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Imaging of Occupational and Environmental Disorders of the Chest

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Foreword

A changing industrial environment in the western world during the past decades has resulted in a considerable change in the spectrum of occupational and environmental lung disorders that we observe nowadays in medical practice. Modern radiological imaging is a important diagnostic tool for the correct management of these diseases.

This volume, unique in its concept, not only covers in a comprehensive way the imaging features of the well-known coal worker's pneumoconiosis and the severe forms of silicosis and asbestosis, but also deals extensively with the effects of new organic and inorganic materials , used in the modern chemical industry as well as with the noxious effects of cigarette smoking.
The eminently readable text is complemented by superb illustrations.

The editors, P.A. Gevenois and P. De Vuyst are well-known experts in the field. The authors of the individual chapters are outstanding specialists in the epidemiology, etiology, immunology, pathology, pathophysiology, and radiology of dust inhalation diseases. I would like to thank and to congratulate most sincerely the editors and the authors for their top-level contributions.

This superb book will be of great value for general and chest radiologists but also for pneumologists and all those active in occupational and environmental medicine. It provides them with the latest information on a very interesting medical field with an important medicosocial impact.

I am confident that it will meet the same success with the readers as many previous volumes in this series.

Leuven — Albert L. Baert

Introduction

Pierre Alain Gevenois and Paul De Vuyst

The spectrum of classical pneumoconiosis has changed during the past decades in industrialized countries: as a result of better control of air dust levels and reduction of workforce in large sectors of industry, the incidence of severe forms of silicosis, coal worker's pneumoconiosis and asbestosis (lung fibrosis), has decreased over time. Most incident cases of disabling pneumoconiosis result from exposures dating back several decades ago.

Parallel to the reduction of exposures in industries using natural minerals, the development of the chemical industry has led to the production of large numbers of organic and inorganic materials, including metallic alloys. More and more of these substances, including manmade organic particles, are reported as causes of interstitial lung disease in groups of exposed workers. Many different patterns of interstitial lung diseases have been reported: lung fibrosis, lung granulomatosis, giant cell pneumonitis, non specific interstitial pneumonia, chronic organizing pneumonia. Without a careful occupational history-taking and/or inquiry, all these forms may mislead the etiological diagnosis towards their respective idiopathic forms.

The major tools for diagnosis of pulmonary and pleural diseases are the imaging techniques to which this book is dedicated. Chest film reading and scoring according to the Classification established by the International Labour Office (ILO) is a standardized and wide-world used method and represents a common language between people working in this field, including in developing countries. This system facilitates for example the interpretation and comprehension of the epidemiological literature on pneumoconiosis. Many compensation systems rely on the presence of grade 1/1 or 1/0 small opacities on a plain chest film. This is however not the most sensitive to detect early changes and not the most specific one to diagnose pneumoconiosis in individuals. Indeed, the prevalence of small irregular opacities in an adult smoking population is high and the interpretation of films is subject to important inter and intra-observer variability in boundary grades, which are crucial in the acceptance of pneumoconiosis. This issue is even more important since incident cases of obvious pneumoconiosis with large opacities or high ILO grades have become exceptional. Computed tomography (CT) has largely been reported as more sensitive and more specific than chest radiograph and is thus now widely used for the diagnosis and compensation of pneumoconiosis. One of the consequences is the detection of abnormalities consistent with pneumoconiosis in patients without symptoms or lung function alterations. On the other hand, CT studies have been invaluable in the description and the distinction of the various forms of dust-related lesions, such as rounded atelectasis, diffuse pleural thickening and pleural plaques.

The majority of workers who are exposed to asbestos nowadays are end-users, in contact with asbestos still in place in buildings such as electricians, plumbers, demolition workers, asbestos removers… Most of them are self-standing workers, without any medical control or surveillance and often working without protective devices. The currently diagnosed cases are principally non malignant pleural lesions with little or no effect on lung function and the main cause of asbestos-related deaths among them is malignant mesothelioma rather than respiratory failure due to lung fibrosis. Since the incident cases of true asbestosis are rare, the development of lung fibrosis in a person with low cumulative exposure and/or low concentrations of asbestos bodies and fibers in bronchoalveolar lavage raise the possibility of idiopathic pulmonary fibrosis (IPF). Unusual exposures may however still be at the origin of severe

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diseases. Environmental exposures to tremolite asbestos have been documented in Turkish residents and migrants with burdens of fibers equal to those seen in industrial settings and subsequent asbestos-related diseases, including asbestosis.

Occupational lung diseases have also extended their links and limits. There is a clear association between silicosis or silica exposure and connective tissue disorders such as rheumatoid arthritis, systemic sclerosis and ANCA-positive vasculitides. Even "IPF" has been shown in several epidemiological studies associated with occupational exposures to metals or wood dusts. These studies beside exclude patients with asbestos or silica exposures of any importance, considering them respectively as having asbestosis or silicosis, irrespective of low cumulative exposures and/or radiological abnormalities not consistent with pneumoconiosis. The proportion of « IPF » cases with exposure to exogenous dust may be more important than previously thought. In this regard, it is interesting to note that coal miners may develop an IPF-like disease with a honeycomb pattern on thin-section CT rather than a classic coal worker's pneumoconiosis, and that these cases are now compensated in France.

Occupational agents may interact with other agents, infectious or not. Drugs can induce or trigger interstitial and/or pleural disease and this may induce confusion if these changes develop in persons with prior occupational exposure. This is particularly true for asbestos, and several cases have been reported of patients with prior asbestos exposure, who developed rapidly progressive pleural thickening or effusion, while being treated with bromocriptine for Parkinson's disease.

There is still important clinical and basic research work in occupational and environmental diseases. The research areas concern the description of new diseases due to organic and inorganic materials, nanotoxicology, mineralogical studies on the lung, genetical and immunological susceptibility to pneumoconiosis…There are indeed differences in the individual susceptibility to the adverse effects of chemicals and metals. Berylliosis and hard metal disease may be observed after exposure to low-doses, and are known to affect only a minority of exposed workers. Important advances have been made in basic research on the immunogenetic basis of berylliosis. A human HLA class II mutated gene was found to be strongly associated with clinical berylliosis and probably with hard metal disease.

Imaging, even by CT, is crucial, but only a part of the diagnosis of occupational disease. Many patterns of interstitial lung disease, can be either idiopathic or due to an exogenous cause. Other diagnostic tools are essential. They include a careful occupational and environmental history taking, which may necessitate a visit of the house or of the workplace. Some diagnoses, especially in the field of hypersensitivity pneumonitis require sagacity worthy of Sherlock Holmes himself! They also may require mineralogical studies on bronchoalveolar lavage, immunological tests (serum precipitating antibodies, lymphocyte transformation tests…) and in some cases lung biopsy.

The diagnostic work-up in occupational and environmental lung and pleural diseases needs sometimes more than a simple chest plain film with lung function tests. In clinical practice, this can not be accepted as sufficiently accurate to confirm or refute the diagnosis of pneumoconiosis in a dust-exposed worker with interstitial lung disease. Advances in imaging, mineralogical, pathological and immunological techniques have been instrumental in describing new patterns of disease and they allow a comprehensive approach to occupational and environmental disorders. This is crucial for making a correct clinical diagnosis and for not missing treatable diseases, in the description of new patterns of diseases, and for making scientifically based expertise of difficult or litigious cases. The changing spectrum of environmental and occupational diseases makes thus essential very close collaboration between radiologists, pneumologists, occupational physicians, environmental hygiene specialists, immunologists, mineralogists, and pathologists.

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Part I:
The Basics for Understanding Imaging

1 Epidemiology and Imaging of Dust Diseases

Daniel E. Banks

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1.1 Epidemiology and Imaging in Occupationally Related Lung Disease – Then and Now

There are a number of reasons why one might have expected an increasing number of work-related adverse chest effects if fibrogenic dust exposures had remained unchanged compared with exposures in the past. Perhaps the most apparent and probably most important is the recognition that life expectancy has increased. In 1950, 40-year-old white men were projected to live 31.2 more years. In 2001, this same population had a projected survival of 37.3 years. All other men (non-whites) in this age group had a projected survival of 27.3 years and 32.5 years at these points in time, respectively (http://www.infoplease.com/ipa/A0005140.html).

One of the hallmarks of these work-related illnesses is the protracted latency period. This increase in projected survival times is relevant to this perspective. For example, with this increase in longevity over the past 50 years, it is reasonable to expect that workers with asbestos-related lung disease would have a longer time to, first, develop the disease and, second, progress to more severe disease. Workers at risk for mesothelioma would have a longer time period to develop this illness. In addition, this illness would have the potential to occur more frequently. Similarly, those with asbestos exposure who smoke cigarettes would have a prolonged time to develop lung cancer, even after they stopped smoking. With these data, if exposures had remained the same, these additional years of survival would result in more frequent and more severe dust-induced chest illnesses.

Yet, the picture that has developed is dramatically different. This is due to a substantial decrease (typically of several orders of magnitude) in respirable exposures. It may well be that these lessened exposures are reflected in longer survival. Although there is no prevalence of truly "representative" illness reports, several of the studies below may be considered "representative" of the decade(s) that the workers were employed and the year of publication. Selikoff, in 1965, reported on a population of asbestos workers with a 40-year latency of asbestos exposure. In this population of 121 workers, 94.2% were reported to have a radiological diagnosis of asbestosis (Selikoff et al. 1965). In a 1979 report of 359 present and retired shipyard workers with at least 10 years of exposure, 44% had parenchymal interstitial disease (Polakoff et al. 1979). More recently, in a population of electricians with at least 20 years of union membership, the prevalence of small opacities was 2.1% (Hessel et al. 1998). These reports show the dramatic decline in dust-induced lung disease.

Even at these dramatically diminished prevalence rates, we cannot dismiss the rate of occurrence of these illnesses. Although the prevalence of disease is substantially less, health issues continue to be recognized, particularly in the older or retired worker. Perhaps the most consequential of these dust diseases is asbestosis, the only major pneumoconiosis to demonstrate an increase in mortality over the past decade (Changing Patterns of Pneumo-

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coniosis Mortality 2004). Mortality from asbestosis peaks 40–45 years after the workers' initial occupational exposure to asbestos (Virta 2003). Since asbestos consumption increased substantially during and after World War II, with a peak in 1975 followed by a steep decrease beginning in the 1980s (Selikoff et al. 1980), asbestosis-related mortality will remain with us and perhaps even increase for another decade. Asbestos-containing materials that continue to be used in some workplaces and remain in buildings represent a potential risk for the next generation.

What happened to cause this dramatic lessening in the number of cases of dust-induced lung diseases? Regulatory agencies have become sensitized to the adverse respiratory effects of dust exposure and responded by lessening permissible exposure limits. Workers have been protected. Decisions made by governmental agencies regarding standard setting have been driven by epidemiological studies. These studies have used years of employment and dust measurements as variables and lung function tests (typically, the forced expiratory volume in one second) and chest radiography [as interpreted by the International Labor Organization (ILO) classification] as outcomes. The notion that these variables determine outcomes in a relatively predictable manner (i.e., dose dependent) is key to protecting the worker. Integrity in the collection of demographic data, lung function testing, and interpretation of chest radiographs in the standardized manner is critical to this process.

1.2 Development of a Standardized Imaging System for Chest Radiographs

There have been several sentinel events in the epidemiological studies of lung diseases in workers. These events focus on the development of a scheme to standardize the interpretation of films for the classification of pneumoconiosis. Arguably, the current system of classifying the severity of radiological simple pneumoconiosis stems from the work of Davies and Mann (1948; Oldham 1970). These investigators postulated that the number of small opacities visualized on the radiograph is the equivalent of severity of pneumoconiosis and introduced the concept of "major" categories of simple pneumoconiosis (based on profusion and extent of opacities). This notion was later incorporated into the ILO 1958 classification of the radiographs of pneumoconioses (International Labour Office 1959), in which an apparent continuum of opacities is separated into four distinct categories - from 0 to 3. Once this initiative had begun, the next steps were to relate these standardized abnormalities on the chest radiograph to demographic data. Liddell is later credited as the first to divide each major category into three subcategories (Liddell 1963).

The International Union Against Cancer (UICC) Working Group on Asbestos and Cancer in 1964 recognized the need to improve comparability and build on the 1958 classification (International Union Against Cancer 1965). In 1965, three groups met to develop a more sophisticated plan to interpret radiographs for pneumoconiosis and formulated a scheme that was to be known as the 1970 UICC/Cincinnati classification (UICC 1970). The effort to structure a meaningful program was international in scope. Working groups included: representatives of physicians from numerous countries asked by the UICC to interpret a series of chest radiographs from workers with dust disease, radiologists from the U.S. Public Health Service who were developing a scheme to interpret films of workers in asbestos manufacturing industries, and physicians keen to categorize the radiographs from workers employed at the Asbestos and Thetford mines in Quebec.

The changes from the 1958 scheme of interpretation form the basis of what is the basically the current ILO system, initially introduced as the 1970 UICC/Cincinnati classification. Changes included the division of pleural changes into "calcified" and "noncalcified," as well as changes in the manner that small opacities were described. As noted above, opacities had been categorized as major categories 0–3 in profusion. With the new scheme, a 12-point scale reflecting a series of "shades of gray" within a major category was put into place. In addition, the lung was separated into three zones for more descriptive imaging, rather than being characterized as a single entity. Finally, this new scheme separated opacities into "rounded" and "irregular" (they had previously been categorized solely as "small opacities") and then further separated irregular opacities from one size (L) into three sizes (s, t, u). Copies of "standardized" radiographs were made available from several investigators. The 1968 ILO classification system was a modification to incorporate asbestos-related diseases based in part on the UICC/Cincinnati classification system.

In 1973, Weill and Jones reported on a National Institutes of Health-sponsored workshop addressing

interpretation of the chest roentgenogram (using the UICC/Cincinnati classification) as an epidemiological tool (Weill and Jones 1973). Their comments are relevant today. Overall, this working group identified problems in the interpretation of standardized radiographs. These include: (1) difficulties in distinguishing between small rounded and small irregular opacities when both are present; (2) correlating measures of profusion that accurately reflect lung function; (3) identifying the best way to use chest radiographs in assessing progression of disease; and (4) understanding how to best avoid biased readings in epidemiological surveys. They proposed several solutions: they (1) provided instructions to enable readers to distinguish small rounded from small irregular opacities; (2) developed ways to correlate profusion with lung function measurements; (3) considered small rounded and small irregular opacities as separate entities; and (4) at least in epidemiological studies, advocated the use of three (or more) readers to minimize inter-observer variability.

The 1980 ILO classification system made several changes. These included the presentation of a new set of 22 standard chest radiographs showing both round and irregular opacities, as well as large opacities. These films were used as examples of the size, shape, and profusion categories of opacities. An estimate of film quality became a part of the protocol, and the description of the pleura was more detailed (Henry 2002).

In 2000, the ILO again gave the scheme a "face lift." The standard films illustrating pleural abnormalities and 'u' shadows were replaced. Additionally, the ability to assess pneumoconiosis was to be judged on a scale from unimpeachable (+) to unusable ("u"). If not "+", then written comments are needed. A minimum width of 3 mm (previously 0–5 mm) was now required for plaques as well as for the margin to the lateral chest wall. Diaphragmatic plaques were not considered for measurement of extent, but only if absent or present. For "diffuse pleural thickening," obliteration of the costophrenic angle was recognized as necessary. New symbols for chest radiological findings were also included (Hering et al. 2003; http://www.chestx-ray.com/BReader/BReport/Compare1980_2000ver.html).

The desire to diminish variability in radiograph interpretation resulted in the formation of the Department of Labor and the National Institute for Occupational Safety and Health (NIOSH)-sponsored "B" reader program. The development of this credentialing program has been organized by NIOSH, with contractual agreements with the American College of Radiology. The goal is not only to provide standardized and reproducible interpretations of chest radiographs in workers with suspect pneumoconiosis but also to educate and teach physicians about the radiographic features of pneumoconiosis. Physicians who complete the educational program and then successfully interpret these radiographs in a manner reasonably similar to the way a series of "experts" interpreted the radiographs gain a "certificate of competence" in interpreting films (Morgan 1979; Wagner et al. 1992). This "B" reader certification can reasonably be described as challenging, with approximately half of those who take the certification test successfully completing the examination and approximately two-thirds successfully completing the re-certification examination (Wagner et al. 1992). Currently, more than 351 "B" readers are certified.

1.3 Reader Variability and the Diagnosis of Work-Related Lung Disease

To continue with the example of dust disease due to asbestos, many factors can lead to parenchymal changes on the chest radiograph that are identical to the interstitial changes of asbestosis. Explanations for these changes might include radiographic technique, aging, obesity, cigarette smoking, obstructive lung disease, as well as other interstitial lung diseases that may or may not be related to occupational exposures (Dick et al. 1992). Knowing the reason for these relatively frequently occurring "mildly abnormal" findings on the chest radiograph (i.e., category-1 irregular opacities) can be difficult.

Variability in chest radiograph interpretation for classification of the pneumoconioses was initially reported in 1949 (Fletcher and Oldham 1949), long before standardized radiographs were introduced and before the "B" reading program was initiated. Disparities in chest radiographic interpretation for pneumoconiosis are well known among physicians who testify in cases where dust-related disability is adjudicated and among the attorneys who try such cases. Yet, those who must feel the most frustrated in such cases are the workers themselves. It is difficult for the worker to understand how one "B" reader determines the worker has an advanced case of pneumoconiosis only to hear from another "B" reader that there is no evidence of dust disease of the lungs.

Despite the introduction of the "B" reader program, an attempt to introduce reproducibility into the system of radiographic interpretation, variability has continued.

In the decade of the 1970s, Reger and Morgan had 2,337 radiographs evaluated by four readers. The percentage of radiographs interpreted to have complicated coal workers' pneumoconiosis (CWP) ranged from 8.0% to 22.5%. In only 56.7% was there agreement between readers (Reger and Morgan 1970). Felson reviewed more than 55,000 radiographs from coal miners. In these films, reader variation was thought to be primarily due to: (1) poor film quality, (2) inexperience among readers with the ILO classification system, and (3) lack of familiarity with the radiographic features of CWP (Felson et al. 1973). In a review of 674 radiographs of naval dockyard workers, the inter-observer prevalence of pleural changes ranged from 14% to 30% (Sheers et al. 1978).

In the decade of the 1980s, additional concerns were expressed by investigators counting on accurate "B" readings. Parker reported that in 1985 in Minnesota, an initial reading of 566 chest radiographs found 30% of them positive for pleural changes. However, only 4% were considered positive by at least two of three readers from NIOSH interpreting the films under "blind" conditions. In this group, selective over-reading, primarily of women participating in the study, created an illusion of a generalized environmental problem (Parker et al. 1989).

In 1986, 700–750 tire workers participated in a medical screening that included posterior-anterior and right and left oblique radiographs. Of the workers, 439 (approximately 60%) were diagnosed as having abnormal chest radiographs due to inhaled asbestos. Yet, a re-reading by a panel of three "B" readers agreed that 7 (1.6%) had opacities exceeding category 0/1; 8 (1.8 %) had pleural abnormalities, and 1 (0.2%) had both. The first assessment of possible asbestos-related disease showed a prevalence rate greater than 40-fold the rate found at the re-evaluation (Reger et al. 1990).

In the decade of the 1990s, and perhaps in response to the above concerns, NIOSH scheduled a workshop addressing the "B" reader program. After considerable discussion, the workshop participants concluded that: (1) the current "B" reader program should continue; (2) in addition to re-certification every four years, ongoing quality assurance was recommended (however, no clear plan was agreed upon, or to my knowledge, initiated); and (3) within the "B" reader program, or through other approaches, the need to train other medical practitioners in the recognition of pneumoconiosis was recognized. Although not described, the authors stated that plans to improve the program were underway (Attfield and Wagner 1992). The author of an accompanying editorial noted that there was no clear consensus as to what was wrong with the program, and, thus, no clear conception of how to change it could be developed. Workshop attendees voiced support for some quality assurance of "B" readers beyond the certification–re-certification program, but no specific plan to resolve problems was thought to be free of significant problems, and no program was implemented (Balmes 1992).

Several years later, the leadership of the faculty of the Division of Respiratory Diseases Studies Group at NIOSH, the group responsible for administering the "B" reader program, addressed the concerns of variability among "B" readers (Wagner et al. 1993). The NIOSH representatives, as well as a number of others who participated in the "B" reading program, recognized that variability in chest radiographic interpretation can be very damaging to concerned parties. First, it may lead to great differences in the outcomes of epidemiological studies. Second, it can add tremendous burdens to a court system already strapped with an already great number of occupational lung disease cases. They realized that readers may disagree widely and persistently among each other when examining the same radiographs (inter-observer error) and also differ with themselves on repeated readings (intra-observer error). They opined that "the 'B' reading examination has undoubtedly contributed to control of variation among readers in the United States," yet did not reference work showing this to be the case. It is of interest to note that well-trained "lay" readers have been shown to be able to provide reliable classification of pneumoconioses (Copland et al. 1981; Peters et al. 1973).

Others have also shown problems in reproducibility of "B" reader results. Ducatman showed a large variation in the interpretation of small opacities among 23 NIOSH-certified "B" readers. To emphasize this point, he noted a 20-fold difference in the prevalence of positive findings between the readers at the two extremes (Ducatman 1991; Ross 2003).

Disagreements among readers may well be understandable when there is difficulty deciding whether a radiographic diagnosis of pneumoconiosis is truly present when the profusion of opacities is only minimally increased. Yet, it is difficult to understand

situations when one "B" reader chooses category-2 profusion of small opacities, while a second "B" reader states that no increase in opacities is noted. Table 1.1 shows a head-to-head comparison between two "B" readers who interpreted the same chest radiographs of coal miners applying for disability and Black Lung benefits. Because of the great disparity between these two readings, such differences cannot be explained by the relatively subtle changes noted at the start of this section. Rather, the concern must be that one of the readers has chosen to deliberately "overread" or "underread" the radiographs.

There has been discussion regarding these disparities. To begin, disparities in chest radiograph interpretation by "B" readers has not escaped the eyes of our legal colleagues. Brickman (2004) has boldly stated "'B' readers and other medical experts are misdiagnosing claimants in order to generate substantial profits. While X-ray readings and medical diagnoses do involve quite subjective judgments, since we are dealing in the aggregate with tens of thousands of X-ray readings, the huge and consistent discrepancies between 'neutral' readers and those profiting from their litigation findings cannot be attributed to 'inter-reader variability.'"

Egilman, an expert witness in areas related to asbestos-related health effects, reported irregularities on the basis of plaintiff lawyers, particularly in the undertaking of mass health "screenings" (Egilman 2002; Egilman et al. 2004). In cited examples, he reported that more money is paid for an abnormal than normal chest x-ray reading, reading sheets for radiographs less than 0/1 are not completed, and in some cases chest radiographs are "shopped around" to other B-readers until the attorney gets the desired reading. A more recent report has placed the interpretation of chest radiographs by physicians certified as "B" readers, particularly those retained by plaintiff's attorneys, under even closer scrutiny (Gitlin et al. 2004). The authors state that "reinterpretation by six independent consultants of chest radiographs read initially by 'B' readers selected by plaintiffs' counsel failed to confirm the conclusions of the initial readers. Whereas the initial readers interpreted 95.9% of the chest X-rays as positive for parenchymal abnormalities - small opacities profusion category 1/0 or higher - the consultants interpreted the same set of cases as positive in only 4.5%." The authors conclude that the magnitude of the difference in the reading of radiographs is so disparate that the data cannot be attributed to chance. In a guest editorial accompanying this article, the authors write that the report "raises considerable concern as to whether interpretations of chest radiographs rendered by B-reader radiologists acting as expert witnesses and offered as testimony in asbestos-related litigation is non-partisan and clinically accurate" (Janower and Berlin 2004).

In a recent and very worrisome episode drawn from the legal experience, a judge in a consolidated case of silicosis litigants, which included 90 lawsuits from eight U.S. states involving nearly 10,000 cases, expressed serious concern about the difference in "B" reading interpretations. She called their ("B" readers contracted by the plaintiff attorneys) findings "fraudulent and stunning" (http://www.lexisone.com/news/nlibrary/m022205l.html; http://www.caller.com/ccct/editorials/article/0,1641,CCCT_840_3635211,00.html). It appears that in a series of such consolidated suits, be they related

Table 1.1. Variability in chest radiograph interpretation in coal miners by two "B" readers. *S* surface miner, *U* underground miner, *BPP* bilateral pleural plaques, *RPP* right-sided pleural plaque. Assuming a radiograph is considered positive at ILO category 1/0, then the prevalence of pneumoconiosis for reader 1 is 16/19 (84%) and for reader 2 is 3/19 (16%)

Job	Reader 1	Reader 2	Job	Reader 1	Reader 2
26 U	1/2 Q/T, BPP	0/0	10 S	1/1Q/T, BPP	0/1 S/T
15 U, 17 S	2/1 Q/T, BPP	1/1 S/T	8 U	1/1 Q/T	0/1 Q/Q
15 U	2/1 Q/T, RPP	0/1 Q/Q	3 U	1/0 Q/T	0/1 P/R
6 U	1/1 Q/T, BPP	0/0	6 U	0/0	0/0
28 U, 2 S	1/0 Q/T	0/1 Q/Q	27 S	1/1 Q/T	0/0
4 U	1/1 Q/T	0/0	13 S	1/1 Q/T	1/1 Q/T
22 U	0/0	0/0	19 U	1/2 Q/T	0/1 S/T
19 S	1/1 Q/T, BPP	0/0	12 U,15 S	0/0	0/0
15 U	1/1 Q/T	0/0	8 U	1/1 Q/T	0/1 S/T
26 S	2/1 Q/T, RPP	1/1 R/Q			

to the diagnosis of silicosis or asbestosis in workers, very often the same "B" readers are responsible for the diagnoses of pneumoconiosis (http://judiciary.senate.gov/testimony.cfm?id=1362&wit_id=3963; http://www.al.com/specialreport/mobileregister/?asbestos/seekdismissal.html).

1.4 What About Other Techniques for Chest Imaging?

If we accept that difficulties exist in the interpretation of chest radiographs for the classification of pneumoconiosis, are there more accurate imaging procedures available? Specifically, what is the role of thin-section computed tomography (CT) in screening for dust-induced interstitial fibrosis?

Early work showing relationships between asbestosis on the chest radiograph and thin-section CT was done by Katz. He showed parenchymal abnormalities consistent with asbestosis in one-third of asbestos-exposed subjects studied by CT, whereas conventional chest radiographs were abnormal in only 16% (Katz and Kreel 1979). Sperber and Mohan (1984) and Yoshimura et al. (1986) found similar results.

Aberle assessed 100 workers occupationally exposed to asbestos by chest radiograph, pulmonary function tests, and thin-section CT (Aberle et al. 1988). In 55 workers with normal chest radiographs, parenchymal abnormalities were identified in 30% using thin-section CT and considered suggestive of asbestosis in another 20%. There was a significant correlation between increasing abnormality on thin-section CT and decreasing lung volumes, consistent with a restrictive pattern. Similar thin-section CT findings were seen by Staples in asbestos-exposed persons with normal chest radiographs (Staples et al. 1989). The lung parenchyma was suggestive of asbestosis in 57 of the 169 subjects scanned. Additionally, these 57 persons had significantly different lower mean vital capacity and diffusion capacity than 76 individuals with normal thin-section CT scans.

Jarad proposed a scoring system for thin-section CT for pleural fibrosis, pleural disease, and emphysema in asbestos-related disease and tested this approach for reproducibility and inter-observer error (Jarad et al. 1992). Two readers assigned thin-section CT scan scores for fibrosis, emphysema, and pleural disease that differed by less than two categories in 96% and 92% of the scans, compared with 78% and 79% of chest radiographs. In addition, there was less intra-observer error for the thin-section CT scores than for the chest radiograph scores for all disorders.

Ameille compared the oblique chest radiograph to thin-section CT in assessing the prevalence of pleural thickening in workers exposed to low levels of asbestos (individuals employed in university buildings insulated with asbestos-containing material) (Ameille et al. 1993). Pleural thickening was recognized by right anterior oblique radiographs in 23, while thin-section CT showed only equivocal plaques in 3 and doubtful plaques in 3 others. The authors concluded that the use of oblique radiographs was not a good screening tool in this population.

Begin compared chest radiographs of long-term asbestos-exposed workers ranked either 0 or 1 by ILO category with routine thoracic CT scan (Begin et al. 1993). Even without the thin-section CT "cuts", CT scans identified significantly more irregular opacities recognized to be consistent with asbestosis than the chest radiograph, despite the absence of ILO criteria for interpretation of CT scans.

Oksa compared thin-section CT to chest radiographic, asbestos exposure and lung function variables in 21 former asbestos sprayers (Oksa et al. 1994). thin-section CT was superior to chest radiography in detecting parenchymal and pleural changes. In 12 radiographs graded category 0/0, 9 were considered to be positive using thin-section CT scan. Of the 21 sprayers, 19 had pleural plaques by thin-section CT but only 5 using chest radiograph. These authors suggest that asbestos workers with less than 1/0 ILO classification using chest radiograph should have a thin-section CT scan. Similar results were seen in the study by Neri et al. (1994). Asymptomatic shipyard workers (n=70) with "normal" chest radiographs were tested using thin-section CT. Of these, 34 were found to have pleural plaques alone, 6 had parenchymal abnormalities alone, and 13 others had both. No radiological abnormalities were shown in the remaining workers. In addition to showing that pulmonary or pleural changes due to exposure to asbestos can be detected using HRCT prior to the onset of any radiological findings, they also showed that thin-section CT findings were identified prior to the development of clinical symptoms.

Talini compared the usefulness of the thin-section CT scan to the chest radiograph in the diagnosis and assessment of the severity of silicosis (Talini et al. 1995). There was better concordance between

readings for thin-section CT with pulmonary function tests and chronic bronchitis compared with the chest radiograph. Concordance for a diagnosis of silicosis between readers was higher for thin-section CT than chest radiography, yet there was no concordance between the chest radiograph and thin-section CT in the early stages of silicosis. This work did not support the hypothesis that thin-section CT is more sensitive than the chest radiograph in the early detection of silicosis.

Murray retrospectively reviewed thin-section CT scans performed at preselected levels in 49 patients exposed to asbestos (Murray et al. 1995). Two teams of thoracic radiologists evaluated: (1) all images, (2) prone images only, and (3) a single prone image through the lung bases for the presence of diffuse interstitial lung disease. A relatively high level of accuracy was obtained with a single prone scan; however, diagnostic accuracy improved to 95% or better when additional prone images were included. Using this approach, a screening study of a relatively large number of workers exposed to asbestos could be performed.

Because there is no developed standardized system for detailing asbestos-related abnormalities by thin-section CT scans, such abnormalities are usually assessed subjectively. Gamsu compared the sensitivity of a subjective semiquantitative scoring system of the extent and severity of asbestosis to a method using an accumulation of the different thin-section CT features of asbestosis in workers with histological proof of disease (Gamsu et al. 1995). He also compared the results of these two thin-section CT methods with chest radiographs in these same workers. Results showed that thin-section CT predicted asbestosis with a higher frequency than chest radiographs classified by the ILO classification and that both the subjective semiquantitative grading system and the method of using an accumulation of features of asbestosis identified using thin-section CT give similar results. Using either or both of these approaches is complementary. Importantly, the authors recognized that asbestosis can be present histologically with a normal or near normal thin-section CT.

The International Expert Meeting on Asbestos, Asbestosis, and Cancer, which took place in Helsinki in 1997, concluded that there was a need for the development of a standardized system for reporting thin-section CT scan results of asbestos-related disorders (similar to the ILO system for chest radiographs), and additional work was needed to show the specificity of lesions of the pleura identified on thin-section CT as markers of asbestos exposure (Asbestos, Asbestosis and Cancer 1997). Yet, this expert meeting concluded that "CT and thin-section CT can facilitate the detection of asbestosis and asbestos-related pleural abnormalities, as well as asbestos-related malignancies; they are not recommended as a screening tool but may be invaluable for individual clinical evaluation and research purposes."

Reliability of thin-section CT scans in detecting discrete pleural lesions was assessed in 100 volunteers employed for at least 10 years in a building with known asbestos contamination (de Raeve et al. 2001). In the first session, pleural abnormalities were detected in 13 subjects. In the second session, the scans were read again by the same radiologist and two other radiologists. The final consensus reading gave a diagnosis of pleural abnormalities in 18 subjects; 8 (44%) were detected by all three readers, 5 (28%) by two readers, and 4 (22%) by only one reader. One scan, rated normal by all readers during the second session, was reconsidered because pleural abnormalities were noted at the first reading. The intra-observer agreement for first reader was good, but the inter-observer agreement between the readers was only fair to moderate in the second reading session. In conclusion, when reviewing the prevalence of pleural abnormalities in subjects with low-level exposure, the potential for a lack of consistency in reporting pleural abnormalities should be recognized.

Savranlar compared chest radiography to thin-section CT in 71 coal workers with and without early and low-grade CWP (Savranlar et al. 2004). Of the workers, 4 were excluded because of the presence of progressive massive fibrosis. Profusion categories 0/1 to 1/1 were defined as "early", and 1/2 and 2/2 were "low-grade." Discordance between the chest radiograph and thin-section CT was high. When coal miners with normal chest radiographs were compared with their own thin-section CT scans, 6 of 10 cases were positive using thin-section CT. This led these investigators to suggest that thin-section CT was a better tool to identify early pneumoconiosis.

In the recent American Thoracic Society statement, a chest film clearly showing the characteristic signs of asbestosis in the presence of a compatible history of exposure is adequate for diagnosis (American Thoracic Society 2004). Although conventional CT is superior to the chest radiograph in identifying parenchymal lesions, rounded atelectasis, and pleural plaques, this has been displaced by

thin-section CT, as it is more sensitive for detecting parenchymal fibrosis. thin-section CT is perhaps most useful when readers disagree about the presence or absence of abnormalities on the chest radiograph, when chest radiographic findings are borderline, when diminished lung function is identified in association with normal chest radiographic findings, and when pleural abnormalities do not allow a clear interpretation of parenchymal markings. thin-section CT can detect early pleural thickening (i.e., 1–2 mm in thickness) with much more sensitivity than the chest radiograph.

In conclusion, there are numerous examples showing that imaging by thin-section CT scan is more sensitive than the chest radiograph for asbestos effects. However, this advantage has not clearly been shown for other dusts. Furthermore, there may well be substantial variability among thin-section CT scan interpretation even by experienced readers, particularly in the interpretation of pleural abnormalities among asbestos workers. There is no standardized protocol for the interpretation of the thin-section CT when addressing potential dust-induced effects.

The usefulness of any screening test depends on the prevalence of illness within the population, the test accuracy, the seriousness of the condition that might be recognized, patient risks, and cost. Such an assessment of parameters in the context of the use of thin-section CT for screening for dust-induced chest illnesses is beyond the scope of this report. No comments regarding screening for asbestos-related adverse health effects using thin-section CT are provided in the recent American Thoracic Society statement (American Thoracic Society 2004). Determining the role of thin-section CT scan in the screening of dust-induced chest illness is of great interest.

1.5 What Conclusions Should be Made?

Although variability in interpretation of chest radiographs has been recognized for a long time, there appears to be an increasing number of examples of "unexplainably" disparate interpretations by "B" readers. There also appears to be a temporal correlation between asbestos screening programs initiated for legal actions and the number and strength of challenges to the accuracy and integrity of the "B" reading program.

In response to the concern that medically inadequate assessments occur when asbestos screening is done for legal action, the American Association of Occupational and Environmental Clinics stated that (http://www.aoec.org/content/principles_1_3.htm#asbestos):

Screening on the basis of chest radiograph and work history alone does not provide sufficient information to make a firm diagnosis of work-related illness, assess impairment, or guide patient management. An appropriate screening program for asbestos-related lung disease includes: properly chosen and interpreted chest radiographs, reviewed within 1 week of screening; a complete exposure history; symptom review; standardized spirometry; and physical examination. Timely physician disclosure of the results to the patient, appropriate medical follow-up, and patient education are essential. Omission of these features in the asbestos-screening process falls short of the standard of care and ethical practice in occupational health. Perhaps key to the above protocol is the formation of a physician–patient relationship.

Is there a way to guarantee integrity of data collection by the care providers in this process? The standards for lung-function testing are widely available and can be objectively implemented. Yet, it appears that the accuracy of interpretation of radiographs by "B" readers is much more difficult to monitor. Perhaps there are ways to better guarantee the accuracy of a single "B" reader between the re-certification examinations (currently required every 4 years). Any such plan would likely require more frequent monitoring of radiograph interpretation. Perhaps the best first step would be for the leadership of NIOSH to begin a discourse regarding these critical concerns.

Independent of the potential loss of credibility in the interpretation of radiographs in medical disability court cases, without our ability to depend on the integrity of "B" readings, the accurate measurement of dust effects on the radiograph may be lost. If this were to occur, the development of new or changes in existing dust standards essential to protect worker lung health may be at risk.

References

Aberle DR, Gamsu G, Ray CS (1988) High-resolution CT of benign asbestos-related diseases: clinical and radiographic correlation. AJR 151:883-891

Ameille J, Brochard P, Brechot JM et al (1993) Pleural thickening: a comparison of oblique chest radiographs and high-resolution computed tomography in subjects exposed to low levels of asbestos pollution. Int Arch Occup Environ Health 64:545-548

American Thoracic Society (2004) Diagnosis and initial management of nonmalignant diseases related to asbestos. Am J Respir Crit Care Med 170:691-715

Asbestos, Asbestosis, and Cancer (1997) The Helsinki criteria for diagnosis and attribution. Scand J Work Environ Health 23:311-316

Attfield MD, Wagner GR (1992) A report on a workshop on the National Institute for Occupational Safety and Health B reader certification program. J Occup Med 34:875-878

Balmes JR (1992) To B-read or not to B-read. J Occup Med 34:885-886

Begin R, Ostiguy G, Filion R et al (1993) Computed tomography in the early detection of asbestosis. Br J Ind Med 50:689-609

Brickman L (2004) On the theory class's theories of asbestos litigation: the disconnect between scholarship and reality 31. Pepperdine Law Review 33:42

Changing patterns of pneumoconiosis mortality United States 1968-2000 (2004) MMWR Weekly 53:627-632 http://www.cdc.gov/mmwr/index.html

Copland L, Burns J, Jacobsen M (1981) Classification of chest radiographs for epidemiological purposes by people not experienced in the radiology of pneumoconiosis. Br J Ind Med 38:254-261

Davies I, Mann KJ (1948) Proc 9th Int Congress Industrial Med, Bristol, John Wrights, pp 769-772

De Raeve H, Verschakelen JA, Gevenois PA et al (2001) Observer variation in computed tomography of pleural lesions in subjects exposed to indoor asbestos. Eur Respir J 17:916-921

Dick JA, Morgan WKC, Muir DFC et al (1992) The significance of irregular opacities on the chest roentgenogram. Chest 102:251-260

Ducatman AM (1991) Variability in the interpretation of radiographs for asbestosis abnormalities: problems and solutions. Ann NY Acad Sci 643:108-120

Egilman D, Rankin Bohme S (2004) Attorney-directed screenings can be hazardous. Am J Ind Med 45:305-307

Egilman D (2002) Asbestos screenings. Am J Ind Med 42:163

Felson B, Morgan WKC, Bristol LJ et al (1973) Observations on the results of multiple readings of chest films in coal workers' pneumoconiosis. Radiology 109:19-23

Fletcher DM, Oldham PD (1949) The problem of consistent radiological diagnosis in coalminers' pneumoconiosis. Br J Ind Med 6:168-183

Gamsu G, Salmon CJ, Warnock ML, Blanc PD (1995) CT quantification of interstitial fibrosis in patients with asbestosis: a comparison of two methods. AJR 164:63-68

Gitlin JN, Cook LL, Linton OW et al (2004) Comparison of "B" readers interpretation of chest radiographs for asbestos related changed. Acad Radiol 11:843-856

Henry DA (2002) International Labor Office classification system in the age of imaging: relevant or redundant. J Thor Imag 17:179-188

Hering KG, Jacobsen M, Bosch-Galethe E et al (2003) Further development of the International Pneumoconiosis classification - from ILO 1980 to ILO 2000 / German Federal Republic version. Pneumologie 57:576-584

Hessel PA, Melenka LS, Michaelchuk D et al (1998) Lung health among electricians in Edmonton, Alberta, Canada. J Occup Environ Med 40:1007-1012

International Labour Office (1959) Meeting of experts on the international classification of radiographs of the pneumoconioses. Occup Safety Hlth 9:2

Janower ML, Berlin L (2004) 'B' readers' radiographic interpretations in asbestos litigation: is something rotten in the courtroom? Acad Radiol 8:841-842

Jarad NA, Wilkinson P, Pearson MC et al (1992) A new high resolution computed tomography scoring system for pulmonary fibrosis, pleural disease, and emphysema in patients with asbestos related disease. Br J Ind Med 49:73-84

Katz D, Kreel L (1979) Computed tomography in pulmonary asbestosis. Clin Radiol 30:207-213

Morgan RH (1979) Proficiency examination of physicians for classifying pneumoconiosis chest films. AJR Am J Roentgenol 132:803-808

Murray KA, Gamsu G, Webb WR et al (1995) High-resolution computed tomography sampling for detection of asbestos-related lung disease. Acad Radiol 2:111-115

Neri S, Antonelli A, Boraschi P et al (1994) Asbestos-related lesions detected by High-Resolution CT scanning in asymptomatic workers. Specificity, relation to the duration of exposure and cigarette smoking (in Italian). Clin Ter 145:97-106

Oksa P, Suoranta H, Koskinen H et al (1994) High-resolution computed tomography in the early detection of asbestosis. Int Arch Occup Environ Health 65:299-304

Oldham PD (1970) Numerical scoring of radiological simple pneumoconiosis. Inhaled Particles 2:621-632

Parker DL, Bender AP, Hankinson S et al (1989) Public health implications of the variability in the interpretation of "B" readings for pleural changes. J Occup Med 31:775-780

Peters WL, Reger RB, Morgan WKC (1973) The radiographic categorization of coal workers' pneumoconiosis by lay readers. Environ Res 6:60-67

Polakoff PL, Horn BR, Scherer OR (1979) Prevalence of radiographic abnormalities among northern California shipyard workers. Ann NY Acad Sci 330:333-339

Reger RB, Cole WS, Sargent EN, Wheeler PS (1990) Cases of alleged asbestos-related disease: a radiologic re-evaluation. J Occup Med 32:1088-1090

Reger RB, Morgan WKC (1970) On the factors influencing consistency in the radiographic diagnosis of pneumoconiosis. Am Rev Respir Dis 102:905-915

Ross RM (2003) The clinical diagnosis of asbestosis in this century requires more than a chest radiograph. Chest 124:1120-1128

Savranlar A, Altin R, Mahmutyazicioglu K (2004) Comparison of chest radiography and high-resolution computed tomography findings in early and low-grade coal worker's pneumoconiosis. Eur J Radiol 51:175-180

Selikoff IJ, Churg J, Hammond EC (1965) The occurrence among insulation workers in the United States. Ann NY Acad Sci 132:139-155

Selikoff IJ, Hammond EC, Seidman H (1980) Latency of asbestos disease among insulation workers in the United States and Canada. Cancer 46:2736-2740

Sheers G, Rossiter CE, Gilson JC et al (1978) U.K. naval dockyards asbestos study: radiological methods in the surveillance of workers exposed to asbestos. Br J Ind Med 35:195-203

Sperber M, Mohan KK (1984) Computed tomography - a reliable diagnostic modality in pulmonary asbestosis. Comput Radiol 8:125-132

Staples CA, Gamsu G, Ray CS, Webb WR (1989) High resolution computed tomography and lung function in asbestos-exposed workers with normal chest radiographs. Am Rev Respir Dis 139:1502-1508

Talini D, Paggiaro PL, Falaschi F et al (1995) Chest radiography and high resolution computed tomography in the evaluation of workers exposed to silica dust: relation to functional findings. Occup Environ Med 52:262-247

UICC (1970) Cincinnati classification of the radiographic appearances of pneumoconioses. A cooperative study by the UICC committee. Chest 58:57-67

Virta RL (2003) Worldwide asbestos supply and consumption trends from 1900 to 2000: US Geological Survey Open-File Report 03–83. Reston, Virginia: U.S. Department of the Interior US Geological Survey. Available at http://pubs.usgs.gov/of/2003/of03-083/of03-083.pdf

Wagner GR, Attfield MD, Kennedy RD et al (1992) The NIOSH B reader certification program. An update report. J Occup Med 34:879-884

Wagner GR, Attfield MD, Parker JE (1993) Chest radiography in dust-exposed miners: promise and problems, pitfalls and imperfections. Occup Med 8:127-141

Weill H, Jones R (1975) The chest roentogram as an epidemiologic tool: report of a workshop. Arch Environ Health 30:435-439

Yoshimura H, Hatakeyama M, Otsuji H et al (1986) Pulmonary asbestosis: CT study of curvilinear shadow. Radiology 158:653-658

2 Responses of the Respiratory System to Inhaled Agents

Andrew Churg, Anna Rask-Andersen, Øyvind Omland, and Benoit Nemery

2.1 Pathological Reactions to Inhaled Particles and Fibers

Andrew Churg

CONTENTS

2.1.1 Introduction

This chapter describes and illustrates the gross and microscopic features of pathological reactions to inhaled particles and fibers. In assembling such a chapter, one needs to make a decision about whether to classify pathological reaction patterns on a generic basis (for example, diffuse interstitial fibrosis) and then list the agents that might produce such a pattern or to describe patterns seen in response to specific agents. I have adopted the latter approach here, but it is important to recognize that many of the pathological reaction patterns described can be seen with a variety of agents. More details, including descriptions of entities too uncommon to be included here, can be found in Churg and Green (1998), Roggli et al. (2004) and Churg et al. (2005a).

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2.1.2 Lesions Caused by Metals and Related Compounds

Metals and related compounds (metal salts, metal oxides) as well as metal fumes (primarily welding fumes) produce a variety of lesions (Table 2.1.1) (Kelleher et al. 2000). However, there is considerable variation in the frequency with which specific lesions are found with particular agents. For example, macules are seen with many different dusts; whereas, relatively few dusts produce interstitial fibrosis, and many of the reports of interstitial fibrosis are of questionable validity (see below and Churg and Green 1998). Some dusts, such as hard metal and beryllium, operate through immunological mechanisms and produce quite different and fairly distinctive lesions; these are described at greater length.

Table 2.1.1. Dusts that commonly produce macules

Metals	Non-metallic dusts
Aluminum	Most non-asbestos silicates
Antimony	Coal
Barium („Baritosis:“)	Cigarette smoke
Iron („Siderosis“)	Particulate air pollutants
Lanthanum and other rare earths	
Tin („Stannosis“)	
Titanium dioxide	
Welding fumes	
Zirconium	

A *dust macule* is theoretically defined as a nonpalpable nonfibrotic grossly pigmented lesion that microscopically consists of dust, either free or in macrophages, around small airways and vessels (Wright and Churg 1998 and Fig. 2.1.1). Many metals and related compounds produce dust macules (Table 2.1.1); however, macules may also be seen with exposure to non-metallic dusts, particularly silicates. When macules are found on pathological

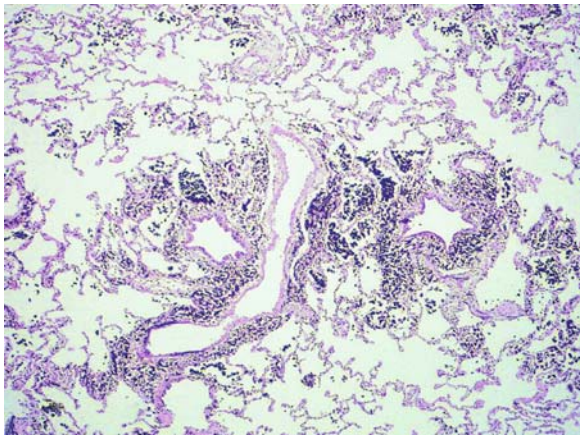

Fig. 2.1.1. Dust macule from the lung of a welder. Note the darkly pigmented dust (iron) that has accumulated in the center of the lobule around the small airways and vessels. There is no significant fibrosis associated with this lesion

examination, or corresponding rounded opacities are present on radiographic examination, specific disease names can be used. For example, in those with iron exposure, the process is called siderosis and, with tin exposure, stannosis. Dusts that produce macules are always more radiodense than air or lung tissues, so that macules appear as fine rounded opacities (simple pneumoconiosis), generally more prominent in the upper zones, on chest radiographs.

On gross examination, dust macules appear as colored "spots" in the centers of the lobules (Fig. 2.1.1); similar (un-named) collections of dust frequently extend along the interlobular septa and pleural lymphatics, and, thus, radiographs may also show Kerley B lines, reflecting collections of dust along interlobular septa. In addition to metals, many other types of dust (coal, silica, silicates, and even cigarette smoke) also produce macules. The exact color of the macule depends on the nature of the dust, and, in fact, the most common macule is the collection of black pigment seen in the centers of lobules in cigarette smokers and many city dwellers, the latter from inhaled particulate air pollutants. Some dusts can produce macules with specific colors, including the red-brown lesions found in hematite (iron ore) miners, the black macules seen in coal miners (Section 2.1.3), the grey lesions caused by tin, and the while macules in those exposed to the paint pigment, titanium oxide.

Macules were originally defined to separate these lesions, which were thought to be nonfibrotic "blemishes" of little functional impact, from the heavily collagenized nodules of silicosis (Wright and Churg 1998), a form of pneumoconiosis that was believed to produce major functional impairment. For this reason, dusts producing only macules were originally considered to be "inert." However, more recent studies have shown that, although macules may initially have little associated fibrosis, with time and/or continued dust accumulation, considerable fibrosis may occur and that, with sufficient exposure, no dust is truly inert. Many dusts that produce macules can also cause fibrosis of the walls of the small airways, presumably as a reaction to the dust accumulating in and around the airways, and the airways may become so distorted and fibrotic as to be almost unrecognizable (Fig. 2.1.2). In addition, enlarged airspaces frequently develop around the fibrotic small airways (Fig. 2.1.2), a process termed focal emphysema.

Focal emphysema is in many ways similar to the centrilobular emphysema seen in cigarette smokers, and it is likely that the combination of distorted small airways and focal emphysema is responsible for the finding of airflow obstruction that is now recognized as a consequence of high levels of dust exposure in some individuals (Churg et al. 1985; Wright et al. 1992; Churg and Wright 2003; Becklake 1985, 1989a,b; Oxman et al. 1993; Garshick et al. 1996; Dimich-Ward et al. 1996). It should be emphasized, however, that the usual cause of airflow obstruction is cigarette smoking and that only a small minority of dust exposed workers appear to develop clinically significant airflow obstruction as a result of the dust (Garshick et al. 1996; Guidotti 1998). It is possible that cigarette smoke and dusts interact in

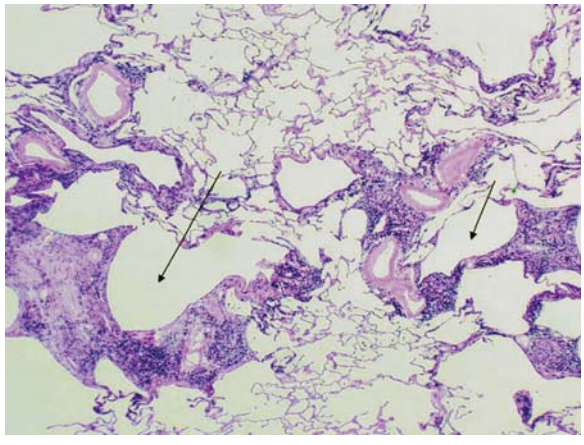

Fig. 2.1.2. Fibrotic macule from the lung of a hematite (iron-ore) miner. In contrast to figure 2.1.1, there is both marked fibrosis and focal emphysema (*arrows*). Lesions of this type may cause airflow obstruction

this regard, since both agents produce lesions in the same location.

Interstitial fibrosis: diffuse interstitial fibrosis is an uncommon finding in workers exposed to metals and related compounds. Because diffuse interstitial fibrosis is a fairly common disease in the general population, it is unclear in many instances whether dust exposure is really the cause of the lesions in a given individual. This is true of the few case reports of workers exposed to rare earths (Vocaturo et al. 1983), copper (so-called "vineyard sprayer's lung" (Villar 1974; Pimental and Marques 1969), and dental technician's pneumoconiosis, a condition seen in workers who make dental prostheses using chromium, cobalt, molybdenum, beryllium, or nickel (Nayebzadeh et al. 1999). Chest roentgenographs have been reported as showing reticulonodular infiltrates; the few pathological specimens have been claimed to resemble berylliosis, silicosis, and hard metal disease (Rom et al. 1984; Brancaleone et al. 1998; Kronengberger et al. 1981; Carles et al. 1978).

However, true diffuse interstitial fibrosis does appear to occur with exposure to beryllium (see below), aluminum (rarely), cobalt/hard metal (see below), silicon carbide (Funahashi et al. 1984; Masse et al. 1986), and probably in a few individuals exposed to very large amounts of iron, particularly from welding (Kelleher et al. 2000). For aluminum, silicon carbide, and iron, the major pathological findings are a combination of diffuse interstitial fibrosis and huge amounts of dust. Inhaled iron particles can be separated from endogenous iron because the former become ferruginated; i.e., they are phagocytized by macrophages and coated with an iron-containing protein that stains with the usual Prussian blue iron stain. In contrast, the inhaled iron particles themselves do not stain with ordinary histochemical stains for iron.

Hard Metal Disease and Disease Caused by Cobalt: Hard metal (cemented tungsten carbide with cobalt) is an extremely hard synthetic compound used in tool bits, drills, and bearings that operate in conditions requiring strength and rigidity at high temperatures (Coates and Watson 1971; Bech et al. 1962). Hard metal is prepared by heating finely divided tungsten and carbon to form tungsten carbide; then cobalt and sometimes other metals are added, and the mixture is fused at a high temperature to form the final product. The fabrication process generates a very fine dust (Coates and Watson 1971; Bech et al. 1962). While most cases of hard metal disease have been described in production workers, disease is also found in those who file or grind hard metal tools for actual use, for example, in some saw mill workers (Kennedy et al. 1995). The sensitizing agent is not the tungsten carbide but the cobalt, and cobalt can be extracted from the metal by liquid lubricants used to cool the work piece; thus, aerosolized coolants are also a source of disease (Sjogren et al. 1980; Cugell 1992). A disease clinically and morphologically identical to hard metal disease has been reported in diamond polishers who use a polishing agent containing cobalt but not hard metal (Demedts et al. 1984).

Hard metal exposure can produce adult respiratory distress syndrome, contact dermatitis, occupational asthma, a syndrome resembling extrinsic allergic alveolitis (hypersensitivity pneumonia), and a distinctive form of interstitial fibrosis (Cugell 1992; Cirla 1994; Chiappino 1994; Migliori 1994). Pathological descriptions exist only for the interstitial fibrosing process, and here the typical picture is that of interstitial fibrosis and interstitial inflammation that is predominantly centrilobular in distribution, accompanied by a desquamative interstitial pneumonia or a giant cell interstitial pneumonia-like picture (Fig. 2.1.3). Giant cells are not seen in every case but when present may be extremely large (Fig. 2.1.3) (Coates and Watson 1971; Davison et al. 1983). Early disease confined to the centrilobular regions appears as ground glass nodules on thin-section computed tomography. With continued exposure, the process spreads, linking centrilobular regions (Fig. 2.1.3). Honeycombing and diffuse severe fibrosis may be seen in very advanced cases.

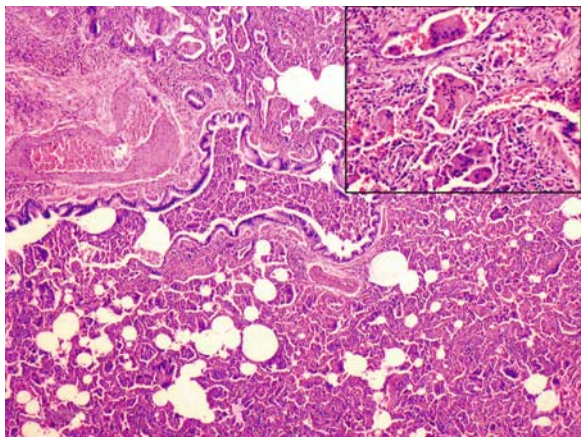

Fig. 2.1.3. Hard metal disease. The lower power view shows fairly advanced diffuse interstitial inflammation and fibrosis with numerous airspace macrophages and giant cells. The inset shows several very large giant cells

The histological picture in classic cases is diagnostic. Black particulate material is sometimes seen in macrophages and giant cells but is never abundant. When the history of exposure is uncertain, tungsten particles can usually be demonstrated by energy dispersive X-ray spectroscopy of histological sections or dissolved tissue, and their presence confirms the diagnosis, since tungsten is never found as a background atmospheric contaminant in the general population. Particles of cobalt may also be found but are less common because cobalt is soluble in tissue fluid (Coates and Watson 1971; Bech et al. 1962; Davison et al. 1983).

Berylliosis: Beryllium and beryllium alloys are used in a variety of applications requiring lightness, strength, and high resistance to fatigue. While berylliosis was prevalent in industries using beryllium prior to 1950 (Sprince 1986), most cases are now seen in workers in the few factories that produce beryllium alloys (Kelleher et al. 2000). Because berylliosis is a form of hypersensitivity reaction, disease may be seen not only in those handling or machining beryllium-containing materials but also in those in the same factory who have no direct contact.

Beryllium disease occurs in acute and chronic forms. Acute berylliosis is a form of adult respiratory distress syndrome and for all practical purposes is no longer seen, since it only occurs with high exposure.

Chronic berylliosis is a systemic granulomatous disease in which the lung is the primary target, and morphologically it is identical to sarcoidosis. Microscopically, one finds noncaseating granulomas that tend to follow the bronchovascular bundles (Fig. 2.1.4). As is true of sarcoidosis, the granulomas may coalesce to produce nodular lesions that gradually scar. In advanced cases, diffuse interstitial fibrosis and honeycombing may be observed (Churg and Colby 1998; Freiman and Hardy 1970). As is true of sarcoid, beryllium granulomas may also be found in hilar lymph nodes and in extrapulmonary sites, including the skin, liver, spleen, pancreas, kidney, adrenals, bone marrow, muscle, and central nervous system (Churg and Colby 1998). There is contradictory evidence for an increased risk of lung cancer in those with beryllium exposure (Saracci 1991; Levy et al. 2002; Hayes 1997; Steenland et al. 1996).

A good history of exposure is important in making the diagnosis. Beryllium lymphocyte proliferation testing (blast transformation and proliferation of a patient's peripheral blood lymphocytes on exposure to beryllium compounds) is valuable as an adjunct to diagnosis and for population screening (Jones and Williams 1983; Kelleher et al. 2000); however, while these tests show beryllium sensitization, it is as yet unclear whether they necessarily indicate the presence of disease. A variety of chemical techniques are available for documenting the amount of beryllium in lung tissue and urine (Churg and Colby 1998), and beryllium particles can also be demonstrated in paraffin tissue sections using atmospheric thin window energy dispersive X-ray spectroscopy (Butnor et al. 2003).

Lung Cancer: Lung cancer has been accepted or proposed to be associated with exposure to a variety of metals and other inhaled dusts (reviewed in Hayes 1997; Steenland et al. 1996) (Table 2.1.2).

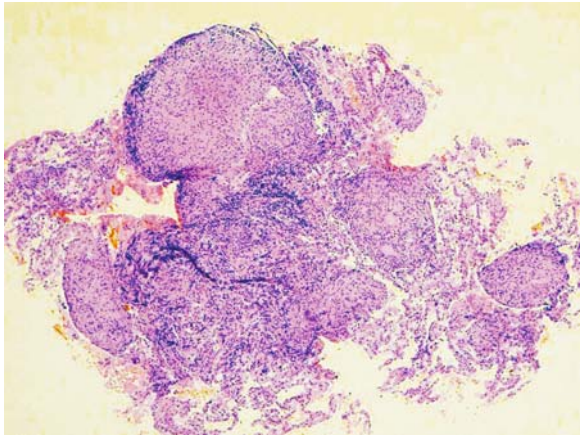

Fig. 2.1.4. Berylliosis. This image is from a transbronchial biopsy and shows several noncaseating granulomas. Histologically this appearance is identical to sarcoidosis

Table 2.1.2. Agents producing carcinoma of the lung in humans

Agent
Accepted/probable carcinogens/exposures
Asbestos
Arsenic
Beryllium
Chromates
Chloromethyl ether
Nickel
Radon and radon daughters
Silica
Smelting (arsenic exposure)
Possible carcinogens/exposures
Aluminum pot-room work
Cadmium
Foundry work
Iron mining
Silicon carbide manufacture
Welding

Many of these associations are controversial. From the point of view of pathological examination, there is usually nothing that would indicate that a particular lung cancer is associated with a particular occupational exposure, and questions of attribution are purely epidemiological. Although arguments have been made about specific locations within the lung or specific histological cell types being indicators of particular causative agents, careful review has shown that neither location nor cell type have any value in assigning causation (Ives et al. 1983; Churg 1994a). The one exception is the presence of asbestosis, which strongly associates a lung cancer with asbestos exposure (Section 2.1.6).

2.1.3 Coal Workers' Pneumoconiosis and Related Diseases

The diseases associated with coal mining are listed in Table 2.1.3, a compilation from a large US autopsy population called the National Coal Workers Autopsy Study (Green 1998). Coal workers' pneumoconiosis (CWP), which encompasses simple and complicated forms, is the most commonly diagnosed condition; the process is considered "complicated pneumoconiosis" or "progressive massive fibrosis" when there are pathological or radiographic lesions greater than 1 cm in diameter. Rounded opacities smaller than this size are termed "simple CWP" (Merchant et al. 1986; Parkes 1982; Lapp and Parker 1992; Love and Miller 1982; Attfield and Hodous 1992). This distinction can be of clinical significance: miners with only simple CWP tend to have minimal functional abnormalities, although a small percentage appears to develop clinically significant airflow obstruction. In contrast, miners with complicated CWP (progressive massive fibrosis or PMF) often have pulmonary impairment, and PMF may be associated with premature death (Cochrane 1962; Ortmeyer et al. 1974).

Table 2.1.3. Types of pneumoconiosis found in the National Coal Workers Autopsy Study, 1971-2000 (From Green 1998)

Lesion	Percentage of cases
Macules	46%
Macules plus focal emphysema	36%
Micronodules	19%
Complicated pneumoconiosis	6%
Silicosis	13%

Pleural and Lymphatic Changes: As is true of other dusts, coal-mine dust accumulates in the sub-pleural connective tissues, interlobular septa, and pleural lymphatics in coal miners. The pleural surfaces are often deeply black pigmented, with pigmentation usually greatest in the upper zones of the lung. The peribronchial, hilar, and associated lymph nodes are generally enlarged and densely black on cut surface. Silicotic nodules are commonly observed in lymph nodes in coal miners, typically in the absence of silicotic nodules in the parenchyma (Green et al. 1989). This does not constitute silicosis, which requires the presence of silicotic nodules in the parenchyma.

Coal Dust Macules: Coal dust macules are the most common finding in CWP and are similar to macules associated with other types of dust in that they consist of pigmented lesions ranging in size from 0.5 mm to 6 mm in diameter centered on respiratory bronchioles. They are frequently associated with surrounding focal emphysema (Figs. 2.1.5, 2.1.6). The density of the macules is greatest in the upper zones of the lung but may involve all regions. Microscopically, the coal dust macule is composed of coal dust-containing macrophages and free coal particles in the walls of respiratory bronchioles (Fig. 2.1.6). Over time, the macules become more collagenized (fibrotic). Focal emphysema is seen in both smoking and non-smoking miners, and some require the combination of macules and focal emphysema for a diagnosis of simple CWP (Kleinerman et al. 1979).

Coal Dust Nodules: Coal dust nodules are usually seen in lungs with numerous macules. They tend to be upper zonal and may be centered on respira-

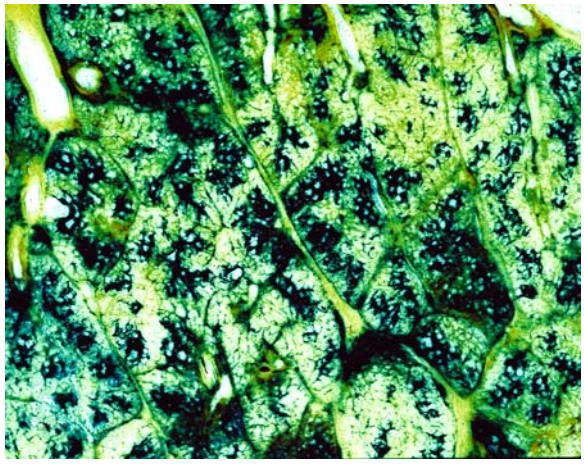

Fig. 2.1.5. Gough (1-mm paper) section of a lung with simple coal worker's pneumoconiosis. Note the black macules and focal emphysema in the centers of the lobules

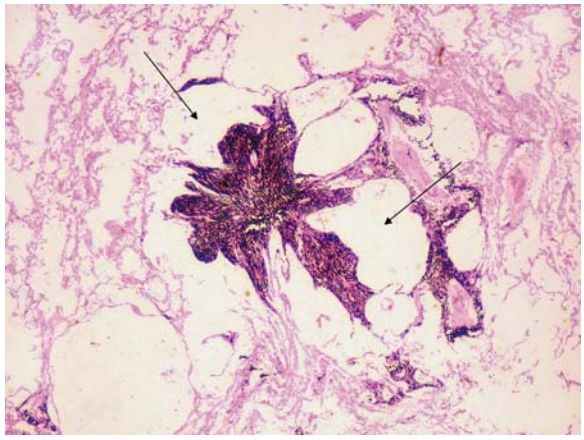

Fig. 2.1.6. Microscopic image of a coal dust macule from a case of simple coal worker's pneumoconiosis. Although the macule represents a fibrotic and distorted respiratory bronchiole, it is impossible to see the underlying airway in this advanced lesion. Focal emphysema is also present (*arrows*)

tory bronchioles; however, they are also frequently seen in the interlobular septa and in the subpleural and peribronchial connective tissues. Nodules are usually distinctly firm to palpation. They tend to have rounded borders and a collagenized center; the greater the silica content, the greater the tendency for the nodules to show concentrically arranged collagen (Fig. 2.1.7). In fact, coal dust nodules probably represent a form of mixed dust fibrosis (coal plus silica).

Progressive Massive Fibrosis: PMF or complicated CWP typically appears on a background of severe simple CWP. PMF lesions are most commonly observed in the upper and posterior portions of the lung and are usually bilateral. They may be round, oval, or irregular and tend to obliterate anatomic boundaries, leading to destruction of the bronchovascular structures and obliteration of interlobular fissures. On cut section, the typical lesion is rubbery to hard, dark black in color (Fig. 2.1.8), and may show cavities of varying sizes containing semi-fluid black contents that can scintillate due to the presence of cholesterol crystals.

Microscopically, PMF lesions show free coal dust, extensive collagen, and macrophages. Necrosis and cavitation are common. Residual outlines of coal dust or silicotic nodules may be observed, although some lesions appear to have little underlying structure. The fibrosing process tends to contract, so that large portions of a lobe may end up as relatively small CWP lesions, and one can often find distorted airways and vessels that disappear into the fibrotic masses; this phenomenon leads to both airflow obstruction, restriction, and pulmonary hypertension.

Rheumatoid Pneumoconiosis (Caplan's Syndrome): Rheumatoid pneumoconiosis occurs in miners with circulating rheumatoid factor but not necessarily evidence of arthritis. It is also seen in workers exposed to silica (Caplan et al. 1962). Radiographic examination typically shows rapidly enlarging, circumscribed nodules ranging in size

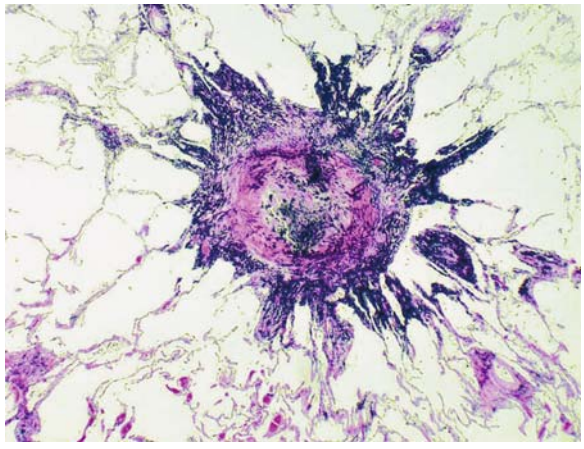

Fig. 2.1.7. Coal dust nodule from a case of simple coal worker's pneumoconiosis. The lesion is rounded with partially whorled collagen in the center and an irregular periphery

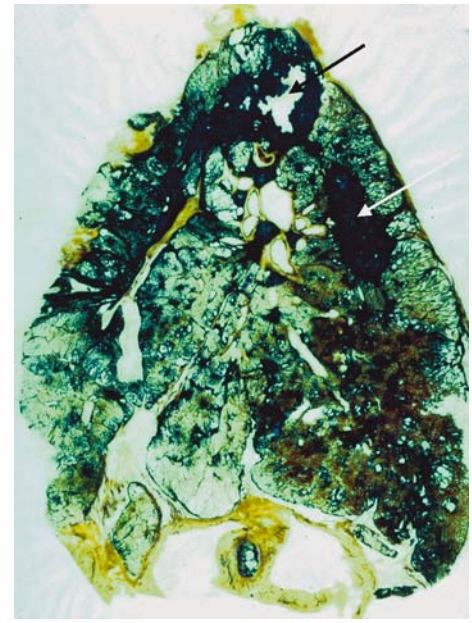

Fig. 2.1.8. Gough (1-mm paper) section of a lung from a worked with complicated coal worker's pneumoconiosis (progressive massive fibrosis). The *arrows* show two large lesions. The lesion in the apex has partially cavitated

from 0.3 cm to 5.0 cm in diameter. Grossly, the nodules are paler and more yellow than PMF lesions and show concentrically arranged dark and light pigmented bands. They may also show central cavitation and calcification.

Microscopically, rheumatoid pneumoconiotic lesions are similar to rheumatoid nodules occurring in the lungs of non-occupationally exposed individuals, except for the presence of rings of coal dust, frequently around the periphery. The central zone is eosinophilic and necrotic, and there is usually a layer of palisaded fibroblasts and macrophages (Wagner and McCormick 1967). It is crucial to rule out infections, particularly tuberculosis, before making a diagnosis of rheumatoid pneumoconiosis.

Silicosis in Coal Workers: Silicotic nodules in the parenchyma are fairly common in coal miners (Table 2.1.3) and are morphologically similar to those seen in silicosis of other causes (Section 2.1.4)

2.1.4 Silicosis and Other Diseases Caused by Crystalline Silica

Silica is silicon dioxide, SiO_2, and "silicosis" is caused by inhalation of crystalline silica. Silicosis has existed for thousands of years and has been found in Egyptian mummies. In industrial times, the disease has been associated with mining, stone cutting, grinding, and sandblasting, although a variety of other occupations are also at risk (Gibbs and Wagner 1998; CDC/NIOSH 1994; Graham et al. 1991; Dumontet et al. 1991; O'Donnell et al. 1991; Cahill et al. 1992; Grobbelaar and Bateman 1991; Norboo et al. 1991; Bar-Ziv and Goldberg 1974; White et al. 1991). There are several different mineralogical forms of silica that are associated with human disease: these include quartz, tridymite, and cristobalite (Gibbs and Wagner 1998). There is some suggestion in the literature that cristobalite is more dangerous than other forms of crystalline silica, but this is not clearly established. Amorphous silica, for example, diatomaceous earth, is not by itself pathogenic; however, on calcining, diatomaceous earth is converted to cristobalite. Despite dust restrictions, cases of silicosis are still encountered in industrialized countries; in some third world countries, the incidence of silicosis in some traditional occupations such as grinding is extremely high. Silicosis (and probably high levels of silica exposure as well) predispose one to mycobacterial infections.

2.1.4.1 Pathological Features

Chronic Silicosis: Table 2.1.4 lists the pathological reactions produced by exposure to silica. Simple silicosis (i.e., nodular lesions less than 1 cm in diameter) constitute by far the most common disease. Simple silicotic nodules are rounded, distinctly fibrous lesions (Figs. 2.1.9, 2.1.10) that are sharply demarcated from the surrounding lung parenchyma and that may be pale green, grey, or blue, or, if there is co-exposure to another dust, more distinct pigments. Silicotic nodules are more common in the upper and posterior regions of the lung and are often found scattered in the visceral pleura, the latter often referred to as "candle wax" lesions (Craighead et al. 1988). Microscopically, mature simple silicotic nodules show concentrically arranged, whorled bundles of mature hyalinized collagen with variable calcification in the central region (Fig. 2.1.10). The nodule

Table 2.1.4. Pathological reactions to silica

Acute silicosis (silicoproteinosis)
Chronic silicosis
Simple silicosis (nodules)
Complicated pneumoconiosis (massive fibrosis)
Rheumatoid pneumoconiosis (Caplan's syndrome)
Lung cancer*

*Disputed association

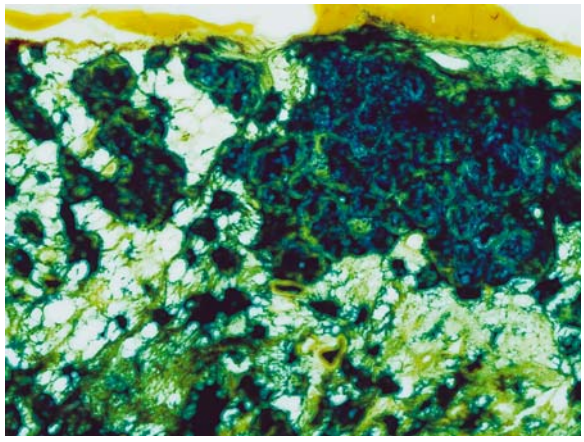

Fig. 2.1.9. Gough (1-mm paper) section of a lung from a worker with simple and complicated silicosis. Note the numerous individual round silicotic nodules. The large lesion on the right is greater than 1 cm in diameter and, thus, represents complicated silicosis. This lesion has formed by conglomeration of individual silicotic nodules

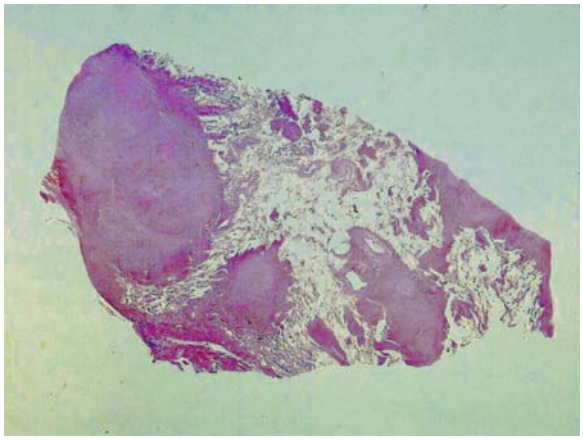

Fig. 2.1.10. Microscopic view of simple silicotic nodules. Note the general sharp borders and eosinophilic centers, the latter indicating the presence of collagen

is usually surrounded by a more cellular periphery, consisting of dust-containing macrophages, fibroblasts, reticulin, and occasional lymphocytes. Polarizing microscopy usually shows poorly birefringent particles consistent with quartz both within the hyalinized nodule and at the periphery; however, silica polarizes poorly in ordinary tissue sections, and, in some instances, the individual particles are below the limit of resolution of the light microscope.

Silicotic PMF or complicated pneumoconiosis consists of lesions with a diameter of 1 cm or more (International Labour Office 1980) (Fig. 2.1.9). As is true with CWP, PMF is usually bilateral and upper to mid-zonal. PMF lesions may undergo cavitation and are associated with destruction of the lung parenchyma and bronchovascular structures. Marked distortion of the adjacent lung is seen due to fibrotic contraction of the lesion. Microscopically, silicotic PMF lesions almost always form on a background of simple pneumoconiosis and, in fact, consist of agglomerated simple silicotic nodules (Fig. 2.1.9).

Accelerated Silicosis and Silicoproteinosis (Acute Silicosis): Classical chronic silicosis takes many years to decades to manifest. However, some patients develop more rapid disease. In accelerated silicosis, there are more cellular nodules that may have a more granulomatous appearance. These consist of histocytic cells enmeshed in a variable amount of mature and immature collagen and reticulin. Hyalinization and circular orientation of the collagen fibers may be seen but are not as well developed as in classic chronic silicosis.

Acute silicosis, or silicoproteinosis, is caused by exposure to high concentrations of freshly fractured silica, usually with very small particle size. Silicoproteinosis has been described in tunnelers, silica flour workers, sand blasters, rock drillers, and workers in the ceramic industry (Davis 1986; Craighead et al. 1988; Gibbs and Wagner 1998). Microscopically, it is characterized by the accumulation of granular proteinaceous fluid containing cholesterol clefts and dense macrophage remnants in the alveolar spaces. Polarization microscopy usually reveals large numbers of weakly birefringent silica particles. A mild chronic inflammatory infiltrate is frequently present. Early silicotic nodules may be seen as well. Most reported cases of acute silicosis have been fatal.

Rheumatoid Pneumoconiosis: Rheumatoid pneumoconiosis or Caplan's syndrome is seen in workers with silica exposure as well as those with coal exposure. Apart from the presence of coal pigment in the lesions in coal workers, the conditions are quite similar in their pathological and radiological appearances (Section 2.1.3).

Emphysema: It has been suggested that there is an association of exposure to high levels of silica and/or silicosis and the development of emphysema, independent of cigarette smoking. However, this idea is controversial (Becklake et al. 1987; Hnizdo et al. 1991, 2000; Hnizdo and Vallyathan 2003; Sharma et al. 1991; Wyndam et al. 1986; Hessel et al. 1990; Cowie and Mabema 1991; Hnizdo 1992).

Silicosis and Lung Cancer: The possible relationship between silica exposure or silicosis and lung cancer is an extremely controversial issue that has yet to be adequately resolved. The International Agency for Research in Cancer classified silica as a group-1 human carcinogen in 1997 (IARC 1997). Epidemiological studies have shown fairly consistently that the presence of radiographic silicosis is associated with an excess incidence of lung cancer, even after accounting for the effects of cigarette smoking (Kurihara and Wada 2004). Whether silica exposure in the absence of silicosis confers an increased risk is much less certain; some studies have found such an association, but others have not (Hughes et al. 2001; McDonald et al. 2001b; Kurihara and Wada 2004).

2.1.5 Disease Caused by Non-Asbestos Silicates

Mineralogy: Silicates consist of silica groups with a cation, such as magnesium, aluminum, etc. Examples of silicate minerals are commonly encoun-

tered: talc, mica, vermiculite, and kaolin. Silicates are ubiquitous in the environment, and, in fact, approximately one-third of all mineral species are silicates. They are a constituent of soil, road dust, and building materials and constitute a major component of suspended particulates in the airborne environment. Silicate minerals are used in a large number of industrial processes ranging from paper, paint, drugs, and drilling muds to ceramics and cosmetics. Asbestos fibers are also silicates; however, their fibrous shape confers somewhat different biological properties, and, hence, they are considered separately in section 2.1.7.

Most silicate minerals are highly birefringent and can be easily detected in tissue sections with polarizing microscopy; indeed, the presence of large numbers of highly birefringent particles in histological sections should always raise a question of silicate exposure. Silicates may form ferruginous bodies in tissue sections; that is, silicate particles to which the lung has added a gold-colored iron protein coating, and these can serve as a guide to the nature of the underlying dust (see Churg and Green 1998 for illustrations).

Pure exposures to silicates are relatively uncommon, and many no longer occur; for example, talc is no longer used as a mold-release agent in rubber tire manufacture, a process that, in the past, sometimes led to talcosis (Fig. 2.1.11). In most instances, the lung diseases produced by the (nonasbestos) silicates appear to be relatively benign and only occur in workers exposed to high concentrations of dust over a prolonged period of time; however, diffuse interstitial fibrosis and progressive massive fibrosis, although uncommon, are associated with serious pulmonary disability.

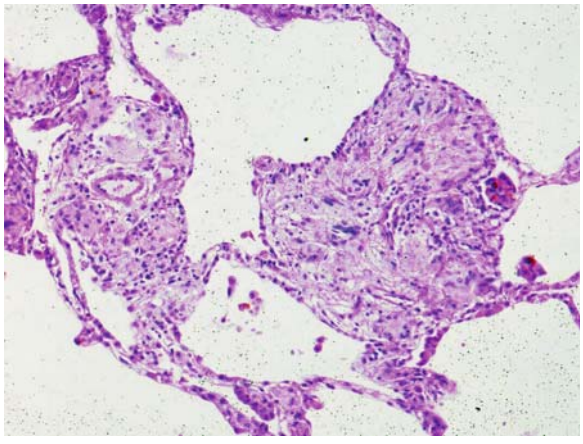

Fig. 2.1.11. Microscopic image of talcosis. The numerous refractile plates of pale yellow talc are visible

Pathological Reactions to Silicate Minerals: Pure silicate exposures can produce a variety of pathological reactions (Table 2.1.5) (Green and Churg 1998), and there is considerable variability from mineral to mineral in regard to the frequency of the reactions observed. Macules are probably the most common finding and are similar to the lesions seen with metal and coal exposure, i.e., collections of dust and dust-laden macrophages around the small airways and vessels. As with metals and coal, silicate macules may become fibrotic. Granulomas are collections of silicate particles that evoke giant cell reactions; when large, these are termed nodules. Diffuse interstitial fibrosis caused by silicate exposure is uncommon but is generally readily recognized because of the presence of innumerable birefringent particles; the classic example of diffuse fibrosis caused by silicates is talcosis (Fig. 2.1.11). Progressive massive fibrosis appears as generally bilateral mid to upper zone mass lesions that microscopically contain collagen and huge numbers of silicate particles. Talc, mica, and kaolin have been reported to cause pleural fibrosis.

Table 2.1.5. Pathological reactions to silicate minerals

Macules
Granulomas
Nodules
Progressive massive fibrosis
Diffuse interstitial fibrosis
Pleural fibrosis

2.1.6 Asbestos-Related Disease

Mineralogy: Asbestos is a name for a set of naturally fibrous silicate minerals. Asbestos minerals have been used because of their high tensile strength, high heat resistance, resistance to chemical attack, and ability to be woven into cloth (Dupres et al. 1984). These properties vary by asbestos fiber type. There are six accepted types of asbestos fibers: namely, chrysotile, amosite, crocidolite, anthophyllite, tremolite, and actinolite. These fibers can be separated into two broad mineralogical groups: chrysotile or amphiboles, the latter including amosite, crocidolite, tremolite, actinolite, and anthophyllite. Table 2.1.6 lists the diseases caused by asbestos. While Table 2.1.6 is correct in broad outline, there are considerable discrepancies in the abil-

ity of the different types of asbestos fiber to cause particular diseases, in part based on the chemistry and stability of the fibers (Morgan et al. 1977; Hume and Rimstidt 1992; Churg 1994b; Hodgson and Darnton 2000; McDonald 1990). Chrysotile, for example, only produces malignant pleural mesothelioma at extremely high exposure levels and does not produce peritoneal mesothelioma at all. Amosite and crocidolite are potent mesothelial carcinogens and also cause asbestosis and lung cancer at lower exposures than are required for chrysotile (Hodgson and Darnton 2000; McDonald 1990; Churg et al. 1989, 1990; EPA 2003). The conditions under which a particular type of fiber causes a particular disease are complex and are beyond the scope of this chapter. A variety of tumors not listed in Table 2.1.6 have also been postulated to be caused by asbestos: these include carcinomas of the digestive tract, larynx, kidney, ovary, and lymphomas. These associations are not generally accepted, and these tumors are not discussed here.

Table 2.1.6. Diseases caused by asbestos

Nonneoplastic pleural disease
Pleural effusions
Pleural fibrosis
Pleural plaques
Rounded atelectasis
Nonneoplastic parenchymal disease
Asbestosis
Carcinoma of lung (when asbestosis is present)
Malignant mesothelioma of pleura and peritoneum

Asbestos Bodies: Asbestos occurs in the lung in two forms. Most of the mineral is present as the bare or uncoated fiber, the form in which it was inhaled. However, a minority of fibers acquire a gold-colored iron protein coating in the lung and are then referred to as asbestos bodies. Asbestos bodies are one form of ferruginous body, i.e., exogenous particles and fibers that are coated by macrophages (Churg and Green 1998; Churg and Warnock 1981; Crouch and Churg 1984). Because of the iron protein coating, ordinary histochemical iron stains are an excellent and sensitive method of detecting asbestos bodies in tissue sections. The presence of asbestos bodies in ordinary histological sections is required for the diagnosis of asbestosis using pathological material, but it should be appreciated that, by themselves, asbestos bodies are only markers of exposure. In and of themselves, they do not constitute a disease.

2.1.6.1 Benign Asbestos-Induced Pleural Disease

Terminology: As shown in Table 2.1.6, asbestos induces several different types of benign lesions of the pleura; some authors have referred to the benign pleural lesions as "pleural asbestosis," an incorrect and confusing usage, since asbestosis by definition refers only to asbestos-induced parenchymal fibrosis.

Epidemiological Features: Clinical studies (Gaensler and Kaplan 1971; Epler et al. 1982) indicate that there is a time sequence in the development of asbestos-related pleural disease. Within the first 10 years of exposure, asbestos effusion is relatively common, while pleural fibrosis and pleural plaques are rare. Thereafter, the frequency of fibrosis and plaques increases, although new effusions may still occur (Rudd 1996; Gaensler and Kaplan 1971; Epler et al. 1982). This sequence supports the notion that fibrosis, and possibly plaques as well, are the organized residua of old effusions.

Clinical and pathological features: Asbestos effusion is defined by: (1) a history of exposure to asbestos; (2) pleural effusion, often hemorrhagic; (3) no other disease that would cause pleural effusion; and (4) no malignancy developing in the pleura within 3 years (Gaensler and Kaplan 1971; Epler et al. 1982; Rudd 1996). Many asbestos effusions are asymptomatic; however, in some instances patients present with pleuritic pain, dyspnea, or hemoptysis and show the usual findings associated with an effusion (Gaensler and Kaplan 1971; Epler et al. 1982; BTTA 1972). Microscopically, biopsies of benign asbestos effusions show a combination of fibrin and organizing pleuritis.

In most patients, pleural plaques and pleural fibrosis are asymptomatic, and the disease is essentially an incidental finding noted by the radiologist or pathologist (Sargeant et al. 1977; Solomon et al. 1979, 1984; Begin et al. 1984; Aberle et al. 1988). Pleural plaques appear grossly as flattened or knobbed very hard, commonly calcified, sharply circumscribed lesions on the diaphragmatic (Figs. 2.1.12, 2.1.13) or chest wall pleura and rarely on the visceral pleura (Roberts 1971; Solomon et al. 1979). In contrast, diffuse pleural fibrosis primarily affects the visceral pleural, where it appears grossly as a thickened and fibrotic pleura, often with obliteration of the fissures (Fig. 2.1.14). Microscopically, pleural plaques show a very typical "basket weave" pattern of collagen and are frequently acellular (Figs. 2.1.13, 2.1.15). Pleural fibrosis often is similar in appearance to the findings in benign asbestos effusion; older lesions may

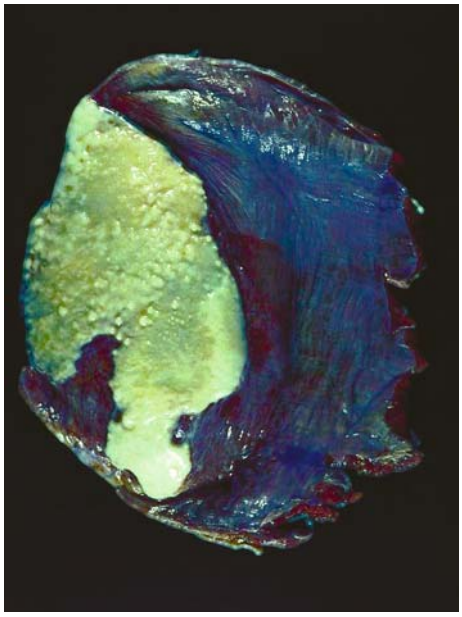

Fig. 2.1.12. Pleural plaque. In this instance, the lesion is situated on the diaphragm, which has been excised at autopsy. Note the typical smooth and knobbly surface. From Churg and Green (1998), used with permission

Fig. 2.1.14. Diffuse pleural fibrosis caused by asbestos exposure. Note the thickened pleura and the obliterated fissure. From Churg and Green (1998), used with permission

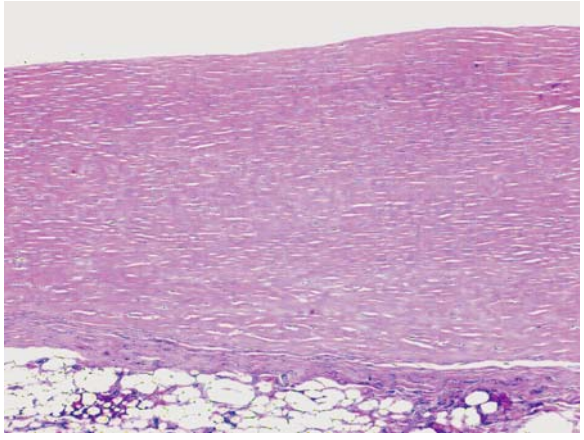

Fig. 2.1.13. Microscopic appearance of a pleural plaque showing the typical basket-weave pattern of collagen

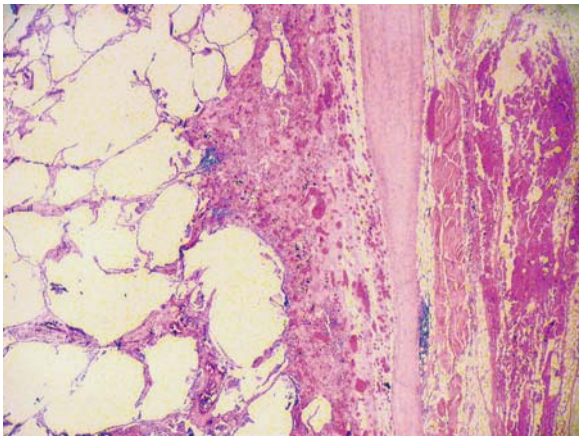

Fig. 2.1.15. Microscopic image showing a pleural plaque (*P*) overlying diffuse asbestos-induced pleural fibrosis (*F*). The visceral and parietal pleurae have fused, and chest wall muscle is visible at the right side of the image

be paucicellular (Fig. 2.1.15). It is not uncommon to find both plaques and pleural fibrosis in the same patient, and, in these instances, the visceral and parietal pleurae are commonly fused by the prior inflammatory process (Fig. 2.1.15).

Rounded atelectasis is a form of scarring of the pleural with contraction to form a pseudo-mass in the underlying lung (Hillerdal 1989; Mintzer and Cugell 1982; Hillerdal and Hemmingsson 1980). On gross examination, lungs with rounded atelectasis show an area of retraction of the lung tissue immediately under a fibrosed pleura or pleural plaque. Often there is obvious distortion of the surrounding lung in a more or less semi-circular fashion (Fig. 2.1.16). The histological findings are those of pleural fibrosis and/or pleural plaque.