the pleural surface, likely from peribronchiolar fibrosis.
- Interlobular septal thickening, or septal lines; these parallel short lines or small nodules are thickened single or branching lines less than 2 cm long, radiating from the subpleural parenchyma extending into the lung, and likely represent thickened interlobular septa.
- Curvilinear subpleural lines running from 1 to 10 cm parallel to the pleura, especially in conjunction with septal lines.
- Parenchymal bands (long scars), non-tapering densities 2–5 cm in length that contact a pleural surface; these represent long fibrotic scars.
- Honeycombing, small cyst-like spaces less than 1 cm in diameter with discrete thickened walls.
- A ground-glass pattern, which persists when altering position, and may correspond to histologically minimal thickening of the alveolar walls and filling of the interlobular septa, possibly reflecting alveolitis.

Unlike the standardized approach with the ILO system for classifying the plain film, HRCT is awaiting a widely accepted and standardized method for classification. Several methods using expanded, subjective semi-quantitative scoring, grading and coding schemes and descriptors, as well as grid systems for classifying HRCT studies, have been proposed (Oksa *et al.*, 1994; Gamsu *et al.*, 1995; Harkin *et al.*, 1996; Kraus *et al.*, 1996). Such schemes need further development and study.

The current role of CT and HRCT should be reserved for the further clinical evaluation of difficult individual cases, and should not be applied to routine screening and surveillance of asbestos-exposed populations. There is no established role for HRCT in

screening for lung cancer, although the CT remains a valuable tool for staging and evaluation of suspected lung cancer or in determining the extent of previously recognized malignancy.

The chest CT and HRCT are helpful in a number of specific clinical settings. Examples include evaluation of the parenchyma for fibrosis when lung function is abnormal and the chest radiograph shows normal or nearly normal parenchymal findings (Oksa *et al.*, 1994); evaluation of the pleura when no pleural abnormalities are seen on plain film but radiographic fibrosis is suspected; evaluation of the parenchyma when a good view of the lower lung fields on radiograph is limited by extensive plaques, soft tissue shadows from muscular development or obesity, cardiac enlargement or dysfunction, or other competing shadows; and excluding the presence of emphysema or other diseases. Other clinical indications can also be envisioned. In general, these more sophisticated radiographic techniques are acceptable to workers undergoing evaluation. Nevertheless, the routine use of these scans for screening or surveillance may be limited due to high cost, and lack of availability, as well as by lack of standardization in interpretation and reporting of abnormalities. However, for diagnostic purposes, the high level of sensitivity to abnormality and the promise of specificity in the recognition of certain dust effects, including pleural disease and parenchymal fibrosis, makes these important for both clinical and research activities.

To summarize, in an individual worker with suspected asbestos-related lung disease, the traditional chest radiograph, supplemented by the chest CT and HRCT, is useful in establishing the presence or absence of pleural abnormalities and provide sufficient detail of the parenchyma to determine whether asbestosis is present, in most cases (Klass, 1993; Harkin *et al.*, 1996). Yet, since the interstitial changes on these imaging techniques only reflects the disturbance of normal pulmonary anatomy by dust-related pathology, it is not surprising that the sensitivity and specificity of tissue analysis exceeds radiologic studies. The histologic diagnosis of asbestosis requires the presence of diffuse interstitial fibrosis deep to the subpleural zone of the parenchyma *plus* the presence of asbestos bodies, and in early asbestosis, the histologic fibrosis is concentrated in the respiratory bronchioles and then spreads to the alveolar septa in a patchy distribution (Craighead *et al.*, 1982). Since, the findings on imaging studies are the result of these pathologic changes, they have similar patterns and descriptions. Finally, with all due respect to the clinicians and the radiologists, tissue examination is sometimes necessary and remains the 'gold standard' for establishing asbestos-related fibrosis.

EXPERIMENTAL APPROACHES TO TREATMENT OF PNEUMOCONIOSES

There is no proven therapy which alters the natural history of pneumoconiosis. 'Compassionate use' medications are not available for even the most aggressive cases. Cases continue despite aggressive enforcement policies by regulatory agencies, dissemination of very readable educational materials aimed at workers and management (Centers for Disease Control, 1992a, b), respiratory dust exposure standards which are in place and appear, for the most part, protective (Graham *et al.*, 1991) [although there are instances of individuals leaving the industry with normal chest radiographs and developing disease in retirement (Kreiss and Zhen, 1996)] and the public health perspective that pneumoconioses can be prevented by engineering controls (Socie *et al.*, 1995). Indeed, we are unaware of any society or culture which has abolished pneumoconiosis.

In European and North American cultures, both the physician and the affected worker are helpless when a diagnosis of pneumoconiosis is made. Dust-induced fibrosis is regarded as an irreversible process. Yet, because pneumoconiosis is a world-wide occupational health problem, other cultures – in particular the Chinese – have considered these diseases in a different light. Silicosis is one of the most serious occupational lung diseases in China, and as such, there have been important efforts to develop therapies for this disease (Li, 1995).

The persistence of dust, the stimulated macrophage with release of many mediators, and the role of other effector cells and their products in the alveolar and interstitial space are the keys to this process. Attempts to alter the natural history should focus on these processes of fibrosis. This may be done by preventing the development of associated diseases (such as mycobacterial infection), by pharmaceutically controlling and theoretically reversing or halting the progression of fibrosis, or by removing the fibrogenic stimuli of dust, activated macrophages and other stimulated effector cells, and cytokines which perpetuate the fibrotic process (Table 9.3). While the effectiveness of experimental treatments have not been proven, these studies have yielded insight as to how therapies for these illnesses might be approached.

It is our intent to discuss experimental therapies which may alter the natural history of silicosis and coal workers' pneumoconiosis. Although those with asbestosis with active alveolitis have been considered responsive to steroid therapy (Rosenstock, 1994), to our knowledge, there have been no structured attempts to alter the natural history of asbestos-related non-malignant diseases.

Table 9.3 Potential means to alter the natural history of silicosis and coal workers' pneumoconiosis

	Mechanism of action	*Therapeutic agent or procedure*
1.	Altering the surface properties of the silica particle	Aluminum citrate complex, PVNO (poly-2-vinylpyridine-*N*-oxide)
2.	Control of the immune and inflammatory response	Immunosuppressive and corticosteroid therapy
3.	Control of fibroproliferative activity	Tetrandrine, xinin
4.	Prevention of associated diseases	Anti-mycobacterial therapy, pneumococcal vaccine
5.	Dust, macrophage and cytokines removal	Whole-lung lavage
6.	Monoclonal antibody therapy	Anti-cytokine therapy
7.	Lung transplantation	Lung transplantation



Figure 9.6 Inhalation of aluminum dust by miners with silicosis or CWP. The rate of dust generation was adjusted by trial and error until the desired amount of dust was collected over 15 minutes. The air compressor discharged into the chamber at a rate sufficient to keep the dust in suspension. A more detailed explanation is available in Kennedy, M.C.S. (1956) Aluminum powder inhalations in the treatment of silicosis of pottery workers and pneumoconiosis of coal-miners. *Br. J. Ind. Med.*, **13**, 85–101 (reproduced by permission).

Aluminum inhalation

Inhalation of aluminum was thought to alter the surface properties of silica in the lung and in that manner protect the macrophage. This notion was recognized early this century. Not only did small quantities of metallic aluminum inhibit the solubility of siliceous material in a test tube, but when rabbits inhaled quartz particles coated with aluminum they failed to produce silicosis, whereas uncoated particles caused frank fibrosis (Denny *et al.*, 1937). Using this same model, inhalation of 1% aluminum citrate independent of the time when silica was inhaled, resulted in a marked decrease in fibrosis. It was hypothesized that prevention of silicosis was the result of a silica–aluminum reaction resulting in a silica particle coated with a protective gelatinous aluminum hydroxide capsule (Denny *et al.*, 1939). Further support of this hypothesis was gleaned from additional animal studies (King *et al.*, 1950). Serial assessment of workers with silica exposure who inhaled aluminum showed few, if any, adverse effects, with some improvement in respiratory symptoms in selected individuals (Crombie *et al.*, 1944; Berry, 1948).

Prospective human trials followed. In 1956, an important prospective report addressed the effectiveness of aluminum inhalation treatment in 120 pottery workers followed for 4 years (Kennedy, 1956) (Figure 9.6). One group of workers inhaled aluminum at what was considered to be an 'effective dose' while the comparison group inhaled an 'ineffective dose'. Although most of the workers reported less dyspnea and symptomatic improvement, there was no significant improvement in pulmonary function or radiograph with inhalation of the 'effective dose'. These data, combined with other studies reporting adverse effects associated with the long-term inhalation of aluminum powder (Shaver, 1948; Jordan, 1961), have been an important reason why these compounds are not used as therapeutic agents.

Since then, other therapeutic trials of inhaled aluminum have been undertaken. In 1973, an aluminum citrate complex developed in China showed a clear protective effect against the development of silicosis in rats. However, significant toxicity existed, including a significant number of nodular deposits of aluminum in hepatic Kuppfer cells. In humans with pneumoconiosis, however, administration of this compound for two 3-month periods, separated by a 3-month period off drug, showed variable symptomatic improvement, and otherwise inconclusive results (Liu and Zou, 1985).

Yet there remains interest in inhaled aluminum as a means to alter the surface properties of silica. In a sheep model of silica inhalation, aluminum inhalation was associated with a reduction in the disease process and accelerated particle clearance from the lung (Dubois *et al.*, 1988). Moreover, in this same model, inhalation of aluminum 1 month after quartz exposure significantly suppressed alveolitis and lessened fibrosis

(Begin *et al.*, 1993). Although aluminum may be considered an effective prophylactic agent in the animal model, the proven adverse effects in humans make it unacceptable for use.

Corticosteroids

Lymphocytic inflammation, in association with an increased number of stimulated macrophages, plays an important role in the development of the silicotic nodule. The use of broncho-alveolar lavage (BAL) to sample the alveolar lining fluid in asymptomatic silica-exposed workers reflects inflammation with elevated numbers of lymphocytes and an increased level of immunoglobulins. BAL findings in workers with chronic silicosis show an increased number of lymphocytes and activated macrophages (Begin *et al.*, 1987; Rom *et al.*, 1987). Based on clinical approaches recognized in other granulomatous diseases, the presence of activated macrophages and an elevated number of lymphocytes (in this instance attributable to the presence of silica dust) are associated with the formation of granuloma in the lung and have the potential to be altered by corticosteroid therapy (Kotloff and Rossman, 1992).

Although theoretically attractive, the evidence for corticosteroid therapy as an effective long-term agent in altering the outcome of silicosis is essentially untested and primarily anecdotal. A 33-year-old surface miner of 12 years' work experience presented with an abnormal chest radiograph showing an alveolar filling pattern, clinical features of inflammation and progressive dyspnea (Goodman *et al.*, 1992) (Figure 9.7a–c). No infectious pathogens were found and an open-lung biopsy showed acute silicosis. Postoperatively, he received high-dose prednisone and empiric anti-mycobacterial therapy. He responded to this therapeutic approach with relatively rapid defervescence, chest radiograph and lung function improvement, and weight gain of 25 pounds (11 kg). Unfortunately, the worker could not tolerate prolonged high-dose corticosteroid therapy and the inevitable decrease in steroid therapy resulted in rapid progression of silicosis. He ultimately succumbed to the disease.

To our knowledge, the effect of steroid therapy on chronic silicosis has been evaluated in only one study. Thirty-four Indian workers with silicosis (ILO category 1 or greater) and VC, TLV or D_LCO <80% predicted initially received prednisolone (30 mg/day) for 6 weeks, which was then tapered to 0.25 mg/kg/day for a total of 6 months of therapy (Sharma *et al.*, 1991). Each worker served as his own control. Respiratory complaints were determined and BAL was performed before entry into the study.

Results were independent of cigarette smoking history or the presence of simple or complicated silicosis, although those with a longer duration of dust exposure were less likely to respond. BAL results showed less inflammation post-therapy. Lung volume measurements post-steroid therapy showed a statistically significant improvement in mean FVC, RV/TLC, FEV_1, PEFR, D_LCO and Po_2 values, but no differences in compliance, K (D_L/V_A) or TLC. Moreover, 24/34 showed a clinical response, defined as improvement in cough and exertional dyspnea, and lung function (FVC and/or D_LCO) of ≥ 15%. Yet, several patients described weight gain, striae and moon facies – recognized complications of steroid therapy. The authors point out that while the results were promising, the potential long-term adverse effects of steroid therapy may not outweigh the benefits.

In summary, corticosteroids appear to lessen inflammation in the short-term in silicotics. Whether these drugs should be indicated for long-term usage in workers with chronic silicosis would require further assessment and raises reasonable concerns regarding the risk for corticosteroid complications. This risk versus benefit ratio should be assessed in a case-by-case basis if such therapy is considered. If steroid therapy is considered, it is reasonable to monitor the worker closely and to also consider empiric mycobacterial prophylaxis.

PVNO (poly-2 [or 4]-vinylpyridine-*N*-oxide); P204

PVNO is a member of a class of large-molecular weight polyvinylpyridine-*N*-oxides first reported by Schlipkoter and Brockhaus, (1960, 1961) to exhibit an inhibitory effect on the development of silicosis in an animal model. The mechanism of drug action has been attributed to alteration of surface properties of the silica particle; specifically, the adsorption of PVNO onto silica particles apparently lessens the level of macrophage activation after the particles are phagocytized (Beck *et al.*, 1963; Fetzer, 1967). Microscopic inspection reveals that the alveolar macrophages concentrate the PVNO–silica particles within lipid inclusions within the cell (Schiller, 1970).

In 1967, the first large-scale clinical initiative of the treatment of pneumoconiosis was begun in China. The 394 workers who participated were categorized according to the ILO profusion category on the chest radiograph and received P204 (molecular weight = 200 000 Da, known in China as 'Kexiping', meaning an antisilicotic) either intramuscularly or by inhalation for four 3-month treatment periods, each separated by a 1-month non-treatment period (Chen and Lu, 1970). Therapy was associated with fewer complaints of chest pain, cough and lesser dyspnea on exertion. During this

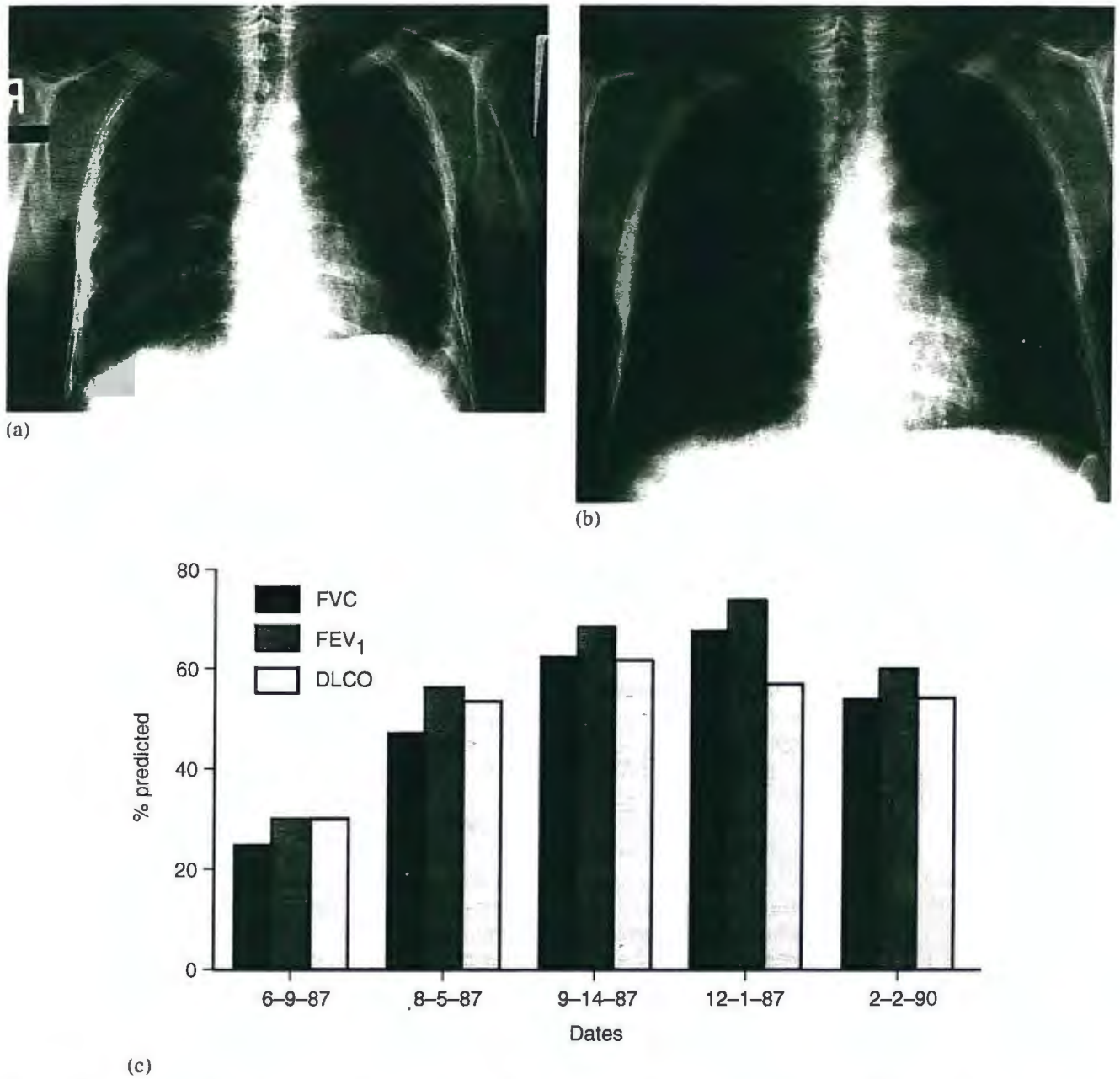


Figure 9.7 A 33-year-old man employed as a surface coal mine driller presented with a 50-pound (22 kg) weight loss, malaise, dyspnea, arthralgias, fever and night sweats. All drilling had been done with a wet process up until 4 years before this evaluation. He was a thin, febrile man who looked chronically ill. Chest examination showed poor expansion and crackles. A chest radiograph (a) showed an infiltrate at the left base and bilateral small rounded opacities. The right major fissure is markedly thickened. An open-lung biopsy showed interstitial inflammation and fibrosis with early silicotic granulomata. Electron microscopic assessment showed needle-shaped and polyhedral intracytoplasmic fragments consistent with silica particles. An infectious etiology was not recognized. Postoperatively, he received high-dose prednisone daily with two anti-mycobacterial medications for 3 months. He defervesced and experienced subjective improvement with an improved exercise tolerance and lung function tests. A chest radiograph taken 3 months after open biopsy (b) showed the profusion score and opacity size to have markedly lessened. His steroid therapy was gradually tapered, and because of intolerance to side effects, was discontinued after 8 months. (c) Lung function tests. These serial tests reflect significant improvement in association with steroid therapy. After 8 months, steroid therapy was stopped and testing several years later shows worsening of these parameters. Despite this apparent improvement over the short term, the radiograph inevitably worsened and progressive massive fibrosis developed and he died 4 years after his initial evaluation for silicosis. (Reproduced with permission from Goodman, G.B., Kaplan, P.D., Stachura, I., Castranova, V., Pailes, W.H. and Lapp, N.L. (1992). Acute silicosis responding to corticosteroid therapy. *Chest*, **101**, 366–70.)

relatively short time, approximately 70% of the radiographs had stabilized and were without progression.

PVNO, however, has been shown to cause severe chronic toxicities in laboratory animals. Chronic subcutaneous injection of PVNO in rats resulted in a significant hepatic and renal accumulation (Cheng *et al.*, 1970; Hasciri and Holt, 1977). Liver toxicity included impaired liver function, formation of foamy cells, abnormal morphologic structures of the hepatic lobules, and necrosis. Cirrhosis was detected in animals as late as 2 years after stopping the drug. Chronic injection of PVNO in rats was also associated with tumor formation at the injection site (Schmadl, 1969). Although intramuscularly delivered ^{14}C-PVNO reached plasma peak concentration 60 hours post-injection (Li and Yao, 1970), much of the toxicity may be due to the long half-life of the drug (only one-third of the dose is excreted in the urine and stool in 30 days) apparently attributable to the large-molecular weight (80 000 to 180 000 Da) PVNO molecules.

Attempts to minimize this toxicity were recently reported in a clinical trial where the outcome of 53 silicotics who received 144 ml of a 1% solution of PVNO instilled intratracheally once or twice and 200 mg of tetrandrine daily over a 2 year period were compared with 27 untreated silicotics. Although symptoms were less in the treated group, changes in the treated group's lung function were no different. Chest radiographs progressed less in the treated group. Therapy was most effective in those with silicosis and a history of exposure to silica alone. The main side effects were pigmentation (72%) and itching (8%) (Zhou *et al.*, 1996).

Tetrandrine

Tetrandrine, a bisbenzylisoquinoline alkaloid isolated from the root of the plant *Stephania tetrandra*, has been in use in Chinese herbal medicine for maladies including hypertension and angina. In these instances its effectiveness may be due to its calcium channel blocking effect (King *et al.*, 1988). It is also the first drug reported to reverse silica-induced fibrosis as determined by a reduction of the number of silicotic nodules in the lung, the total lung weight, and the lung collagen content in rat lung (Li *et al.*, 1981; Yu *et al.*, 1983).

Tetrandrine has a marked inhibitory effect on many of the important features of inflammation and fibrosis. These include inhibitory actions on lymphoproliferation and immunoglobulin synthesis (Seow *et al.*, 1988a), chemotaxis of neutrophils, monocytes, and alveolar macrophages into the alveolar space (Seow *et al.*, 1988b), and particle-induced respiratory burst and production of fibrogenic factors. In addition, the inhibitory action of tetrandrine on the dust-induced respiratory burst and production of interleukin-1 from alveolar macrophages and on fibroblast proliferation mediated by macrophage-derived growth factors (Castranova *et al.*, 1991; Ma *et al.*, 1991, 1992; Kang *et al.*, 1992), and synthesis and secretion of collagen, glycosaminoglycans and phospholipids (Chen *et al.*, 1982; Liu *et al.*, 1983) has been recognized. This drug, as well as PVNO, has the ability to block the increase of type I and type III collagen mRNA, a very early stage in the fibrotic process, caused by inhalation of silica dust in the rat model (Liu *et al.*, 1994). Altering collagen metabolism is a critical approach because collagen is a major constituent of the silicotic nodule.

The diverse action of tetrandrine may be due to its structural specific interactions with the plasma membrane of various cell types via its calcium channel blocking effect (King *et al.*, 1988). Tetrandrine binds strongly to the microtubular cytoskeletal system of alveolar macrophages, an effect which can be inhibited by the combined use of agents known to alter the microfilament and microtubular structure (Chen *et al.*, 1988; Liu *et al.*, 1988; Ma *et al.*, 1991, 1992). This binding action prevents cells from activation by either non-specific stimuli or receptor-mediating factors (Kang *et al.*, 1992).

Tetrandrine is excreted from urine and feces mainly as intact drug (Yin *et al.*, 1982). Toxicity appears to be species dependent. In rats given tetrandrine in 120–150 mg/kg doses once weekly for 1–3 months, there was no liver or kidney toxicity, yet, when these same animals received doses of 120–150 mg/kg/week over 5–9 months, histologic evidence of hepatocyte fatty degeneration and necrosis was observed, without impairment of liver or kidney function (Yu *et al.*, 1983). In dogs receiving the same therapy, there was an increased erythrocyte sedimentation rate and elevated levels of serum alanine transferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase enzymes. Histologic assessment of the chronic toxicity showed fatty degeneration and necrosis of liver cells and necrosis of the renal epithelial cells of the convoluted tubule (Li *et al.*, 1983).

In a 1980 open clinical trial with tetrandrine, 240 Chinese workers with silicosis (Lu and Li, 1983) were divided into three groups and received an oral tetrandrine dose of 100, 200 or 300 mg/day six times weekly. The regimen included a 3-month treatment period alternating with a 2-month resting period for a total of 1 to 3 years. Fifty-three of the 188 workers receiving the 200 or 300 mg/day doses exhibited radiographic improvement, as both small and large opacities were described to appear thinner and smaller and the bronchial shadows were described as sharper and more

clearly defined. Workers receiving therapy, in general, had fewer complaints of chest tightness, dyspnea, cough, sputum production and upper respiratory infection. After the drug had been discontinued for 3 months, no further improvement was observed and, in some instances, there was radiographic progression. The results also showed that tetrandrine may prevent the progression of silicosis. In patients treated with 200 or 300 mg/day doses, progression of silicotic lesions was observed in only 13% and 4%, compared with a 53% progression rate in those treated with the 100 mg/day dosage. Although improvement of the chest radiograph was reported in only a relatively small percentage of the total patients (22% of all who received any therapy), this study has received attention because of the apparent ability of this drug to alter the natural history of silicosis.

There were, however, several concerns regarding this impressive work. First, the symptomatic improvement, which may indicate the anti-inflammatory action of the drug, did not appear to be dose-dependent. More workers receiving the 200 mg dose improved compared with those who received the 300 mg dose. There were suggestions that some of the improvement may have resulted from better patient care. Second, there was no untreated group of silicotics, so we cannot know what the placebo effect might have been. Third, it is not clear whether the drug effect has a relationship with the pretreatment disease state of the patients (i.e. it would seem intuitive that those with the least amount of fibrosis might be most sensitive to the effects of tetrandrine). Furthermore, since this study was carried out in numerous clinics with diverse facilities and personnel, it is difficult to judge whether the chest radiograph qualities and their interpretations were comparable and internally reproducible.

Nevertheless, this is exciting work, and has formed the starting point for continuing research into the use of this drug as a therapy of silicosis. However, despite its apparently strong antifibrogenic activity *in vitro*, the therapeutic value of tetrandrine is not yet defined. This may be attributed, in part, to the persistence of dust in the lungs. Perhaps recent advances, like packaging tetrandrine in a water-in-oil-in-water emulsion, will allow equally effective therapy with lesser amounts of tetrandrine with less toxicity (Chao *et al.*, 1996).

Xinin

Xinin, a Chinese word which carries the meaning of 'rendering silica harmless', is another example of the exploratory efforts by Chinese scientists to develop an effective anti-fibrotic agent. This drug is a bisbasic ethoxyfluorene derivative similar in structure and activity to tilorone but with reduced systemic toxicity (Cheng *et al.*, 1989). In experimental animals, the antisilicotic activity of xinin is comparable with that of tetrandrine (Han *et al.*, 1989; Cheng *et al.*, 1990), yet *in vivo* studies have shown it to have less potential for chronic toxicity than tetrandrine (Han *et al.*, 1987; Cheng *et al.*, 1992).

Xinin is distributed mainly in the liver, adrenal glands, kidney and lungs, and eliminated as an intact molecule through urinary exertion. Administration of oral doses (240 mg/kg/week) of xinin to rats for a 6-month period did not adversely alter blood, liver or kidney function. Histologic examination of the liver showed mild formation of foamy cells, an effect which reversed after the termination of drug administration (Han *et al.*, 1987). Xinin's mechanism of action against silicosis has been attributed to its ability to prevent silica-induced alveolar macrophage death and to inhibit biosynthesis of phospholipids and collagen. The cellular action of xinin is similar to that or tetrandrine. Although to a lesser extent than tetrandrine, xinin interacts with alveolar macrophages and has an inhibitory effect on particle-stimulated macrophage respiratory burst, macrophage productive production of interleukin-1 in response to stimulation by liposaccharides, and release of growth factor-mediated thymocyte proliferation (Kang *et al.*, 1992).

Whole-lung lavage (WLL)

The cited reports have focussed on altering the natural progression of pneumoconiosis by intervening at one or more of several points in the fibrotic process. While the outcomes of therapeutic trials of pneumoconiosis have remained largely inconclusive (often due to inadequate testing of the hypotheses), these studies have added insight into potentially effective strategies for the treatment of pneumoconiosis. Yet, while these various agents may retard a certain step in the fibrotic process occurring after dust inhalation, the therapeutic effect(s), when recognized, are transient and only temporize an inevitable clinical effect. This is likely due to the persistence of dust which perpetuates the inflammatory and fibrotic processes. This is the rationale for considering WLL as a method of treatment for pneumoconiosis. Removing dust, activated cells and inflammatory mediators is a logical step and may serve as a therapy in itself, or in association with drug therapy, potentiate the effect(s) of a therapeutic drug.

In addition to removing dust, WLL removes activated cells and cytokines, agents which amplify and perpetuate the stimulus for fibrosis. In an animal model exposed to tagged aluminosilicate particles, most of the particles removed by large volume were located in macrophages (Ellender *et al.*, 1992). If an appreciable

amount of the particle load in the human lung is harbored within the macrophages, then removal of a considerable number of macrophages may mean that slowing the rate of dust-induced progression is a possibility.

WLL is the removal of alveolar material by repeated large volume saline lavage (up to a total of 15 liters or more per lung) of each lung. It is performed under general anesthesia. As early as 1963, Ramirez *et al.* (1963) reported the therapeutic efficacy of WLL in patients with pulmonary alveolar proteinosis (PAP). Since then, this technique has also been proposed for the removal of alveolar filling material associated with alveolar microlithiasis (Palombini *et al.*, 1981), acute silicosis (Lavandier *et al.*, 1989), accidental inhalation of radioactive particles (Nolibe *et al.*, 1989), and even obstructive lung diseases (Kylstra *et al.*, 1971). The value of WLL in the exploration and management of interstitial lung diseases has recently been updated in reports of the European Task group on BAL (Klech and Hutter, 1990; Klech *et al.*, 1992).

At this time, WLL is only an accepted therapy of PAP, a rare idiopathic disorder with a pattern of lung injury which closely resembling acute silicosis. In PAP, WLL has been found to be safe, with no adverse effects attributable to this procedure in patients followed for as long as 25 years (Green and Griner, 1987). Complications, when they infrequently happen, occur during or soon after the procedure, and include hydropneumothorax, bronchospasm, pneumonia and lung abscess (Claypool *et al.*, 1984; Watters, 1988; Nolibe *et al.*, 1989).

Mason *et al.* (1982) first reported the use of WLL in the treatment of dust-induced lung disease in a foundry worker. Although the worker had symptomatic improvement after the procedure, there was no associated lung function change. Information regarding long-term changes in lung function or respiratory symptoms was not reported.

Chinese studies involving a larger number of CWP patients have been reported (Liang *et al.*, 1992). Under general anesthesia the authors inserted a double lumen endotracheal tube into the airways (ventilating one lung while lavaging the other), infused saline at a rate determined by gravity at a level 30 cm above the patient's chest, and then drained the fluid by gravity. Each lung was lavaged an average of 10 times with 1000–2000 ml saline each time. Close auscultatory monitoring of the chest is essential to ensure that fluid from the lavaged lung does not overflow into the ventilated lung. Liang and colleagues also showed that applying positive pressure (administered as 100% oxygen) during WLL via positive-pressure bag ventilation to the lavaged lung improved oxygenation, perhaps by lessening a shunt-like effect, as well as significantly increasing the amount of dust and cells removed.

In those with minimal disease (ILO category 1) and no or negligible impairment, one lung was lavaged after the other during the same period of general anesthesia. In this situation, the recovery period between lavages (typically lasting 1–2 hours) was sufficient to allow the compliance and peak ventilator pressures in the lavaged lung to approximate pre-lavage values; thereafter, the second lung was lavaged. When both lungs are lavaged during one period of general anesthesia, the procedure typically lasted 5 or 6 hours. When pneumoconiosis is more severe or is associated with significant functional impairment, each lung was lavaged on a separate occasion. Overall, the average recovery of the total amount of lavage fluid exceeded 95% of that instilled. When the fluid was in the lung, added pressure, delivered as manual compressions of 100% oxygen by 'ventilation-bag', resulted in a two- to three-fold increase in dust removal and about 500-fold increase in the removal of alveolar macrophages from the lungs. We modified the technique of WLL to include a pressure manometer attached to the positive-pressure bag ventilation of the lavaged lung to minimize the possibility of barotrauma (Wilt *et al.*, 1996) (Figure 9.8).

As in Mason's work, the Chinese study reported improvement in respiratory symptoms in nearly all workers. Six-month follow-up showed the procedure to be without residual adverse effects; only one patient developed a respiratory tract infection. The average pulmonary function and arterial tension measurements from 16 of the 25 workers who had undergone whole lung lavage was obtained one week or 3–6 months after the treatment and were not significantly different when compared with pre-treatment values. There was no long-term follow-up and the results were not controlled, therefore, conclusions regarding whether this procedure altered the natural history of pneumoconiosis are not possible. In addition, studies which addressed whether the cellularity, inflammatory mediators and dust content of the alveolar lining fluid either before, or following WLL, was changed were not performed. Similarly, work by Borm *et al.* (1988) which showed differences in blood cytokine levels in miners with abnormal radiographs compared to those with no abnormality, could be applied to attempt to measure alterations in the lung which could be measured systemically before and after the procedure.

Several comments may be made regarding Liang's work (1992). First, most workers undergoing WLL had minimal disease which may never have progressed or become disabling. Second, it is difficult to assess whether the use of average values of these physiologic

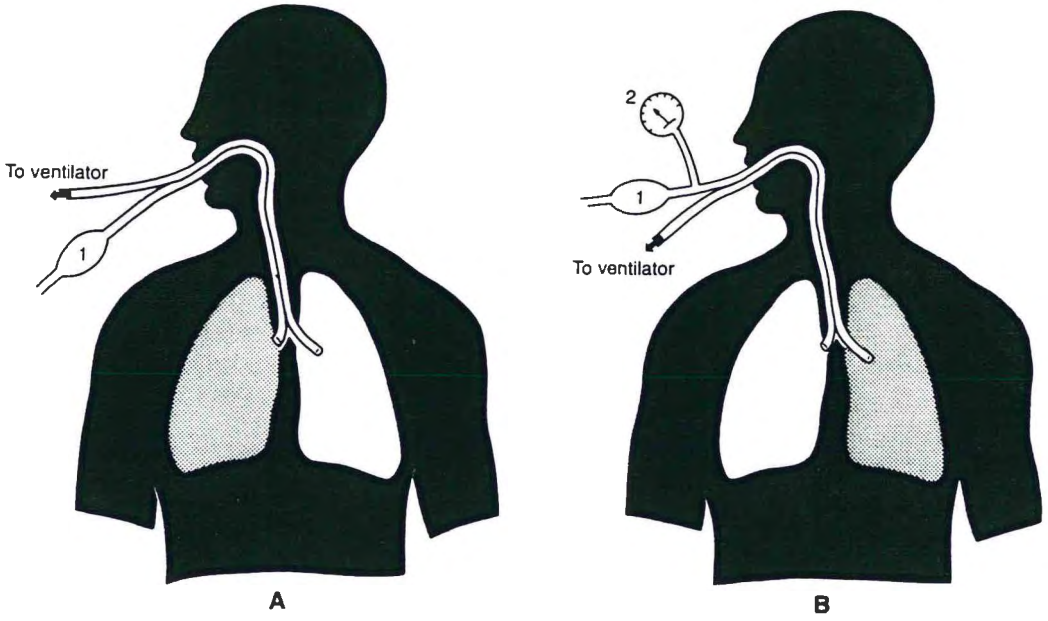


Figure 9.8 Diagram of the WLL aparatus used to limit peak airway pressure. Panel A represents the set up for WLL of the right lung without a pressure manometer to minimize the risk of barotrauma. Panel B represents a modification of this set up with an in-line manometer. This limits the peak airway pressure of the lung being lavaged to 40 cm H_2O. 1, anesthesia bag; 2, manometer. (Reproduced by permission from Wilt, J.L., Banks, D.E., Weissman, D.N. *et al.* (1996). Reduction of lung dust burden in pneumoconiosis by whole-lung lavage. *J. Occup. Environ. Med.*, **38**, 619–24.)

measurements truly represent the effect of this procedure in all workers. Improvement in an individual miner might have been missed by this type of data analysis. Third, the results were reported at the end of 6 months, likely too short a time to show a clinically important effect. Nevertheless, the manuscript breaks important ground in therapeutic approaches.

In two patients (four lungs), dust removal and cellularity has been evaluated (Wilt *et al.*, 1996). Although discrepant amounts of dust, cells and cytokines were recovered in the two reported cases (as well as between lungs within the same individual), all lungs showed on-going inflammation. Nearly 2 g of dust were removed from a lung of a coal miner with ILO category 2 pneumoconiosis by WLL (Figure 9.9). This approximates the mean mineral dust burden in the lung of coal miners with a similar pneumoconiosis profusion score as assessed by ashing the lung at autopsy (Rivers *et al.*, 1960). A critical issue is whether dust in the lung is in a 'dynamic state', i.e. is a significant amount of dust transported intracellularly into and out of the interstitium? Studies in animals have shown that dust particles in the interstitial spaces can be carried into the alveolar space by migrating neutrophils (Adamson and Bowden, 1992). Furthermore, repeated lavages in animals continue to remove dust which may originate in the interstitial spaces and progress into the alveolar spaces with recurrent washings (Brain, 1980). Overall, the dynamics of dust transport within the lung is not well understood (Sorokin and Brain 1975; Brody and Overby, 1989; Scheule and Holian, 1991).

Since WLL has not been widely tested in independent laboratories, critical review of its clinical significance is not yet possible. Whether the risks outweigh the benefits is not yet clear; however, this appears to be a relatively safe clinical procedure which is capable of removing a significant amount of dust and activated cells. WLL, in association with effective antifibrotic drug therapy, may be an approach which may be beneficial.

WITH AN EYE TO THE FUTURE

Fibrosis represents the end-stage of lung inflammation. However, targeting inflammatory areas around parenchymal fibrosis may be important. Treatment strategies will likely be aimed at removing the dust-induced stimulus of inflammation and interrupting the pathogenetic mechanisms. *In vivo* studies could employ animal models of fibrosis in conjunction with *in situ* probes which better determine sites of cellular activation associated with dust exposures (Scheule and Holian, 1991). For example, collagen mRNA probes might determine which fibroblasts are actively depositing matrix. Studies designed to target specific responses

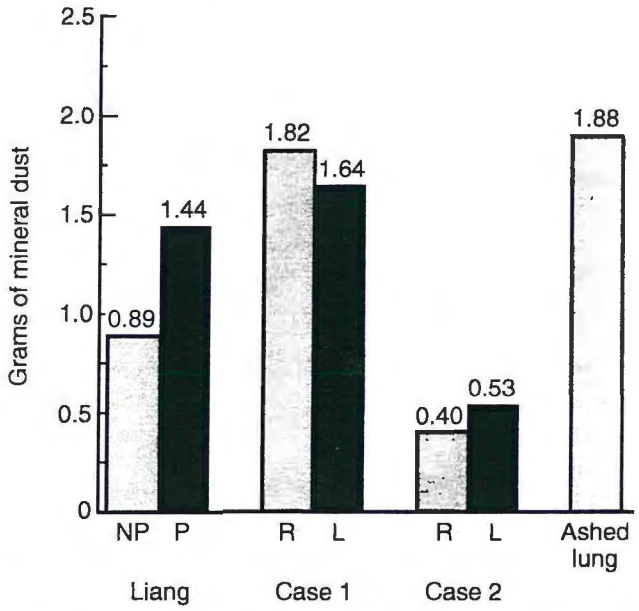


Figure 9.9 Amounts of dust removed using the technique of Liang *et al.* (1992), which first compared the amount of dust removed by infusing and then draining saline instilled into the lung (NP or no pressure) with 'agitating the fluid' within the lung by gentle compression of a ventilation bag (P or pressure) from different lungs within the same individual. These values are then compared with the amount of dust removed in two cases who underwent WLL with gentle ventilation bag bagging [described as the right (R) and left (L) lung from cases 1 and 2] (Wilt *et al.*, 1996), and then to mean data from an autopsy study by Rivers *et al.* (1960) who ashed lungs of coal miners with a comparable degree of pneumoconiosis and measured the amount of mineral dust removed. It appears that a significant amount of dust can be removed by the using WLL, although the effect of removing this dust on the natural history of pneumoconiosis is unknown.

might delineate mechanisms which can be affected by therapeutic interventions. Yet, even this process has limitations because *in vitro* techniques often lack adequate the complex cellular milieu present in the organism. Other evaluations could target mediators derived from additional cells involved in the pathogenesis of fibrosis.

It is likely that there will need to be more than one therapeutic strategy. One phase could be the removal of dust, using the procedure of WLL. A second phase could be the use of multiple drugs which might modulate the inflammatory response associated with silica exposure. For example, in silicotic rats receiving tetrandrine and PVNO, greater amounts of products of collagen breakdown were measurable in the serum compared with the levels in silicotic animals which did not receive these drugs (Yu *et al.*, 1995). This implies that the use of multiple drugs may accelerate collagen breakdown. Yet, before reaching decision points regarding what drugs might be indicated in workers who develop silicosis, well-designed controlled studies will need to be performed to determine the effects of these interventions on the natural history of these illnesses.

Acknowledgments

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