ASBESTOS

Risk Assessment, Epidemiology, and Health Effects

Edited by
Ronald F. Dodson
Samuel P. Hammar

CRC Taylor & Francis
Taylor & Francis Group

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Taylor & Francis
Taylor & Francis Group
Boca Raton London New York

A CRC title, part of the Taylor & Francis imprint, a member of the Taylor & Francis Group, the academic division of T&F Informa plc.

Published in 2006 by
CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-2829-2 (Hardcover)
International Standard Book Number-13: 978-0-8493-2829-9 (Hardcover)
Library of Congress Card Number 2005048604

Library of Congress Cataloging-in-Publication Data

Asbestos : risk assessment, epidemiology, and health effects / edited by Ronald F. Dodson, Samuel P. Hammar.
p. ; cm.
Includes bibliographical references and index.
ISBN 0-8493-2829-2 (alk. paper)
1. Asbestos--Toxicology. 2. Asbestosis. I. Dodson, Ronald F. II. Hammar, Samuel P.
[DNLM: 1. Asbestos--adverse effects. 2. Asbestosis--epidemiology. 3. Risk Assessment. WA 754 A7988 2005]

RA1231.A8A74 2005
363.17'91--dc22 2005048604

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Dedication

This book is dedicated to Sandy and Judy

Acknowledgment

We acknowledge Dinah Fleming for editorial assistance during the preparation of this book.

Preface

Asbestos is a naturally occurring fibrous form of mineral. It has been used in numerous applications owing to its unique properties. With the more complex evolution of industrialized societies came an increasing demand for lightweight, thermally and chemically resistant materials, which in many applications also required components to provide high tensile strength. Various types of asbestos met these requirements and were used in numerous applications. The use of asbestos in building components was as much attributable to the ease with which these minerals could be formed or troweled into desired shapes as to other characteristics. The fire-retardant properties of asbestos have often been an important feature justifying its use in many applications. The problem with the widespread use of asbestos is that exposed individuals are at risk for development of asbestos-related diseases. These diseases usually occur following long latency periods from first exposure before they are clinically detectable. Asbestos is also unique among dusts in that its inhalation can result in the development of cancer of the lung and in extrapulmonary sites.

There have been various books that looked at the issue of asbestos and human health through specialized emphasis on certain facets of the subject. However, the aim of this book is to provide a resource in which the reader can find comprehensive, interdisciplinary, state-of-the-art information regarding the various aspects of the asbestos and human health. This information includes a historical view of the use of asbestos, sampling techniques, and instruments needed to define the levels of asbestos in air, bulk, or surface samples.

To understand the methods necessary in assessing levels of exposure, it is critical to understand the techniques used in sampling for asbestos including those used in establishing the levels as defined in Federal and State regulations. The differences in the inherent detection levels for the various techniques used for asbestos will be discussed as applicable to the various types of environmental and human samples. This will include comparison of recommended and required sampling schemes as well as the parameters associated with the instruments used in each method.

Asbestos induces disease in man has been confirmed through clinical observations, pathological assessments of tissue, and epidemiological data obtained from exposed cohorts. The focus of three chapters as presented by specialists in these respective fields will offer state-of-the-art data regarding asbestos exposure and the resultant development of disease. The screening process needed for identifying asbestos-related disease and an overview of the pathological states associated with these diseases will be addressed. The epidemiological overview will discuss findings from the world's literature as applicable to specific types of asbestos exposure and the development of resultant diseases.

The respiratory system is the primary portal of entry for asbestos into the human body. Thus it is relevant that the reader is provided with an overview of the normal anatomy and functions of the respiratory system as a background before discussions focus on mechanisms by which asbestos (and other inhaled particulates) induce temporary and permanent changes. Just as it is relevant to understand the applicability of

techniques and selected instrumentation for analysis of environmental samples, it is equally important in determination of asbestos content from biological samples that a recognition is established as to what was observed and what cannot be observed with the instrumentation and techniques used in a given study. Such a comparison and examples are illustrated in this chapter. Fiber length related to the potential for inducing pathological responses is also discussed in this chapter.

Asbestos is recognized as being a pathogenically active dust based on its fibrous morphology. However, there are constantly evolving findings about the cellular, biochemical, and molecular influences that asbestos has once inhaled into the lung. These mechanisms are presented as complementary stimuli which when coupled with the fibrous morphology of asbestos can result in irreversible cellular damage and in some cases the development of tumors. Therefore, a review of these mechanisms will be provided from a molecular biology perspective.

Various countries have sought to deal with asbestos and public health through regulatory guidance documents. These will be discussed in a chapter focusing on the regulations that exist in more industrialized countries, and examples of governmental regulations that attempt to impact on the levels of potential exposures in some developing countries.

One of the most under served specialties in medicine is that of occupational or environmental medicine. The data indicate that medical school curricula today offer only a few hours on the subject as training provided to physicians. It is, therefore, not a surprise that histories taken from patients are often incomplete about historical exposure to asbestos in the workplace or in environmental settings. Thus making the diagnosis of asbestos-related disease is potentially only as likely as the accuracy of the establishment of such historical exposure links. It was, therefore, deemed appropriate to have an overview on the subject of clinical or postgraduate education on the subject of asbestos-related diseases, which would have applicability to a wide range of healthcare professionals.

The fact that asbestos is capable of inducing diseases including cancer in man has stimulated considerable interest of subjects. The issues associated with asbestos exposure or potential for exposure involve professionals including those from state and federal agencies charged with protecting human health, as well as industrial specialists who must consider replacement materials and the suitability of these replacements in applications previously met with asbestos. Public health officials including physicians, nurses, allied health professionals, and related support professionals must make decisions regarding causation of potential diseases that can be induced by exposure to asbestos. Ultimately all members of society can be potentially exposed to asbestos in place either at home or work and as components of products made from minerals which contain small amounts of asbestos. Asbestos exposure and related liabilities have also become major legal issues within many countries.

The purpose of this book is to offer the interested professional in any of the aforementioned specialties a single "state-of-the-art" reference, which provides data that by design is interdisciplinary in nature. The content is styled so that the depth is sufficient to be appreciated by the specialist in a given field as well as provide useful information from which individuals in other areas of specialization may draw reference that will better enable them to deal with asbestos-related problems.

The Editors

Ronald F. Dodson Ph.D., received his B.A. in biology and general sciences (double major) from East Texas State College, and M.A. in biology and chemistry from East Texas State University. His doctorate was from the Life Sciences Division of Texas A&M University with an emphasis in biological electron microscopy. After 7 years in the faculty at Baylor College of Medicine in Houston, he was recruited to develop a research program at the University of Texas Health Center at Tyler. His work for the last 20 years has concentrated in defining dust burden in tissue, body fluids, and environmental samples by light and analytical transmission electron microscopy. His laboratories have developed some of the techniques which enable quantitative studies of tissue burden to be carried out.

He has authored or coauthored over 90 scientific articles on the subject of dust-related diseases with most of these focusing on asbestos-related issues. He has also authored or coauthored ten chapters in books and given numerous presentations on the topic of asbestos and human health. These presentations include those at scientific meeting and to more selected audiences such as the National Conference of State Legislatures and the Defense Research Institute. His academic achievements have been recognized in that he holds the status a Fellow in the American Heart Association and Fellow in the College of Chest Physicians.

He has held various administrative titles during his academic career including Chief of Department, Chairman of Department, Associate Director for Research, Vice President for Research, and co-Director of the Texas Institute for Occupational Safety and Health. He has served on numerous academic committees and as well as a reviewer for numerous journals. He has directed an EPA/Texas Department of Health (Model Accreditation governed) approved training division and holds licenses through the Texas Department of Health of the State of Texas as an Inspector/Manager Planner and Supervisor/Contractor in the area of asbestos-related activities. Dr. Dodson and Dr. Hammar have authored or coauthored the majority of the world's literature on asbestos content in extrapulmonary sites as well as defined tissue burden (including shorter fibers) in unique cohorts such as individuals with mesothelioma.

Samuel P. Hammar, M.D., is a board-certified anatomic and clinical pathologist who specializes in lung disease, cancer, and diagnostic techniques used to investigate cancer. He obtained a B.A. degree in chemistry in 1965 and attended the University of Washington Medical School from 1965 to 1969 where he obtained an M.D. degree. He did his training in pathology at the University of Washington School of Medicine including time in experimental pathology and electron microscopy.

For the last 15 years, Dr. Hammar has been primarily interested in asbestos-related lung disease, especially mesothelioma. He is a member of the U.S.-Canadian mesothelioma panel and a member of the International Mesothelioma Pathology Group. In conjunction with Dr. Dodson, Dr. Hammar has done extensive research on asbestos-related lung disease and sees asbestos-induced lung disease on a regular basis as a pathologist in Bremerton, Washington, the home of Puget Sound Naval Shipyard.

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CHAPTER 1

The History of the Extraction and Uses of Asbestos

Arthur L. Frank

CONTENTS

1.1 ASBESTOS AND HISTORY

Asbestos is a commercial term used to describe two families of naturally occurring minerals. Amphiboles, containing five fiber types and the serpentine variety, chrysotile, were materials known to the ancients. More than 4000 years ago, pottery in Africa and Finland contained asbestos, and Finnish homes were known to contain asbestos rock to pack crevices in log huts. The lamps of the Vestal Virgins in ancient Rome had wicks made from asbestos so the lamps would burn continuously, as long as they were filled with oil. Various Roman historians noted slaves working in asbestos mines were not as healthy as others, and were thought to die young.[1]

Selikoff and Lee[1] also reported that Charlemagne, Emperor of the Holy Roman Empire, was said to have possessed a tablecloth woven of asbestos, and would astonish his guest by cleaning his tablecloth in a roaring fire. Body armor from the 15th century was noted to contain asbestos, and in the 1700s, Norway manufactured asbestos wicks and paper. Major deposits of asbestos were found in the Ural Mountains around 1720 and led to the establishment of an asbestos industry at

that time with production of textiles, socks and gloves, and handbags. Benjamin Franklin, while in Europe, was noted to have a purse made from asbestos. The resilience of asbestos cloth and paper was duly noted, and a suit made entirely of asbestos protected a young Italian as he walked through a roaring fire in the 1820s. Pope Pius IX was reported to have developed asbestos paper to keep important documents safe from fire at the Vatican. Additional history of the early use of asbestos can be found in the paper by Abratt et al.[2]

Modern asbestos history can be traced to the discovery, or rediscovery, of asbestos in Canada and South Africa. By 1850, chrysotile deposits were known around Thetford, in Canada, and these deposits were again appreciated following a forest fire when in the mid-1870s out croppings of rocks were noted to not have burned. By 1876, some 50 tons of asbestos was being mined in Quebec and brought to market through a specially built railroad. By the 1950s, over 900,000 tons per year were being mined with a value of almost 100 million dollars.[1]

In the early 1800s, asbestos was noted to exist in South Africa,[2] particularly in the northwest area of Cape Province, and the name crocidolite was given to a blue-colored stone otherwise known as "wooly stone." Further interest did not occur until the 1880s and the first records of serious production did not take place until early in the 20th century. The amount of asbestos produced was far less than from Canada, remaining below 10,000 tons per year until 1940. In the Transvaal of South Africa a different form of asbestos was mined and was called amosite, an acronym for the Asbestos Mines of South Africa. By 1970, some 80,000 tons per year of amosite was being produced. The mines from which the majority of amosite was derived were run by a small number of Europeans with 6500 local workers of color.

Other locations with significant production of asbestos included Italy, Russia, the United States, Rhodesia (now Zimbabwe), and more recently, China. Italy was never a major producer of asbestos, not being able to compete with the larger quantities available in Canada. Russian production was substantial, rivaling that produced in Canada. In the United States small deposits were mined in Vermont, Arizona, and California. Smaller deposits of anthophyllite were mined in North Carolina and Georgia. In Zimbabwe, mines became operative early in the 20th century and reached a peak production of 95,000 tons.

China has become a major producer and rivals Canada and Russia in terms of asbestos production. In 2000, Russia led the world with 700,000 tons, followed by 450,000 tons from China and 335,000 tons from Canada. In 2000, the United States was producing only some 7000 tons from mines in California and elsewhere, this from a worldwide production of 2,130,000 tons.[3] Not surprisingly, Russia and China accounted for most consumption of asbestos followed by Brazil, India, Thailand, and Japan. The United States used about 15,000 tons of asbestos in 2000, down from a peak of 750,000 tons per year in the early 1970s.

On a per capita basis, the greatest use of asbestos is in Russia and former Soviet Republic countries, and in Thailand. Among the countries with lowest per capita usage, other than in countries that have now banned asbestos, are Canada, the United States, and several others at one tenth of a kilogram per capita per year. Although on a per capita basis India ranks low, it stands fourth in the world's

total usage. China, while second in the world, has a relatively low per capita amount, given its large population base. Major use in the United States is for asbestos cement and roofing materials. In much of the rest of the world asbestos containing cement, construction materials, friction products and textiles are made, used, and exported.

1.2 COMMERCIAL USES OF ASBESTOS

Although there has been historical use of asbestos, it was more a curiosity than a meaningful commercial material. This changed in the last half of the 19th century as asbestos began to be used in many commercial settings. For example, with industrialization and the use of steam to drive equipment, it was recognized that asbestos could serve a useful purpose as insulation material. Older products, including the use of dried dung, were not very efficient insulators.

Increasingly, it became apparent that asbestos, because of its various properties, was extremely useful in many situations. Asbestos resists degradation under heat and cold, does not conduct electricity, and is extremely chemically resistant, including resistance to many industrial acids. Because of its heat, cold, and chemical resistance asbestos was used in many products. Different types of asbestos were found especially useful for different purposes. For example, amosite was especially resistant to degradation by sea-water, and was the asbestos of choice as an insulation material on sea-going vessels.

Naturally, asbestos came to be used in a number of ways. The first systematic use of asbestos was for sealing and packing materials, soon followed by its use in insulation for heat conservation. The manufacturer of asbestos roofing felt and cement came soon thereafter, as did the development of textile made from asbestos. Even brake bands were noted to have contained asbestos.[1] All this took place in the later part of the 19th century.

Around the turn of the century asbestos containing cement pipe was produced, the asbestos allowing for added strength, creating lighter and thinner cement materials. The first use of asbestos as a brake lining occurred in 1906, and clutch facings were developed in 1918. In Great Britain a technique for spraying asbestos as a fireproofing material was developed in the early 1930s, and this technique was imported into the United States a few years later. Considerable use of asbestos was noted during the ship-building era in and around World War II. For the first time millions, including many women, were exposed to asbestos.

After World War II asbestos was used as filtering agent, and over time was used for filtering wine, beer, and pharmaceutical products. Asbestos was incorporated into plastics, paint, and asphalt. Asbestos paper had been used for many years and many purposes. Crocidolite asbestos was even used as a component of a cigarette filter between 1952 and 1956.

Raw asbestos was used in many other products, and was used as a filler in many products. Asbestos found its way into plasters and stuccos, was used in drilling mud for oil wells and other similar operations, and was used in automobile body undercoatings. Yarns made from asbestos were used in a wide variety of ways, including

rope, sewing threads, gas mask filters, and for steam hoses, among others. Cloth made from asbestos was incorporated into blankets, mailbags, theater curtains and commercial products such as ironing board covers. Other consumer products, including hair dryers, toasters, play sand, and baby powders were shown to contain asbestos.

Construction materials containing asbestos included millboards, cements, laboratory table tops, electrical pump insulation and mountings, and flooring. Asbestos was found to be present in 3000–4000 commercial products.

Increasingly, the use of asbestos is being banned around the world. The current use of asbestos includes building supplies, such as roofing materials and asbestos cement pipes. Automobile brake components continue to contain asbestos, and asbestos cloth is still used in firefighting protective gear. For some countries the continued sale of asbestos is a significant economic issue. Even in Canada, where only around 1500 miners are still employed, there is a fierce effort to maintain the use and sale of Canadian chrysotile on a worldwide basis. This is in the face of growing evidence of the health hazards of all forms of asbestos, and continuing evidence, especially in developing countries, of no real "controlled use" of asbestos, including chrysotile.

With the recent decision to ban the use of asbestos in Japan, only developing countries continue to use large quantities of asbestos. China and India, for example, continue to mine and use asbestos, the most frequent use being in construction materials. Thailand, another growing economic power in Southeast Asia, continues to use large quantities of asbestos as well. Encouragement for the use of asbestos in such countries comes from the West, where the hazards are increasingly well recognized and actions are being taken to reduce or eliminate the use of asbestos containing products.

1.3 PUBLIC HEALTH ISSUES AND THE USE OF ASBESTOS

The world has a long history of asbestos use, with some suggestions of potential health hazards by the ancients. The real history, appreciating the hazards of asbestos, begins in the last part of the 1890s.

The term pneumoconiosis, having been coined by Zenker[4] in 1867 after examining the lungs of a man with siderosis, was applied to an increasing number of dust diseases of the lung. In 1924, Cooke coined the term asbestosis.[1]

Morris Greenberg, who served as a medical member of the Inspectorate of Factories in Great Britain and is a true scholar of the historical aspects of asbestos-related disease, wrote an excellent historical overview of the development of the hazards of asbestos.[5,6]

In Great Britain, as early as 1898, the Lady Inspector of Factories made note of the fact that asbestos was causing disease among asbestos textile workers.[7] In 1899, Dr. Murray conducted a post-mortem examination on a young man in his mid-thirties who died of respiratory insufficiency. He reported, during his hospitalization, that he was the tenth individual in his particular work area to die, and that his working brethren had all preceded him in death at a young age from similar problems. Dr. Murray noted the man had extensive interstitial fibrosis, and what

was described as "curious bodies" in his lungs. In 1907, the autopsy findings, with commentary, were published and unfortunately concluded that proper ventilation was now thought to be in place to spare additional workers disease in the future.[8] Unfortunately, this was far from correct.

In 1915 Collis, after giving a series of lectures, wrote up his findings on pneumoconiosis and discussed the problems of silicosis and asbestos-induced fibrosis, not yet called "asbestosis."[9] The term asbestosis was not used until 1924 when Cooke coined the term to describe pulmonary fibrosis due to the inhalation of asbestos dust.[10] By 1930, Merewether wrote of the principles to protect workers in England,[11] and Lanza in the United States showed that suggested levels of asbestos in the late 1930s were often too high to protect workers.[12]

Although previously unnamed, the disease entities caused by exposure to asbestos were not unappreciated. In 1918, the Prudential Life Insurance Company, which insured workers in Canada and the United States, had called to its attention by one of its vice presidents, who was a statistician, that there was harm in breathing asbestos dust. At that point in time Prudential ceased issuing policies on the life of asbestos workers.

Although not reported in the scientific literature until many decades later, relatively recent revelations, written up by Tweedale, revealed that at least one major asbestos company in England knew, beginning in the 1920s their workers were dying of lung cancer and mesothelioma, and they worked diligently to suppress that information.[13]

The first actual suggestion of the relationship of asbestos exposure and lung cancer was by Drs. Lynch and Smith, making observations of workers at a South Carolina asbestos textile plant.[14] They did not have definitive proof this occurred, but by 1942 Hueper, then director of occupational cancer studies at the National Cancer Institute, felt the data then available was sufficient for him to write that he felt asbestos caused lung cancer.[15] This was repeated in the scientific literature several times in the 1940s and early 1950s. In 1955, should there have been question in anyone's mind, Doll reported on lung cancer in excess in Great Britain due to asbestos.[16] Interestingly, this data came from the Turner and Newall Company, where lung cancer cases and pleural cancers, had been accumulating since the 1920s, but had not been previously reported.[13]

For the problem of mesothelioma, case reports began accumulating in the 1940s, and by the early 1950s there were studies relating asbestos to the development of this form of malignancy. The work of Wagner et al., in South Africa, published in 1960, clearly related exposure to crocidolite asbestos and the development of this disease and cited earlier cases.[17] Interestingly, the cases reported by Wagner were not seen only among workers, but nonoccupational exposure was documented as causing mesotheliomas.

Over the years, studies have shown that other forms of cancer can be caused by asbestos. While there continues to be some controversy, it is generally accepted that gastrointestinal tract cancers, laryngeal cancers, and kidney cancers are all found in excess following exposure to asbestos the risk increasing with increasing exposure. In the United States various government agencies and organizations interested in cancer accept these findings.

As more and more groups of individuals exposed to asbestos have been looked at, evidence of asbestos-induced disease is found. While there clearly appears to be a threshold phenomenon with regard to the development of asbestosis, no such threshold appears to exist for asbestos cancers, although a dose–response relationship exists.

While most studies of asbestos and the development of human disease have focused on individuals occupationally exposed, there is an increasing body of evidence that non-occupational exposure, usually called environmental or bystander exposure, can lead to the development of asbestos-related disease.[18,19] This is true for findings such as pleural plaques, where in Finland individuals living near an asbestos mine developed plaques with some regularity, but similar individuals in areas where no asbestos mines exist do not. Wagner et al., in their classic 1960 paper regarding mesothelioma, spoke to the issue of individuals with environmental exposure developing mesothelioma as fibers were moved from the site of extraction to enter the delivery system, on their way to entering general commerce.[17] In the United States a current issue of environmental exposure is the situation in Libby, Montana, where a tremolite containing vermiculite mine has injured workers and townspeople, and the product has caused additional disease after entering general commerce.[20]

A somewhat more specific phrase, either called household exposure or familial exposure, exists when family members develop asbestos-related disease. Anderson looked at family members of asbestos-exposed workers. Even family members moving into a contaminated household after the worker has stopped bringing in asbestos can lead to the development of disease.[21] Environmental exposures can also apply to those living near asbestos utilizing facilities. Newhouse, in London, showed that a number of individuals developed mesothelioma simply from living near an asbestos utilizing facility.[19]

With increasing regulation or banning of asbestos there will undoubtedly be fewer cases of asbestos-related disease in the future, although it will probably take several decades until this comes to pass. Given the long latency of asbestos-related disease it has been projected that such problems will be noted for several decades yet.[22] In the developing world, with continued use of asbestos, this problem will likely worsen over time, until proper regulations or bans on the uses of asbestos-containing materials come into place and protect asbestos-exposed individuals.

A particularly contentious issue is the well-documented synergistic effect of asbestos and cigarette smoke exposure leading to a marked increase in lung cancer. Knowledge currently existing in industrialized countries should be disseminated to countries that continue to use asbestos and often also have high rates of cigarette consumption.

1.4 CONCLUSION

While asbestos has been utilized for its many useful properties in many products for a long time, it is now clearly recognized as causing significant injury and disease. Society has decided to function adequately without use of this dangerous material. Among the concerns for the future would be inappropriate continuing use in some

parts of the world, and inappropriate methodologies for removal of asbestos already in place in the more developed parts of the world. While there are unanswered questions regarding the biological affects of asbestos, and have differing views of scientists on specific aspects of asbestos toxicology, it is clear that asbestos is a dangerous material with serious consequences for human health.

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CHAPTER 2

Asbestos Analysis Methods

James R. Millette

CONTENTS

2.1 INTRODUCTION

The value of a standard method is that it defines procedures in such a way that different laboratories working independently will achieve similar results when using the same method. There are over 30 different "standard" methods available for the analysis of asbestos in a variety of media. The methods include those for

determining the amount of asbestos in air, water, bulk building materials, surface dust, carpet, soil, and specific product materials such as vermiculite and talc. Some methods, although in draft or interim forms, have become generally recognized and used as standard methods by the analytical community. Governmental agencies, such as the Occupation Safety and Health Administration (OSHA), the National Institute of Safety and Health (NIOSH), the U.S. Environmental Protection Agency (EPA), the California Air Resources Board (CARB), and the New York State Department of Health, have promulgated some of the methods. Consensus standards groups such as the American Society for Testing and Materials (ASTM), the International Standards Organization (ISO), and the American Water Works Association (AWWA) have published other methods. A number of methods have gained acceptance after being published in the scientific literature. Which method to use in a particular situation depends on the media to be tested and level of information required.

Because the concern with asbestos is related to its fibrous nature, microscopy is the chief analytical tool used for its analysis. Different microscopes have advantages and disadvantages in regard to cost and the ability to provide information about asbestos fibers. Polarized light microscopy (PLM) is the standard way to analyze for asbestos in bulk materials. Phase-contrast microscopy (PCM) is the instrumental technique used for many occupational air sample analyses. Transmission electron microscopy (TEM) and, in some cases, scanning electron microscopy (SEM) are used for all types of samples when small fibers are involved or specific identification of individual asbestos fibers is desired.

2.2 SAMPLE COLLECTION

The collection of samples for analysis depends on the media to be tested and the specific procedures for sample collection are usually provided in the particular analysis method. In general, air samples are collected on membrane filters, water samples in glass or plastic bottles, surface dust by microvacuum or wipe samplers, and solid materials such as building materials, soil and specific products in plastic bags, or rigid plastic containers. Air samples are collected on either mixed cellulose ester (MCE) or polycarbonate (PC) filters using either 37 or 25 mm air cassettes. To be quantitative, air samples must be collected with a measured amount of air volume and surface dust samples must be collected from measured areas of a surface.

2.3 POLARIZED LIGHT MICROSCOPY

A PLM (Figure 2.1) is a compound light microscope, which contains a piece of polarizing material in the light path below the sample and another in the light path above the sample. The "PLM method" uses a stereo light microscope (Figure 2.2) to help in taking apart a bulk sample and a polarizing light microscope to identify the fibers among the binders and fillers. Work in the 1980s by McCrone

Figure 2.1 Analyst using a PLM for asbestos analysis.

established the procedures for asbestos fiber identification by PLM.[1,2] The PLM identification of asbestos fibers depends on several optical crystallographic properties: refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle.

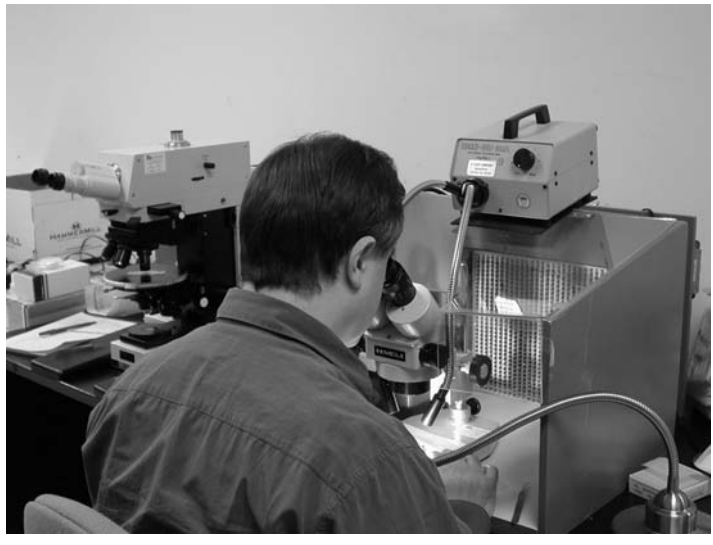

Figure 2.2 Analyst using a stereo-binocular microscope in a HEPA-filtered Hood to examine a bulk sample for asbestos.

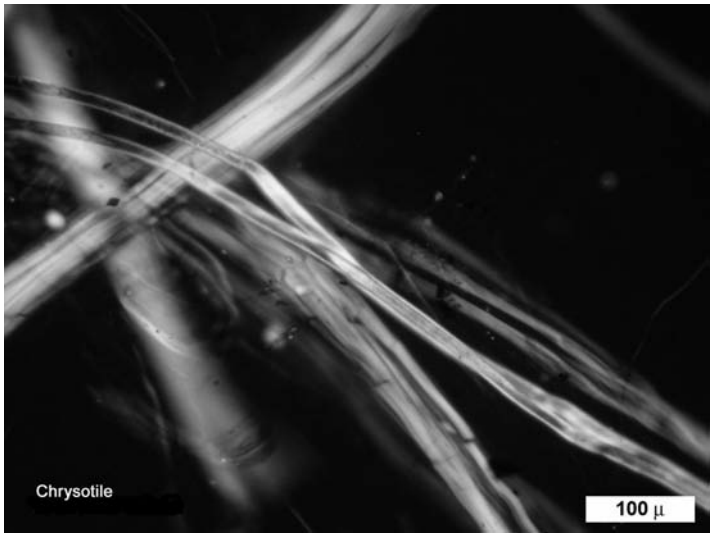

Figure 2.3 Image of asbestos as seen with a PLM.

The *refractive index* of a substance is numerically equal to the ratio of the velocity of light in a vacuum to its velocity in a substance.[1] The velocity (of light) in any given substance depends on composition; in general, the higher the atomic number of the atoms involved, the lower the velocity and the higher the index.[1] *Dispersion staining* produces its color, not by any chemical interaction but by virtue of the difference between the dispersion of refractive index for a particle and the liquid medium in which the particle is immersed.[1] *Birefringence* refers to the difference between the two refractive indices at right angles to the axis of the microscope.[2] Elongated particles are said to have a positive *sign of elongation* when they have a greater refractive index in the parallel direction than in the perpendicular direction.[1] *Extinction* refers to the behavior on rotation of the microscope stage when a crystalline substance is observed between crossed polarizing sheets. Each particle will show alternate brightness (polarization colors) and darkness (extinction). The particle shows parallel extinction when a prominent direction, for example, length of a fiber, is oriented parallel to the polarizer or analyzer vibration direction in its darkness position.[2]

Because of the size of the wavelength of light, PLM methods of identification are limited to fibers approximately 1 μm in diameter (Figure 2.3).

2.4 BULK ASBESTOS METHODS

The U.S. EPA has defined asbestos-containing material as any material or product that contains more than 1% asbestos.[3,4] The bulk analysis procedure most often specified is the "Method for the Determination of Asbestos in Bulk Building

Materials (EPA-600/R-93/116)" published in 1993.[5] Although it is generally accepted as an improvement over the USEPA "Interim Method for the Determination of Asbestos in Bulk Insulation Samples (EPA-600/M4-82-020)" published in December 1982,[6] the 1993 method has never been formally adopted by the EPA. NIOSH Method 9002 and OSHA Method ID-191 involve similar procedures as the 1993 EPA bulk method.[7,8]

Bulk asbestos analysis performed by PLM methods involves identifying the type of asbestos present on the basis of optical properties and then estimating the relative amount of asbestos in relation to the rest of the bulk sample. The estimates are given in terms of volume percents or, in some cases, area percents. PLM analysts practice with samples of known asbestos percentages until they can visually estimate the values on a consistent basis. The PLM visually estimated asbestos percent values do not necessarily correspond to the weight percent of asbestos in a product. When all components of a bulk material have similar densities, the volume percent value is expected to be similar to the weight percent value. However, if the sample contains 12% chrysotile asbestos by weight in a binder of a denser material such as calcium carbonate (limestone), then the PLM analytical result may show 30–40% asbestos by volume. Similarly, if a sample contains 45–50% chrysotile asbestos by weight in a material that contains the same weight of a lighter component such as cellulose (paper fibers), then the PLM analytical result may show 5–10% asbestos by volume. In most asbestos-containing materials, the precise determination of the percent of asbestos by weight is not of great importance, because once a material is shown to contain over 1% asbestos, it is considered a regulated asbestos-containing building material. In most building products such as insulation, fireproofing, acoustical plasters, and pipe covering where asbestos was intentionally added; the amount of asbestos present is significantly above 1%.

In some materials such as some ceiling tiles, floor tiles, caulks, paints, and joint compounds, the amount of asbestos may have been added in the low range, around 1%. For these materials, special procedures should be used. One special procedure is called "point counting."[9] In this procedure, the particles of the sample material are dispersed on a microscope slide and 400 nonempty points on the slide randomly selected for examination. If, on one of the points, an asbestos fiber happens to line up with the center of the microscope eyepiece crosshairs, the fiber is counted. Percentage of asbestos is calculated based on the number of positive "hits" during the count. Counting three asbestos fibers out of 400 nonempty points, for instance, corresponds to an asbestos percent of 0.75%. A stratified point-counting method is available as a method in the Certification Manual of the New York State Department of Health Environmental Laboratory Approval Program (ELAP).[10,11] The item states "For samples containing high amounts of asbestos the stratified point-count technique invokes labor-saving semi-quantitative counting rules. The stratified method is based on the premise that accurate quantitation is unnecessary for materials that contain substantial amounts of asbestos. In contrast, extensive analytical effort is still required for samples that contain positive but small amounts of asbestos."[10] Although more quantitative, the point-count technique has been criticized as not being statistically valid at the 1% level.[12] For a sample in which a value of exactly 1% was determined by the 400 point-count procedure, repeated

point-count analyses would be expected to fall variously within the range of 0.27–2.6% asbestos on the basis of Poisson statistics. To provide a more statistically valid analysis when low levels of asbestos may be present, matrix reduction is used to concentrate the asbestos fibers. When possible, combustible material is ashed away, acid-soluble material is dissolved away, and density separation is used to prepare the sample of bulk material so that low levels of asbestos fibers can be readily found. Electron microscopy can also be used to help provide quantitative values for low levels of asbestos. The EPA 1993 bulk method, the NIOSH 9002, the OSHA ID-191, and ELAP Item 198.4 all contain some discussion of matrix reduction and use of electron microscopy.[13] A bulk microscopy method that incorporates various forms of matrix reduction for particular sample product types and use of electron microscopy is being drafted concurrently by task groups in both ASTM and ISO. A comparison of several of the bulk methods is shown in Table 2.1.

2.5 PCM: AIR ANALYSIS

The PCM (Figure 2.4) is a compound light microscope, which illuminates a specimen with a hollow cone of light. The cone of light is narrow and enters the field of view of the objective lens. Within the objective lens is a ring-shaped device, which introduces a phase shift of a quarter of a wavelength of light. This illumination causes minute variations of refractive index in a transparent specimen to become visible. The phase-contrast mode pushes the ability of the light microscope to see fibers as thin as 0.25 μm in diameter, but it does so at the expense of identification. PCM is not used to identify asbestos fibers.

The most commonly used PCM method, NIOSH 7400, requires a positive PCM (dark) with green or blue filter, an adjustable field iris, ×8–10 eyepieces, and a ×40–45 phase objective (total magnification is about ×400).[14] Most PCM analysts use binocular PCMs. Within one of the eyepieces, there is a Walton–Beckett type graticule, which forms an analysis area of approximately 0.00785 mm^2 at the specimen plane. The other U.S. Government promulgated PCM method, OSHA ID-160, has similar requirements.[15] Under the PCM methods, fibers are counted when they are greater than 5 μm in length and have an aspect ratio (AR) (length to width) of at least 3:1. The NIOSH 7400 method "A" counting rules used for counting asbestos fibers have no upper limit on the diameter of the fiber counted. A fiber that appears to be partially obscured by a particle is counted as one fiber. If the fiber ends emanating from a particle do not seem to be from the same fiber and each end meets the length and AR criteria, they are counted as separate fibers. Results of the PCM methods are given in terms of fibers per cubic centimeter of air.

2.6 TRANSMISSION ELECTRON MICROSCOPY

The TEM (Figure 2.5) uses electro-magnetic coils as lenses to form magnified images with an electron beam in the same way that a light microscope uses glass lenses and a

Table 2.1 Comparison of Common Methods for Measuring Asbestos in Bulk Building Materials

	EPA-600/M4-82-020 1982	EPA-600/R-93/116 1993	NIOSH 9002	OSHA ID-191	ASTM and ISO Bulk in Progress
Instrument	Stereo + PLM XRD	Stereo + PLM and TEM	Stereo + PLM	Stereo + PLM with mention of SEM and TEM	PLM and TEM
Sample preparation	As is and some matrix reduction	As is and some matrix reduction, gravimetric	As is and some matrix reduction	As is and organic and carbonate matrix reduction	As is and detailed matrix reduction, gravimetric
Magnification	×1–1000	×1–20,000	×10–400	—	×1–20,000
Minimum fiber diameter	Approximately >1 μm	Approximately >1 μm	Approximately >1 μm	Approximately >1 μm	Approximately >1 μm
AR	NA	Generally >10:1	NA	3:1 with mention of 100:1	Not known at this time
Measurement	Volume or areal estimation	Visual estimation	Areal estimation	Areal estimation	Volume estimation + weight measure
Identification	Refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle	Refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle	Refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle	Refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle. Mention of SEM and TEM	Refractive indices, dispersion staining, birefringence, sign of elongation, and extinction angle + TEM ID
Reporting	% asbestos	% asbestos and possible weight percent	% asbestos	% asbestos	Volume or areal and percent asbestos or weight percent

Figure 2.4 Analyst using a PCM for asbestos analysis.

light beam to form images. Electrons can be accelerated with high potential energies, which produce a beam with a very small wavelength and thus allow much higher magnifications than can be achieved with the wavelengths of light. The commonly used TEM methods call for a TEM that can operate at an accelerating potential of 80,000 (80 kV) to 120,000 V. If operating properly at 80–120 kV, a

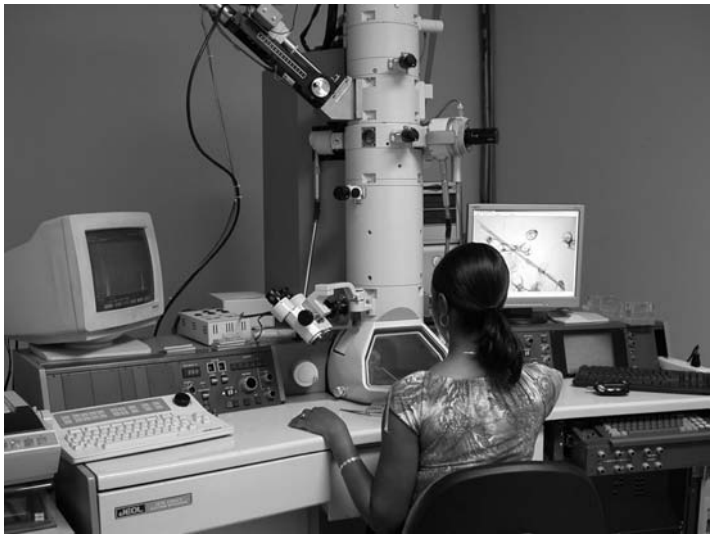

Figure 2.5 Analyst using a TEM for asbestos analysis.

TEM is easily capable of obtaining a direct screen magnification of about $\times 100{,}000$ with a resolution better than 10 nm. This allows the smallest asbestos fibers, which are approximately 20 nm (0.02 μm) in diameter, to be examined. In addition to the analysis of fiber morphology by TEM (Figure 2.6), selected area electron diffraction (SAED) and x-ray energy dispersive spectroscopy (EDS) can be used to gain information about a particle's crystal structure and elemental composition. TEM with SAED and EDS is referred to as analytical electron microscopy (AEM). Examples of a chrysotile SAED pattern and EDS spectra from reference asbestos minerals are shown in Figure 2.7 and Figure 2.8.

The NIOSH 7402 method is the complementary TEM method for the PCM Method 7400.[16] With 7402, fibers greater than 5 μm in length and have an AR (length to width) of at least 3:1 and a width of at least 0.25 μm are characterized by SAED and EDS. These fibers are then classified as nonasbestos or asbestos. The type of asbestos is also determined. A value of percent asbestos is determined and this percentage applied to PCM results of the same sample. No concentration of fibers per cubic centimeter is reported under Method 7402. The ASTM method for the PCM analysis of workplace exposures, D4240, has been removed from official ASTM practice and a new method with more discussion of identification of the fibers is currently being balloted.[17]

Early TEM measurements of airborne asbestos such as those used by Nicholson involved the collection of fibers on a membrane filter followed by an indirect-transfer method.[18,19] In the TEM specimen procedure known as the "rubout"

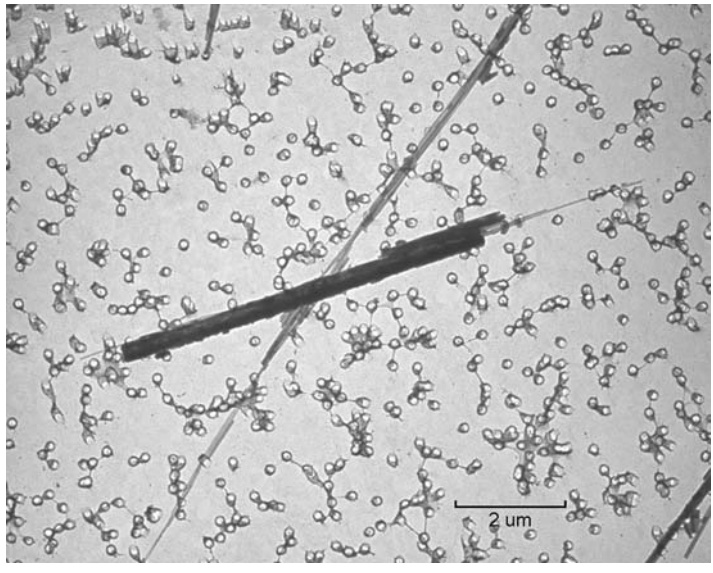

Figure 2.6 Image of crocidolite and chrysotile asbestos fibers as seen with a TEM. Crocidolite is the thicker fiber; chrysotile is longer and thin. The circles are carbon replicas of the PC filter.

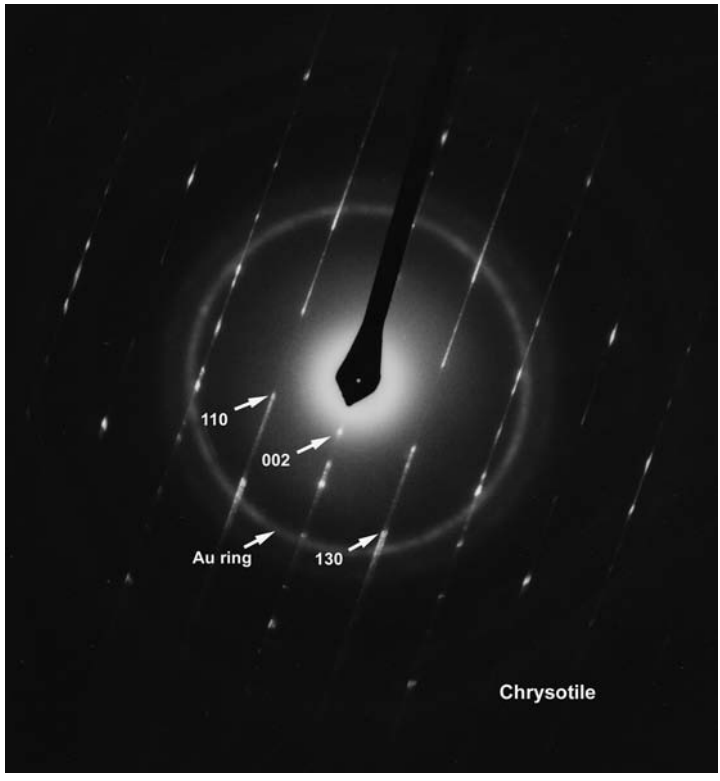

Figure 2.7 Chrysotile SAED pattern. The gold ring results from coating the fiber with a thin layer of gold and is used for calibration.

method, air samples collected using MCE filters were ashed in a low-temperature plasma asher and the residual ash was dispersed in a solution of nitrocellulose. The dispersion was "rubbed out" or spread as uniformly as possible on an optical microscope slide. After the solvent had evaporated, a portion of the film containing the particles from the filter residue was mounted on a TEM grid for examination. The value of asbestos was reported in terms of nanograms per cubic meter of air. The values were determined by summing the masses of the fibers that were calculated from the TEM dimensions of each fiber and an appropriate density for the type of asbestos found.

In 1978, Samudra et al., published the first methodology for determination of the numerical concentration of asbestos fibers in ambient atmospheres using a direct preparation method.[20] The provisional methodology developed under contract for the USEPA recommended air sampling using a 0.4 μm pore size PC filter and preparation of TEM specimen grids by carbon coating followed closely by chloroform extraction to remove the filter polymer. The Samudra methodology was never taken beyond the provisional status.

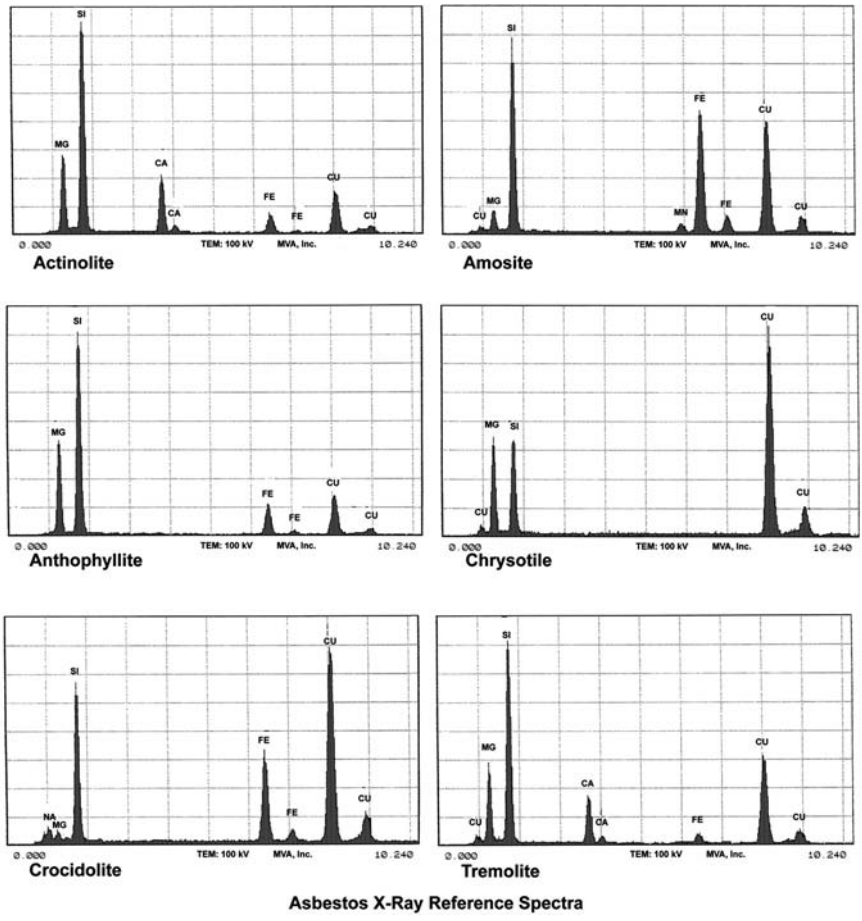

Figure 2.8 EDS x-ray spectra for NIST reference asbestos fibers.

In the early 1980s, Yamate at the Illinois Institute of Technology Research Institute (IITRI) was asked under contract to EPA to take the methods that were being used by various labs and put together a TEM method for airborne asbestos.[21] His document, circulated in draft form in 1984, was never officially adopted by EPA. Although it remained in draft form, it became the generally accepted method for TEM analysis of airborne asbestos. As a fiber definition, it used the minimum AR of 3:1 from the NIOSH and OSHA methods but had no minimum fiber length. However, fibers less than 1 mm at the fluorescent screen magnification level were characterized as being 1 μm. At the analysis magnification of $\times 20{,}000$, the 1 mm size corresponded to 0.5 μm. In addition to asbestos fibers, the method classified asbestos-containing objects as bundles, clusters, and matrices; see Table 2.2 for a comparison of fiber definitions used by several airborne asbestos analysis methods. Yamate also included the concept of levels of analysis because he realized that

Table 2.2 Comparison of Fiber Definitions Used in Measuring Asbestos in Air

Fiber — NIOSH 7400 (PCM)	Longer than 5 μm with a length to width ratio equal to or greater than 3:1
Fiber — NIOSH 7402 (TEM)	All particles with a diameter greater than 0.25 μm that meet the definition of a fiber (AR greater than or equal to 3:1, longer than 5 μm)
Fiber — OSHA ID-160 (PCM)	A particle that is 5 μm or longer, with a length to width ratio of 3:1 or longer
Fiber — Yamate (TEM)	Particle with an AR of 3:1 or greater and with substantially parallel sides
Fiber — AHERA (TEM)	A structure greater than or equal to 0.5 μm in length with an AR (length-to-width) of 5:1 or greater and having substantially parallel sides
Fiber (fibre) — ISO 10312 (TEM)	An elongated particle which has parallel or stepped sides. For the purposes of this international standard, a fiber is defined to have an AR equal to or greater than 5:1 and a minimum length of 0.5 μm
Bundle — NIOSH 7400 (PCM)	Not defined in method
Bundle — NIOSH 7402 (TEM)	Not defined in method
Bundle — OSHA ID-160 (PCM)	Not defined in method
Bundle — Yamate (TEM)	Particulate composed of fibers in a parallel arrangement, with each fiber closer than the diameter of one fiber
Bundle — AHERA (TEM)	A structure composed of three or more fibers in a parallel arrangement with each fiber closer than one fiber diameter
Bundle — ISO 10312 (TEM)	A structure composed of parallel, smaller diameter fibres attached along their lengths. A fibre bundle may exhibit diverging fibres at one or both ends
Cluster — NIOSH 7400 (PCM)	Not defined in method
Cluster — NIOSH 7402 (TEM)	Not defined in method
Cluster — OSHA ID-160 (PCM)	Not defined in method
Cluster — Yamate (TEM)	Particulate with fibers in a random arrangement such that all fibers are intermixed and no single fiber is isolated from the group
Cluster — AHERA (TEM)	A structure with fibers in a random arrangement such that all fibers are intermixed and no single fiber is isolated from the group. Groupings must have more than two intersections
Cluster — ISO10312 (TEM)	A structure in which two or more fibres, or fibre bundles, are randomly oriented in a connected grouping
Matrix — NIOSH 7400 (PCM)	Not defined in method
Matrix — NIOSH 7402 (TEM)	Not defined in method
Matrix — OSHA ID-160 (PCM)	Not defined in method
Matrix — Yamate (TEM)	Fiber or fibers with one end free and the other end embedded or hidden by a particulate
Matrix — AHERA (TEM)	Fiber or fibers with one end free and the other end embedded in or hidden by a particulate. The exposed fiber must meet the (AHERA) fiber definition
Matrix — ISO10312 (TEM)	A structure in which one or more fibres, or fibre bundles, touch, are attached to, or partially concealed by, a single particle or connected group of nonfibrous particles

analytical tools available with the AEM provided progressively more specific identification of asbestos fibers depending on the amount of time devoted to the task. The method's levels are known among the TEM asbestos analytical community as Yamate Level 1, Level 2, and Level 3. Level 1, requiring the least amount of identification, was designed for those situations where the airborne particulate was well characterized. If a particular process was known to emit only chrysotile, Level 1 permitted identification based on morphology alone. For Level 2, asbestos identification was determined by morphology and visual diffraction characteristics for chrysotile. For amphiboles, Level 2 included some x-ray elemental information. Asbestos identification in Yamate Level 3 began with the identification steps in Level 2 and added diffraction pattern indexing to more specifically identify the amphibole.

The Yamate method also contained a section for the situation where an air filter was overloaded. The preparation was an indirect procedure where a portion of the filter was ashed and the ash suspended in water. A second filter was prepared with a portion of the suspension and then processed using the same direct procedures described in the main method.

On October 22, 1986, President Reagan signed into law the Asbestos Hazard Emergency Response Act (AHERA).[22] The Act required that EPA describe the methods used to determine completion of response actions such as the abatement of school buildings. Following the deliberations of a panel of asbestos analysis experts, the "Interim TEM Analytical Methods" were published in the Federal Register on October 30, 1987 as Appendix A to Subpart E of the EPA's "Asbestos-containing Materials in Schools; Final Rule and Notice." Following an asbestos abatement and before the protective plastic barriers are removed, leaf blowers and fans are used to aggressively stir the air and resuspend any settled dust while five area air samples are collected. For abatement clearance, the five area air samples collected inside the containment were to be compared with five or more area air samples collected outside the containment. No aggressive disturbance of the air outside the containment was to be done. If there was no statistical difference between the two sets of samples, the abated area was cleared and prepared for reoccupancy. A simplified version of the Yamate draft method was needed to create a rapid method for the clearance of school buildings. The AHERA method maintained many of the method particulars of the Yamate method but simplified the counting and recording for a rapid clearance procedure. As in the Yamate method, structures were counted. A structure was defined as a microscopic bundle, cluster, fibers, or matrix which may contain asbestos. A matrix was defined as a fiber or fibers with one end free and the other end embedded in or hidden by a particulate. The exposed fiber must meet the fiber definition. Under the AHERA method, an asbestos fiber was defined as a structure greater than or equal to 0.5 μm in length with an AR (length to width) of 5:1 or greater and having substantially parallel sides. Individual dimensions of structures or fibers are not recorded under the AHERA method but information about the overall structure size is classified as either between 0.5 and 5.0 μm or greater than 5.0 μm. The size data is not used to determine compliance with the AHERA regulations but is included so if an area does not pass, the project manager might infer something about the source of the contamination.

Many large structures found in the air would suggest improper cleaning, while small structures could have come from a source external to the cleaning effort. During the deliberations of the expert panel, the question was raised about whether all ten samples needed to be analyzed if no asbestos structures were found on the five inside-the-containment samples. On the basis of experience of some of the panel in finding occasional asbestos fibers on blank (unused) PC filters, it was decided a sample was clearly above the blank filter level if it had a filter loading greater than 70 structures per millimeter square (str/mm^2). In the real world abatement industry, the 70 str/mm^2 became the generally recognized clearance level and contractors were and still are normally instructed to reclean if the average of the five inside samples exceeded that value. Only rarely today is the comparison made of the five inside and five outside samples. Those few cases are usually where a contractor believes that asbestos contamination outside the containment area is contributing to the air within the abatement area.

2.7 SCANNING ELECTRON MICROSCOPY

In 1987 when the AHERA method mandated the use of TEM, the scanning electron microscope was determined to be inadequate for building clearance (Figure 2.9). The reasons given in the AHERA document were (1) currently available methodologies were not validated for the analysis of asbestos fibers, (2) SEM was limited in its ability to identify the crystalline structure of a particular fiber, (3) the National Bureau of Standards found that the image contrast of the microscopes was difficult to standardize between individual scanning electron microscopes, and

Figure 2.9 Analyst using an SEM for asbestos analysis.

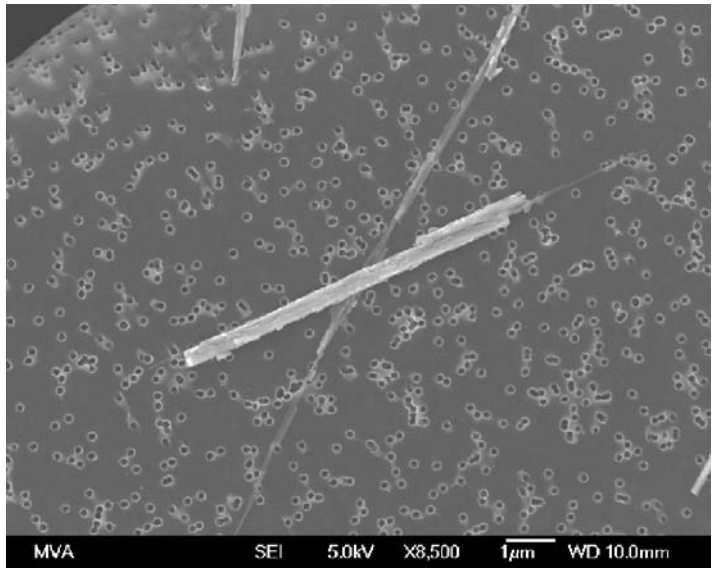

Figure 2.10 Image of crocidolite and chrysotile asbestos fibers as seen with an SEM. Same fibers as shown in Figure 2.6.

(4) no current laboratory accreditation program existed for accrediting SEM laboratories.[22] NBS had determined that the only SEM method recognized at that time, the Asbestos International Association (AIA) protocol,[23] had inherent difficulty when examining certain types of asbestos. In 2004, there are still no laboratory accreditation programs for SEM laboratories. In the United States, no standard SEM method is in use for asbestos, although it is mentioned in the OSHA ID-160 method. However, there is interest internationally and the ISO method 14966 for SEM analysis of inorganic fibrous particles that includes asbestos (Figure 2.10), ceramic fibers, and glass fibers in air was approved in 2002.[24]

2.8 TEM BEYOND AHERA

In 1987 when the AHERA method was published in the Federal Register as an interim method, it contained a provision that the method would be updated by the National Institute of Standards and Technology (NIST). As of 2004, no updated version of the method has been published by NIST or any other federal agency. The AHERA method became the generally accepted TEM method for the analysis of asbestos in air. However, its lack of specific size data for individual asbestos structures was considered a deficiency for some situations. A Yamate Level 2 analysis was requested on occasions when information about fiber size was needed. In March 1988, the CARB issued Method 427 for the determination of particulate asbestos emissions from stationary sources using stack sampling, light microscopy,

and electron microscopy.[25] Although the NIOSH 7400 PCM method may be used with the CARB Method 427, it is evident that the TEM portion is the focus of the method. Recording of fiber size data is done on the basis of the Yamate method.

A rather more complete TEM airborne asbestos analysis procedure developed largely by Dr. Chatfield of Chatfield Technical Consulting was released in 1995 by the ISO.[26] The International Standard 10312 contains counting rules, which expand on the Yamate and AHERA concept of asbestos structures. Clusters and matrices are subdivided into dispersed and compact structures. A dispersed cluster contains asbestos fibers that can be measured and reported separately while a compact cluster has fibers too intertwined to be reported individually. In this method, cluster and matrix components are identified, measured, and recorded separately up to a maximum of nine substructures. The ISO 10312 was followed in 1998 by the ASTM Standard Test Method D6281-98, which was a translation of the ISO 10312 method into ASTM format with a few improvements and changes.[27] The ASTM Method D6281 was reapproved in 2002 as D6281-02. For samples that contain any appreciable amount of asbestos, analysis by either ISO 10312 or ASTM D6281 is considerably more time consuming than an AHERA analysis and therefore more expensive. The data produced by ISO 10312/ASTM D6281 was designed to allow another analyst to review the data of the original analyst and understand how the asbestos structures were present on the filter grid. The method of data recording was designed to allow re-evaluation of the counting data as new medical evidence or regulatory requirements become available. From the results of an ISO 10312 (or ASTM D6281) analysis, it should be possible to determine several different airborne asbestos structure concentration values based on a number of fiber size classifications. For instance, it should be possible to extract what a structure per cubic centimeter concentration would have been if the sample had been analyzed by AHERA counting rules. Both ISO 10312 and ASTM D6281 have an annex, which describes procedures for the determination of concentrations of asbestos fibres (International spelling of fiber) and bundles longer than 5 μm, and of PCM-equivalent (PCME) asbestos fibers. For improved analytical sensitivity and statistical precision, the larger fiber counts are done at lower magnifications so more area of the filter may be examined. A comparison of four common asbestos methods for the analysis of air samples is shown in Table 2.3.

In 1999, ISO 13794 (indirect air) was published.[28] The asbestos structure and fiber counting procedures in this method are the same as those presented in ISO 10312 and ASTM D6281. ISO 13794 provides an indirect-transfer procedure so overloaded filters can be analyzed. The filter preparation methods described in both ISO 10312 and ASTM D6281 are direct-transfer procedures. In steps similar to the Yamate indirect preparation procedure, a portion of the original filter is ashed and the ash suspended in water. A second filter is prepared with a known portion of the suspension and then processed using the same direct procedures described in ISO 10312 and ASTM D6281. Although the method states "This International Standard is applicable to measurement of airborne asbestos in a wide range of ambient air situations, including the interior atmospheres of buildings, and for detailed evaluation of any atmosphere in which asbestos fibres are likely to be present," the user is

Table 2.3 Comparison of Common Methods for Measuring Asbestos in Air

	NIOSH 7400	NIOSH 7402	AHERA	ISO
Instrument	PCM	TEM	TEM	TEM
Filter Preparation	Direct	Direct	Direct	Direct: 10312; Indirect: 13794
Magnification	450×	10,000×	~20,000×	~20,000×
Fiber length, diameter	$L > 5$ μm; $W > 0.25$ μm	$L > 5$ μm; $W > 0.25$ μm	$L > 0.5$ μm; $W > 0.002$ μm	$L > 0.5$ μm; $W > 0.002$ μm; PCME: $L > 5$ μm, $W > 0.25$ μm
AR	>3:1	>3:1	>5:1	>5:1 or 3:1
Counting	Fibers	Fibers	Structures	Structures and fibers
Identification	None	Morphology, crystal structure, elements	Morphology, crystal structure, elements	Morphology, crystal structure, elements
Reporting	Fibers/cm^3	% Asbestos	All Asbestos Str/cm^3 and >5 μm structures	All Asbestos Str/cm^3 and >5 μm fibers and PCME fibers/cm^3

cautioned that comparison of results using this indirect-transfer procedure with those from a direct-transfer procedure may not be done *a priori*.[28] The best study of the differences between direct and indirect air sample preparation remains the study by Chesson and Hatfield.[29] Their findings supported the generally accepted opinion that TEM analysis of air samples using indirect-transfer methods provides estimates of the total airborne asbestos structure concentration that are higher than those using direct-transfer methods. They concluded that no single factor can be used to convert measurements made by one method to a value that is comparable with measurements made by the other. They also concluded that the breakdown of larger structures into smaller ones during indirect preparation does not appear to be sufficient to explain the difference in measured concentrations. Interference by debris and association of unattached structures may also be important. They recommended that additional research was needed to determine which transfer method more accurately reflects biologically meaningful airborne asbestos concentrations.

2.9 WATER ANALYSIS

There are three standard methods available for the analysis of drinking water for asbestos: EPA 100.1, EPA 100.2, and the AWWA 2570.[30–32] These methods are all TEM methods and are compared in Table 2.4.[33] The EPA has set a maximum contaminant level of 7 million fibers longer than 10 μm/l of drinking water and has listed both the 100.1 and 100.2 methods as acceptable for the analysis of waterborne asbestos. The EPA 100.1 method is a research report produced in 1984 before

Table 2.4 Comparison of Common Methods of Measuring Asbestos in Water

	EPA 100.1	EPA 100.2	AWWA 2570
Instrument	TEM	TEM	TEM
Filter preparation	Indirect PC	Indirect (PC and MCE)	Indirect (PC and MCE)
Magnification	~20,000×	~20,000×	~20,000×
Fiber length diameter	$L > 0.5$ μm; $W > 0.002$ μm	$L > 10$ μm; $W > 0.002$ μm	$L > 0.5$ μm; $W > 0.002$ μm
AR	>5:1	>5:1	>5:1
Counting	Fibers	Fibers	Fibers
Identification	Morphology, crystal structure, elements	Morphology, crystal structure, elements	Morphology, crystal structure, elements
Reporting	Millions of asbestos fibers per liter (MFL)	MFL > 10 μm	MFL

the EPA drinking water regulations and describes counting procedures that include asbestos fibers longer than 0.5 μm. EPA 100.2 describes counting only those fibers longer than 10 μm. Guidance as to the modifications of EPA 100.1 necessary to comply with the EPA drinking water regulations was published by Feige et al.[34] The ELAP Certification Manual Item 198.2 describes a modification to Method 100.2 required for New York State Department of Health compliance.[35] In the modification, the ozone generator is considered optional *only* if all samples are filtered within 48 h.

2.10 SURFACE DUST ANALYSIS

In 1989, the ASTM subcommittee D22.07 began work on methods for the analysis of asbestos in settled dust.[36] Three ASTM methods are currently available for the analysis of surface dust for asbestos. These methods include two microvacuum methods: ASTM D5755-02 (structure count) and D5756-02 (mass) and one wipe method, ASTM D6480-99.[37–39] An EPA carpet method, EPA/600/J-93/167, was developed during a research study that was published as an article in 1993.[40] The EPA number was assigned in 2001. The three ASTM methods are nondestructive, while the carpet method requires that a piece be cut from the carpet and sent to the laboratory. A comparison of the methods is shown in Table 2.5.

Because dust particles can be arranged in layers more than one particle thick, direct preparation techniques are of limited value for TEM because the electron beam must be able to penetrate the sample. Indirect preparation procedures are used for all four of these methods. The results of the analysis are expressed in numbers or mass of asbestos structures per square centimeter of surface sampled. The number count methods were originally designed with an analytical sensitivity of about 1000 str/cm^2 but can achieve much better sensitivities on clean surfaces. A nominal analytical sensitivity for the mass determination is 0.24 pg of

Table 2.5 Comparison of Common Methods for Measuring Asbestos in Surface Dust

	ASTM D5755-02	ASTM D5756-02	ASTM D6480-99	EPA/600/J-93/167
Instrument	TEM	TEM	TEM	TEM
Sample preparation	Microvacuum (indirect)	Microvacuum (indirect)	Wipe (indirect)	Piece of carpet (indirect)
Magnification	~20,000×	~20,000×	~20,000×	~20,000×
Fiber length diameter	$L > 0.5$ μm; $W > 0.002$ μm	$L > 0.5$ μm; $W > 0.002$ μm	$L > 0.5$ μm; $W > 0.002$ μm	$L > 0.5$ μm; $W > 0.002$ μm
AR	>5:1	>5:1	>5:1	>5:1
Counting	Asbestos structures	Asbestos structures	Asbestos structures	Asbestos structures
Identification	Morphology, crystal structure, elements	Morphology, crystal structure, elements	Morphology, crystal structure, elements	Morphology, crystal structure, elements
Reporting	Asbestos str/cm^2	Asbestos μg/cm^2	Asbestos str/cm^2	Asbestos str/cm^2 of carpet

asbestos/cm^2. There are no federal government levels with which to compare the results of the surface dust methods and there is some disagreement on how to interpret the data.[41–49] Because the amount and type of dust collected by each method differ, it is clear that results of one method cannot be necessarily compared directly with data from another. For instance, the bulk carpet method, EPA/600/J-93/167, is an analysis of the total amount of dust in a carpet. Because carpets are known to be excellent traps for dust and dirt, the amount of asbestos in the carpet may be considerably higher than that collected from the surface of the same carpet using the D5755 microvacuum method. It is not appropriate to compare bulk carpet values with results of the D5755 method, although both are given in terms of structures per square centimeter. In one set of tests, the EPA/600/J-93/167 results were found to be about 100 times higher than that of the D5755 type analysis, because the bulk carpet method involves all dirt trapped in the carpet and the microvacuum method only analyzed the top, readily-releasable dust.[40] Asbestos in dust deep in the carpet may not be releasable under normal activities and may only be of concern when the carpet is being removed. Asbestos fibers that are in a sticky film on a surface and therefore not readily releasable are collected by the D6480 wipe method. The wipe method gives an index of all the asbestos fibers on a surface regardless of how much they are stuck, whereas the microvacuum method gives an index of the readily releasable fibers.

2.11 SOIL ANALYSIS

Soil is a difficult medium for the analysis of asbestos because soil minerals are not easily separated from the asbestos fibers. In a method used by the USEPA Region 1,

Table 2.6 Comparison of Common Methods for Measuring Asbestos in Soil

	EPA Superfund	EPA Region 1 Screening
Instrument	Transmission electron microscope	Polarized light microscopy
Sample preparation	Elutriator (to generate air samples)	Sieving (to reduce matrix)
Magnification	~20,000×	10–1000×
Fiber length diameter	$L > 0.5$ μm; $W > 0.002$ μm	$W > \sim 1$ μm
AR	>5:1	>5:1
Counting	Structures	Areal %
Identification	~ISO 10312 Morphology crystal structure elements	Refractive indices, dispersion staining, birefringence, sign of elongation, Becke line extinction angle
Reporting	Various including "protocol" fibers	% Asbestos

sieving is used to enhance the ability to find asbestos fibers that are then identified using essentially the standard PLM bulk analysis procedure.[50] A more complicated procedure which looks at the airborne asbestos fibers that might be released from the soil is called the Superfund method.[51,52] The soil sample is placed in a rotating drum and air samples collected in a vertical elutriator. The samples are analyzed by TEM according to procedures based on the ISO 10312 method. The counting procedure may be modified to count "protocol" fibers. Protocol fibers are asbestos fibers with certain length and width characteristics as determined by studies in biological systems. At one point in time, fibers longer than 40 μm were thought to be of greatest interest and the method was modified to count more grid openings at a lower magnification for better counting statistics. A comparison of the two soil methods is shown in Table 2.6.

2.12 VERMICULITE ANALYSIS

Vermiculite is also a special case for bulk asbestos analysis. Sometimes referred to as "The Cincinnati Method," the EPA research method for the sampling and analysis of fibrous amphibole in vermiculite attic insulation (VAI) uses a flotation step to separate the vermiculite from the more dense amphiboles.[53] The fibrous amphiboles found in the Libby, MT vermiculite can be hand picked from the "sinks" using a stereomicroscope and weighed to get a direct weight percent estimate. The method also includes a TEM portion for the analysis of amphibole fibers that might be present in the "suspended particle" fraction of the water used in the flotation step. Criteria for examination of the TEM specimens are specified in ISO 10312 or ISO 13794. Early in 2004, EPA held a day and a half workshop for a panel of experts to meet and propose a method to determine whether Libby amphibole is present in a sample of VAI. The objective of the method is to be accurate with respect to identifying Libby amphibole, affordable to the average homeowner, and adaptable to most current commercial fiber

analysis laboratories. This more routine vermiculite method, based on the Cincinnati research method, is expected to be released in late 2004.

2.13 METHODS FOR ASBESTOS ANALYSIS IN OTHER MEDIA

In addition to media such as air, water, soil, and dust, methods for analyzing asbestos in clothing, talc, and biological specimens have appeared in the scientific literature.[54–57] Only a few of the many scientific papers that contain descriptions of asbestos analysis methods are referenced here. Sample preparation procedures are generally different for each type of sample matrix, but the type of microscopy to be used and the counting rules are usually borrowed from one of the standard methods described earlier.

2.14 ASBESTOS DEFINITIONS AND TERMINOLOGY

The definition of a "Federal Asbestos Fiber" depends on the federal agency involved. The Occupational Safety and Health Administration (OSHA) uses a definition of a fiber that is at least 5 μm long with an AR (length to width) of 3:1. The EPA uses a definition of a fiber that is at least 0.5 μm long with a 5:1 AR. The ISO and ASTM TEM methods use the 0.5 μm long with a 5:1 AR definition in their main procedure and provide an annex, which describes counting fibers greater than 5 μm long with an AR of 3:1. Other ARs such as 10:1 and 20:1 have been suggested for defining an asbestos fiber but have not been adopted.

From the microscopical analyst's point of view, an asbestos fiber is defined by the counting method being used. Under the AHERA counting rules, a fiber is a structure having a minimum length greater than 0.5 μm and an AR (length to width) of 5:1 or greater and substantially parallel sides. The appearance of the end of the fiber, that is, whether it is flat, rounded, or dovetailed, is to be noted. However, AHERA does not use this information about fiber ends, nor does it say whether to record this information. Under Section 3.22 of the ISO 10312 counting rules (and a similar section in ASTM D6281), a fiber is defined as an elongated particle which has parallel or stepped sides.

Individual chrysotile fibers, called fibrils, are too thin to be seen by the light microscope during the PCM analysis by NIOSH 7400. The fibers of chrysotile that are seen in the light microscope are actually bundles of fibrils. During the analysis by TEM using the NIOSH 7402 method that considers only elongated particles longer than 5 μm in length and greater than 0.25 μm in width with a 3:1 AR, the chrysotile "fibers" are more correctly listed as bundles. As stated in the ISO 10312 method: "For chrysotile, PCME fibres will always be bundles."[26] During the analysis by TEM using the AHERA method, chrysotile fibrils are listed as fibers. These AHERA chrysotile "fibers" (actually fibrils less than 0.05 μm in diameter) are not visible with the light microscope. Similar terminology is used in the water methods and in the dust methods. With the exception of the NIOSH 7402 method, all TEM chrysotile fibers are actually fibrils and not visible with the light microscope.

2.15 PCM EQUIVALENCY

The US NIOSH Standard Method 7400 uses PCM and involves counting only those fibers that can be seen with the light microscope (thicker than 0.25 μm) and longer than 5 μm. The TEM companion method NIOSH 7402 considers the same fiber characteristics as the 7400 method but because the TEM can resolve thin asbestos fibers, 7402 analysis is restricted to fibers greater than 0.25 μm. The TEM fibers analyzed under NIOSH 7402 are then PCME fibers. However, the NIOSH 7402 method is not established to provide concentrations of asbestos fibers. The determination and reportable value from 7402 is a percentage of asbestos fibers of all fibers in the PCME range in the sample. This percentage can thereby be applied to 7400 values to determine asbestos fiber concentrations in fibers/cm^3. Other TEM methods (primarily ISO 10312, and also occasionally AHERA) have been used to determine PCME concentrations. It is important when interpreting the data to understand the differences in counting rules between methods. Appendix B of Method NIOSH 7400 contains a description of the asbestos fiber counting rules (referred to as "A" Rules) as they apply to labeled objects in Figure 2.2 of the 7400 method. For Object 2 in Figure 2.2, the method states: "Although the object has a relatively large diameter (>3 μm), it is counted as a fiber under the rules. There is no upper limit on the fiber diameter in the counting rules." The ISO 10312 Method defines a PCME fibre as "any particle with parallel or stepped sides, with an AR of 3:1 or greater, longer than 5 μm and which has a diameter between 0.2 and 3.0 μm." Using the ISO 10312 method for PCME counting will therefore not provide a count of PCM fibers equivalent to the NIOSH 7400 Method unless it is modified, so that fibers of all diameters are included.

More serious cautions are appropriate for the attempt to use AHERA counts to estimate PCME concentrations. It is important to realize that the NIOSH 7400 method includes fibers associated with other particles. For Object 6 in Figure 2.2, the NIOSH 7400 method states: "A fiber partially obscured by a particle is counted as one fiber. If the fiber ends emanating from a particle do not seem to be from the same fiber and each end meets the length and AR criteria, they are counted as separate fibers." The AHERA method counts all asbestos objects as structures. Objects that contain one or more fibers partially obscured by a particle are counted as matrices. Under the NIOSH PCM method, several fibers meeting the length and AR criteria, which are overlapping but do not seem to be part of the same bundle, would be counted as separate fibers. Under the AHERA TEM method, these would all be counted as one cluster. If an analyst tries to use the AHERA data to estimate a PCME fiber count and chooses only those structures identified as bundles greater than 5 μm, they will miss PCME fibers that are parts of matrices or clusters. Because AHERA uses a 5:1 AR while the PCM method uses a 3:1 ratio, an AHERA count would not have included a fiber over 5 μm with only a 3:1 AR. Considering the differences in the two methods, it does not seem appropriate to attempt to estimate PCME fiber concentrations from AHERA data. However, an AHERA analysis in which no asbestos structures are found is considered to be consistent with no PCME fibers detected. It would be a most unusual

sample to have no AHERA countable asbestos structures but still have some large fibers with ARs between 3:1 and 5:1.

2.16 CLEAVAGE FRAGMENTS

Most asbestos methods dictate the counting of the asbestos forms of six minerals: one serpentine type (chrysotile) and five amphiboles (amosite, anthophyllite, actinolite, crocidolite, and tremolite). Elongated particles with ARs greater than 3:1 or 5:1 that did not come from a population of asbestos fibers are sometimes called cleavage fragments. The distinction of how to tell an asbestos fiber from a cleavage fragment is currently being debated within the scientific community. A population of fibers as observed in a bulk sample having the asbestiform habit is generally recognized by several characteristics.[5]

These include mean ARs in the range from 20:1 to 100:1 or higher for fibers longer than 5 μm. Asbestos is characterized by very thin fibrils, usually less than 0.5 μm in width, and two or more of the following:

- Parallel fibers occurring in bundles
- Fiber bundles displaying splayed ends
- Matted masses of individual fibers
- Fibers showing curvature

It is more difficult to classify individual fibers as to asbestiform or cleavage fragments because individual fibers do not exhibit all the characteristics of a population. With the exception of the requirements given in the TEM standard methods that the asbestos fibers have substantially parallel or stepped sides, there is little specific information for the analyst in the way of asbestos or cleavage fragment differentiation. Research has shown that a population of cleavage fragment particles has a smaller mean AR than a population of commercial asbestos fibers has. However, the AR distributions of the two populations can overlap, and on an individual basis, some fibers could be classified either way. In Figure 2.11 the ARs of tremolite fibers found in a talc sample are compared with the ARs determined from the National Institute for Standards and Technology (NIST) standard reference tremolite asbestos sample SMR 1876. The population of tremolite fibers in the talc is considered to be nonasbestiform because the mean AR is less than 20:1. However, some individual tremolite fibers in the talc like the one shown in Figure 2.12 would be counted as an asbestos fiber under standard methods if found by itself.

2.17 AMPHIBOLES

For most standard asbestos methods, "asbestos" means chrysotile and the asbestiform varieties of the five amphiboles: crocidolite (riebeckite), amosite (cummingtonite–grunerite), anthophyllite, tremolite, and actinolite. Other amphiboles can also exhibit asbestiform habits. The difference between nonregulated asbestiform amphiboles and

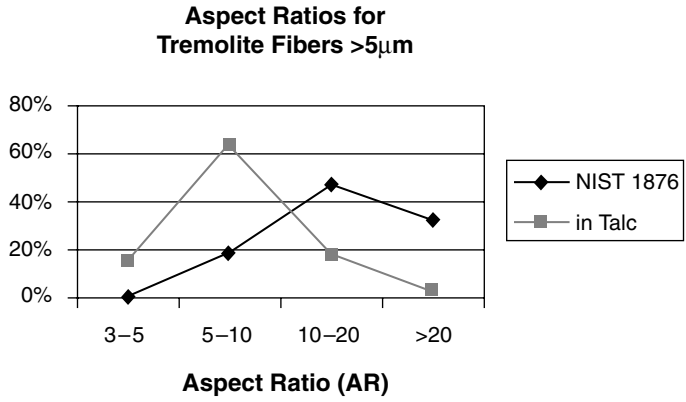

Figure 2.11 Comparison of ARs for tremolite fibers from the Standard Reference Material 1876, tremolite asbestos and tremolite from a talc sample.

those that are regulated is the amount of elemental substitution that has occurred when the mineral was formed in the Earth. The different amphibole names as defined by different elemental compositions are described in Leake et al.[58] Among the amphiboles present in the vermiculite from the Libby area of Montana are tremolite, richterite, and winchite.[59–62] The specific mineralogical determinations were made after extensive mineralogical studies. Distinguishing between tremolite, richterite, and winchite by PLM is difficult because the minerals have very similar optical properties. Figure 2.8 shows the elemental spectra produced by NIST reference asbestos materials using TEM–EDS methodology. As seen in Figure 2.13, the elemental

Figure 2.12 TEM image of a tremolite fiber found in a talc sample.

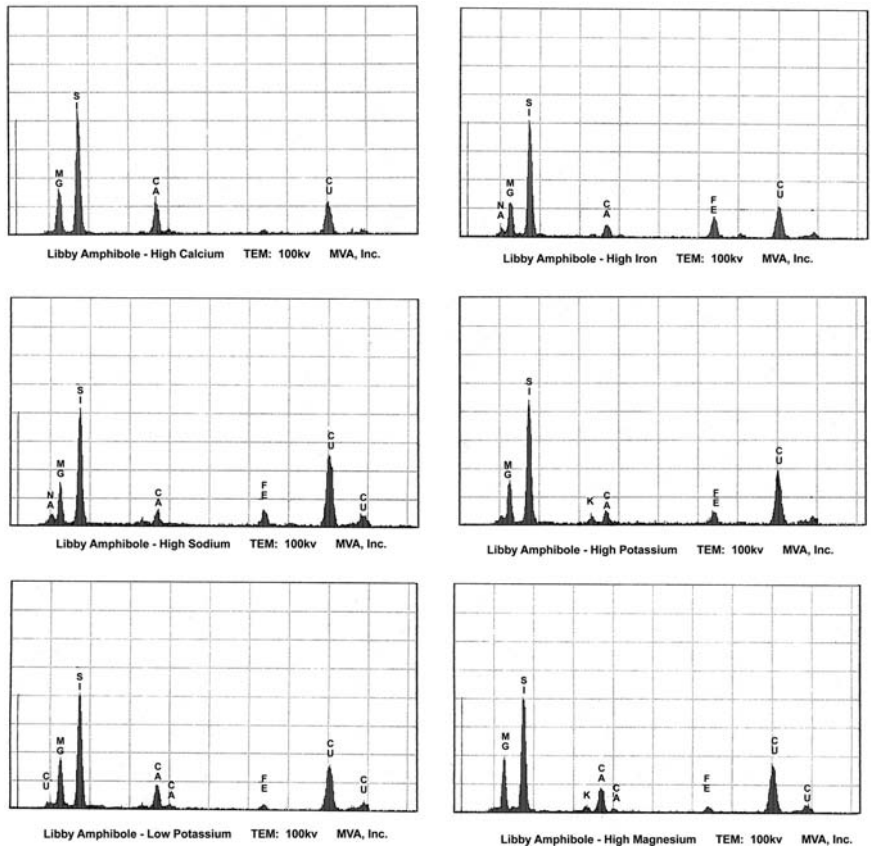

Figure 2.13 EDS x-ray spectra for Libby amphiboles.

spectra from several Libby amphibole fibers are similar to tremolite or actinolite reference materials but differ in small amounts of sodium and potassium.

ACKNOWLEDGMENTS

The author would like to thank Bryan Bandli, Randy Boltin, Pronda Few, Al Harmon, Whitney Hill, Bill Turner, and Beth Wortman for their help in providing figures and editing assistance for this chapter.

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CHAPTER 3

Analysis and Relevance of Asbestos Burden in Tissue

Ronald F. Dodson

CONTENTS

3.1 RESPIRATORY SYSTEM AND WHY IT IS VULNERABLE TO INHALED DUST

To appreciate the significance of asbestos in body tissues, it is first relevant to understand how it got there and normal functioning of the major portal of entry for dust

into the body — the respiratory system. The design of the respiratory system has evolved into highly functional anatomical regions. The upper airways are designed to warm, moisten, and filter the incoming air. These can be thought of primarily as conducting tubes or conduits for two-directional airflow. In the ideal situation, the first contact with the external air is as it passes through the nasal cavity. As with the other conducting passage ways, the nasal chambers create directional changes in air flow (via the angular changes in the passages) and are provided at initial levels with hairs to further initiate turbulence. During exercise or talking, humans shift to "mouth breathing," thus bypassing the nasal passages and the inhaled air as well as its dust component goes directly through the mouth to the trachea. There are some 32 branches of the conducting airways in the normal adult lung before reaching the distal acinus.[1] This anatomical branching impacts on the direction of air flow, which further serves to increase the potential for dust entrapment. This is due to the fact that any deviation in the direction of air flows, particularly when it creates "whirlpools" or changes in velocity of flow, increases the chances of sedimentation to occur among the suspended dust particles. These currents can also induce perpendicular flow to the walls of the airways, which result in the dust being brought into physical contact with the surfaces. The result of this anatomical design combined with the fact that most surfaces of the conducting ways are lined with "sticky" substances results in highly efficient entrapment of many inhaled particles in the upper airways. The entrapment of larger particles on the mucosa (lining) of the major bronchi is especially prominent where both the direction of flow and air velocity change abruptly.[1] Lippmann et al.[2] have reviewed this process and noted that the result of decreasing airway sizes distally, combined with the increasing number of tubes in total cross-section, results in decreases in air velocity. The impact of these physical events is that the larger particles get deposited by impaction. At the level of the smallest airways, where there are the lowest velocities, the particle entrapment is via sedimentation and diffusion.[2]

The importance of entrapment of inhaled dusts in the conducting airways is critical in preventing it from reaching the lower respiratory tract and potentially compromising the functional respiratory units of the lung. The lung is particularly vulnerable to the toxic gases and dusts in the environment as it represents the largest surface within the body exposed to the external environment.[3] The lungs are responsible for providing oxygen to all cells in the body and for elimination of carbon dioxide produced by these cells. The critical impact of the lungs on the well being of all parts of the body is emphasized by Witschi[3] in that it is the "only organ in the body in man to receive within 1 minute from one to five times the circulating blood volume." To achieve this objective, the normal lung "filters about 12,000 l of air per day to 'extract' the fuel needed for survival"[4] and is perfused with more than 6,000 l of blood per day to permit normal gas exchange critical for cellular function.

The functional unit that makes up the majority of the lung parenchyma is the terminal and respiratory bronchioles and the alveoli or air sacs that give the lung its sponge-like appearance (Figure 3.1 and Figure 3.2). Ochs et al.[5] reported that the average number of alveoli in six adult lungs was 480 million. Weibel[6] equated this very large internal surface as being nearly that of a tennis court. This

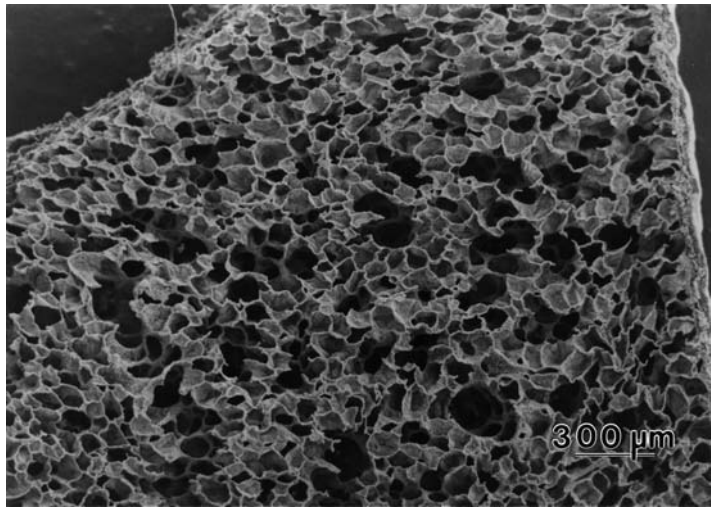

Figure 3.1 The lung parenchyma as seen in this lower magnification scanning electron micrograph shows the three-dimensional morphology of the alveoli, smaller airways, and associated circulatory components that result in the lung appearing to be comprised of small sack-like structures.

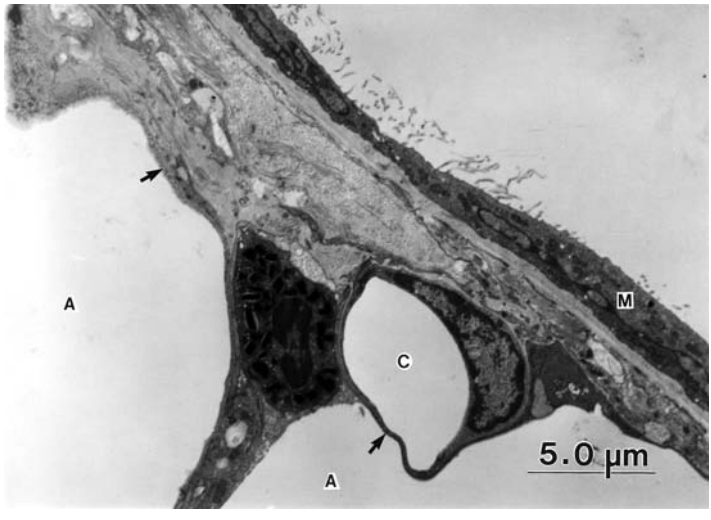

Figure 3.2 This low-magnification transmission electron micrograph shows the thin visceral pleura surface consisting of a layer of mesothelial cells (M). The alveoli (A) are lined by type I (arrow) and type II pneumocytes. A cross-section through an interstitial capillary (C) shows the close association between the vascular space and the alveolar spaces.

surface is designed to be relatively sterile, and inhaled materials are prevented from reaching this level only if the previously described entrapments at the upper airways remove the inhaled particulates. Turino[7] appropriately described the lung parenchyma as a "dynamic matrix" comprises predominately of collagen, elastin, glycosaminoglycans, and fibronectin. The appropriate balance of these components combined with the proper functional capabilities of the cells, which make up the lung parenchyma, are critical for a healthy lung. Response to inhaled dusts can acutely or chronically alter the balances and result in reduced lung function and a permanent loss of respiratory functions.

3.2 DUST ELIMINATION FROM THE LUNG

The potential for dust entrapment in the larger airways has been discussed. The result of this upper airway defense mechanism is that the majority of dust particles larger than 3 μm in diameter never reach the alveolar surfaces.[8] Gross and Detreville[8] projected the defense mechanisms of the lung function at a level of 98–99% efficiency. The inefficiency of 1–2% accounts for the resultant development of pneumoconiosis (dust diseases). The defense mechanisms of the lung are divided between levels of anatomical divisions. The conducting airways are lined with a sticky blanket of mucous. Columnar lining cells making up a part of the surface lining of the larger conducting airways have specialized hair-like extensions from their surfaces called cilia. There are several hundreds of these per cell and their role is to expedite the movement of the mucous layer and entrapped particulates from the level of deposit to the next higher levels toward the pharynx for elimination as a component of sputa. The cilia beat approximately 1000 times/min in a coordinated scheme to assure rapid upward movement of the surface layer and any entrapped materials.[9] The combination of the mucous and cilia form a critical clearance mechanism from the lung often referred to as the mucocilary escalator.

The final level of the respiratory tract consists of the alveoli that comprise the majority of the lung parenchyma. These fragile appearing air sacs consist of thin-walled structures formed by the close apposition of a cytoplasmic extension of an epithelial cell on the airway side, an area of basement membrane, and the thin wall of the smallest circulatory blood vessel in the body — the capillary. The extremely thin wall of this region gives it a "spider web" appearance in sections when viewed by light microscopy. It is specifically designed anatomically to permit the easy exchange of gases from the air–blood–air compartments. The morphological appearance of the delicate nature of the wall of this structural unit at the light microscopy level led some to consider it initially to be acellular. In reality, the components of the two cell types which populate the air–blood barrier (Figure 3.3 and Figure 3.4) form a total thickness ranging from 0.2 to 0.5 μm, which is up to 20 times thinner than a sheet of airmail paper.[4] For proper gas exchange to occur, these sacs must remain open, with minimal congestion and the normal wall structure is maintained to assure flexibility as needed for contraction and expansion. The surfaces of normal alveoli are protected from foreign material by the previously

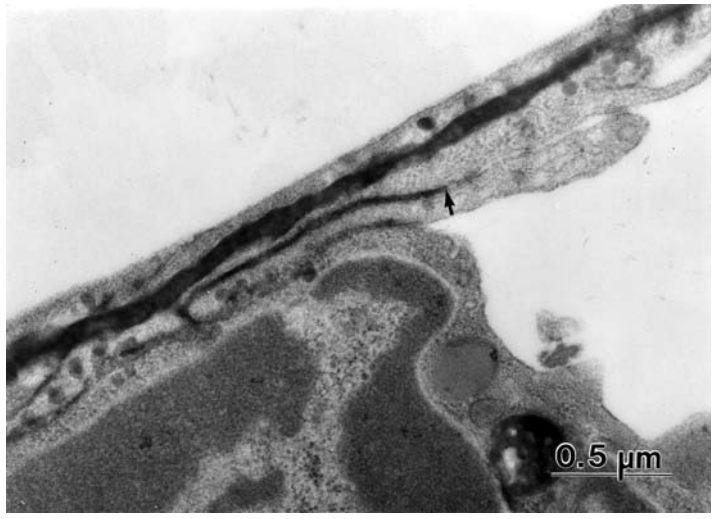

Figure 3.3 This transmission electron micrograph shows the boundaries of the alveolar–air/blood barrier. The dark material illustrates the penetration of the tracer horseradish peroxidase to the level of the junctions between the alveolar cells (arrow) that prevents its leakage into the airway.

described defense filtrations that occur in the conducting airways. The alveolar surfaces are ideally maintained in a sterile state. In normal tissue, secreted glycolipoprotein (surfactant) from type II alveolar cells assists in assuring a low surface tension on the surface of the alveoli and helps prevent it from collapsing at low

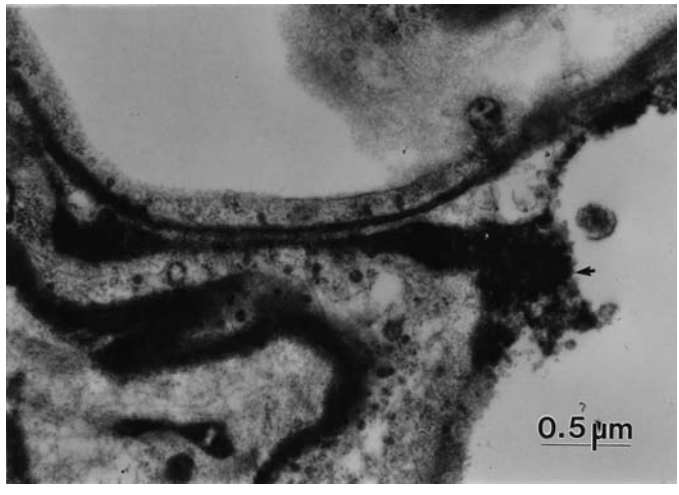

Figure 3.4 In contrast with the micrograph shown in Figure 3.3, the air/blood barrier in this section from an experimental animal model shows the leakage of horseradish peroxidase (arrow) through the barrier onto the surface of the alveolar sac. The change was induced as an early response to asbestos exposure.

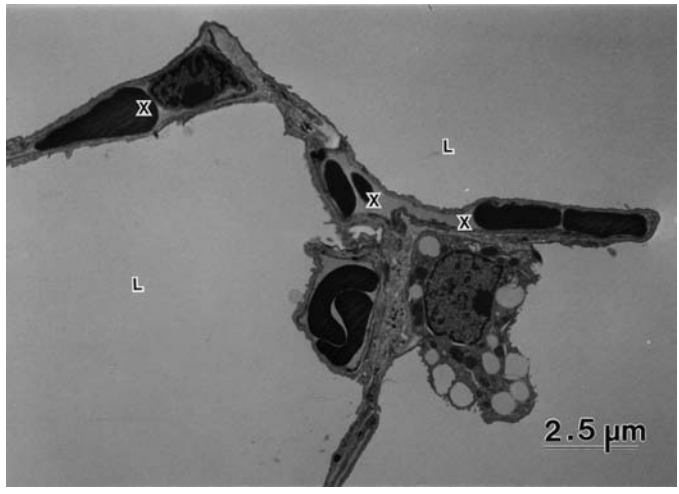

Figure 3.5 The delicate architecture of the alveolar level is shown in this transmission electron micrograph. The thin cellular separation between the blood compartment-capillary (X) and the alveolar lumen (L) facilitates efficient and critical gas exchange between the two compartments.

lung volumes (Figure 3.5).[10] If congestion occurs in the air sacs as a result of the inflammatory response of defense cells to inhaled particulates or if the walls of the sacks become thickened so that gas exchange is difficult, their functional state as the major respiratory units in the lung are compromised.

Particulates that reach this lowest level of the respiratory system represent a population of the smallest structures in the inhaled dusts. These have successfully bypassed the upper level defense mechanisms and reached a respiratory level where clearance is less effective.

The primary response to dust particles that reach the alveoli is a "call up" of macrophages. These defense cells migrate from the interstitium onto the surface of alveoli. The cells convert to a form capable of functioning in an aerobic environment and display chemotaxis features that permit them to move along the alveolar surface to deposited particulates (Figure 3.6). Macrophages are the major defense mechanisms of the lower respiratory tract and function by attempting to clear the alveoli of infectious, toxic, and allergic particulates that have evaded the mechanical defenses of the nasal passages, glottis, and mucociliary transport system.[11] Pulmonary macrophages attempt to ingest and isolate foreign particulates (Figure 3.7) and contain internal chemical packages that work to denature or "digest" some ingested microorganisms. Macrophages have been attributed to having a life expectancy of weeks or months.[12] A population of macrophages is also capable by some yet to be understood mechanisms, of relocating to the surface of the more proximal levels of the airways where the more rapid clearance of macrophages and their phagocytized dust particles occur via the mucociliary escalator. Camner et al.[13] studied the efficiency of clearance

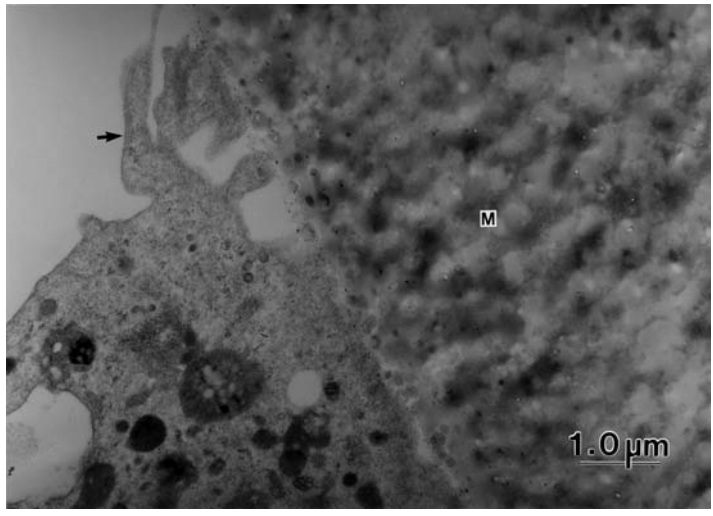

Figure 3.6 This micrograph illustrates the cross-section of an activated macrophage that has been cultured on medium (M). The stimulated macrophage shows surface projections (arrow) that extend from the cell surface and provide the mechanism by which the cells move toward a stimulus either on culture medium or in tissue.

for various sized particles and found that the deeper the particulates were inhaled, the longer the time was required to clear them from the lung.

The average retention after 24 h was around 100% for particles deposited in generations 13–16 (ciliated bronchioles) and around 20% in generations 0–12

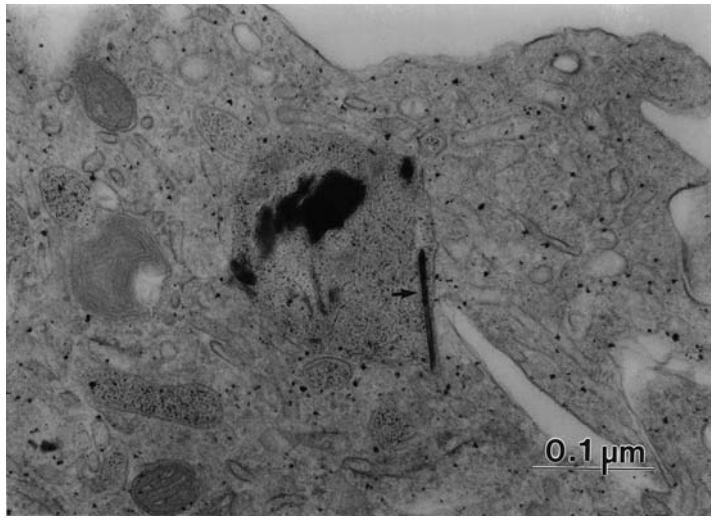

Figure 3.7 This small amosite fiber (arrow) in this transmission electron micrograph is being isolated within a sidersome of a macrophage.

(both large and small ciliated airways). It should be recognized that clearance is an ongoing event, thus periods of elevated dust accumulation may not be totally represented by tissue burden at the time of sampling, particularly if the period from last exposure has covered an appreciable period of months or years. The impact of smoking and asbestos as combined causal agents of disease in man is discussed in appreciable detail in the section on clinical issues. However, it is appropriate to note that exposure to tobacco smoke alters the cellular composition of the upper airways (resulting in squamous cell metaplasia and goblet cell hyperplasia) and negatively impacts on the effectiveness of the mucocillary escalator to properly function. Thus, clearance in a smoker of all types of dust including asbestos[14,15] is less efficient than that in a nonsmoker.[2] Churg and Stevens[16] found that in the case of asbestos-exposed individuals, asbestos recovered from the airway mucosa or parenchyma of smokers was shorter than that in nonsmokers. They concluded smoking lead to enhanced retention of short fibers. The other observation is a given that many more short fibers were cleared over time in an individual if they had not had compromised clearance.

3.3 DUST OVERLOADING AND THE IMPACT ON THE RESPIRATORY TRACT

The process as described for clearance from the lung represents the ideal response to dust inhalation and its rapid elimination from the lung. In many instances, exposure to dust can result in periods of "dust overloading" of the defense mechanisms.[17–20] This phenomenon is due to alterations in the capabilities of macrophages to respond to the dust burden partly because of overwhelming the phagocytic component and the number of macrophages stimulated to meet the elevated burden of inhaled dust. This results in "macrophage congestion," congestion at the level of the alveoli and small airways. This results in some macrophages not being able to leave the congested area. These phagocytic cells eventually die and release the ingested particulates which in turn triggers an influx of more phagocytic cells in response to the freed dust. Oberdorster[17] suggested that impaired alveolar macrophage-mediated lung clearance and the accumulation of high levels of pulmonary dust can result in adverse chronic effects including inflammation, fibrosis, and tumors. For example, it has been shown that poorly soluble, nonfibrous particles (carbon black, coal dust, diesel soot, nonasbestiform talc, and titanium dioxide) elicit tumors in rats when deposition overwhelms the clearance mechanisms of the lung creating the condition of overloading.[21] The impact of elevated dust burden and the risk of developing permanent pathological changes in the respiratory system lie in part with the level of inherent toxicity associated with the accumulated dust. There is increasing appreciation that the same macrophages that provide front line defense in the lower respiratory system carry a liability for inducing injury to lung tissue. The macrophage is a cell type characterized by Brody[22] as being on the "one hand a potential defender of the alveolar environment and on the other hand as a central mediator of lung disease." Simplistically, the surfaces of alveolar

sacs in the ideal state are devoid of cells and debris and when inhaled dust such as asbestos stimulates the call up of macrophages and neutrophils[23,24] the balance of the alveolar environment changes, potentially resulting in long-term or permanent pathological changes. The anatomical area that normally consists of open spaces for gas exchange becomes filled with defense cells. As the macrophages interact with the inhaled dust the potential exists for there to be a release of oxidants,[25,26] chemo attractants for other inflammatory cells,[27,28] proteases,[29,30] and growth factors that stimulate fibroblasts to replicate from these cells[31–33] and secrete collagen.[34] The latter two events are pivotal in the induction of fibroproliferative disorders in the lung such as intraalveolar/interstitial fibrosis[31] or in the case of asbestos-induced fibrosis-asbestosis. Bowden[35] reported these combinations of deleterious events associated with macrophages in the lung are direct contributors to the development of emphysema and interstitial fibrosis.

Secretions from macrophages occur in the normal process of phagocytois of bacteria, virus, or dust particles. However, if the dust particulates are particularly toxic the macrophage may be killed and the release of internal chemicals occur immediately. If dust overloading occurs the macrophages may not be able to escape from the airway due to lack of clearance and when the macrophage reaches the end of its life expectancy release the dust (which triggers the call up of more macrophages), enzymes, and other chemicals that negatively interact with the cell wall and adjacent cells. Such a scenario would be expected to occur with generation after generation of newly attracted macrophages and thus result in a constant reinforcement of the negative events as described earlier. In part this concept should be considered as a factor in the continuing development of fibrosis in an asbestotic lung, which can progress long after the individual's contact with asbestos had ceased. Thus, as summarized by Brain,[36] "though the macrophages serve as the first line of defense for the alveolar surface, they may also be capable of injuring the host while exercising their defensive role."

3.4 RELOCATION OF PARTICULATES FROM THE LUNG VIA THE LYMPHATICS

The most efficient mechanism for dust clearance from the lung follows a pathway back up the same route as it entered the airways by the mechanisms described. However, there is another route for clearance or relocation of particulates from the lung and that is by the lymphatic drainage into the lymph nodes via the lymphatic channels.[2,37–42] This translocation to the lymphatics and lymph nodes has been attributed in part by Cullen et al.[43] as a consequence of dust overloading. The logic of this explanation is that clearance of dust from the deep lung is impaired. Relocation of dust from the lung to the lymph node and the lymphatic drainage has resulted in these sites becoming "reservoirs of retained material" or in the case of the nodes as "repositories for dust."[8,44] With sufficient dust accumulation the lymph nodes become "densely mineralized and stony hard."[8] If dust accumulated in the nodes has appreciable cytotoxicity, pathological changes can occur

including the formation of nodules.[45] This same route through the lymphatic system has been suggested as the mechanism by which asbestos fibers relocate to extrapulmonary sites.[46,47]

3.5 MORPHOLOGICAL FEATURES OF ASBESTOS THAT DETERMINE ITS POTENTIAL FOR INHALATION

Asbestos minerals have been used by intent in more than 3000 commercial applications.[48] Asbestos is sometimes a component of minerals mined for many different products that are considered as not containing asbestos or having less than a "regulated percent of content 1%" which trigger the definition of asbestos-containing material. Thus, millions of individuals are exposed to asbestos-containing products in the workplace or thorough secondary or bystander exposures from occupational settings.

The widespread use of asbestos results from their unique properties including high tensile strength, flexibility, insulating properties, fire resistance, and resistance to strong chemicals — both alkaline and acids.[49] These attributes in the past made asbestos an important commercial contributor to the economic development of industrialized societies.[50] The problem arises when asbestos is disturbed, resulting in the fibers breaking down into respirable-sized dust particles. This fibrous dust is easily inhaled and can cause pathological damage to the lung (e.g., lung cancer) and extrapulmonary sites in the body including cancer (e.g., mesothelioma).[51]

The term asbestos refers to a group of six different fibrous forms of minerals and is generally used in society as a generic nomenclature. The mineral name and the name given to the asbestos and nonasbestos form or anthophyllite, actinolite, and tremolite are the same. The most widely used form of asbestos in commercial applications (90–95%) is chrysotile, which is a serpentine form of mineral.[52–54] The other five forms of asbestos (amosite, crocidolite, actinolite, tremolite, and anthophyllite) are the asbestiform habits of the amphibole family of minerals groups. The nonfibrous form of these minerals can break along cleavage lines and create elongated cleavage fragments[55] that are sometimes confused with the fibrous form. Although an indepth discussion of the differentiation between the cleavage fragment and asbestiform habit is outside of the scope of this chapter, suffice it to say that the former are not considered "asbestos" under the definition of regulated fibers. This is not to imply that cleavage fragments of these minerals may not carry their own risk to health if sufficient numbers are inhaled.

Amosite and crocidolite were used in commercial applications in the United States while only a limited utilization of anthophyllite occurred. In the past, actinolite, temolite, and anthophyllite have been considered "noncommercial asbestos types." However, their presence in products such as vermiculite and talc provide a vehicle for their widespread use even if often less-intense exposures as those encountered by exposure to commercial forms of asbestos. Tremolite asbestos is considered as a mineral component (often referred to as a contaminant) of Canadian

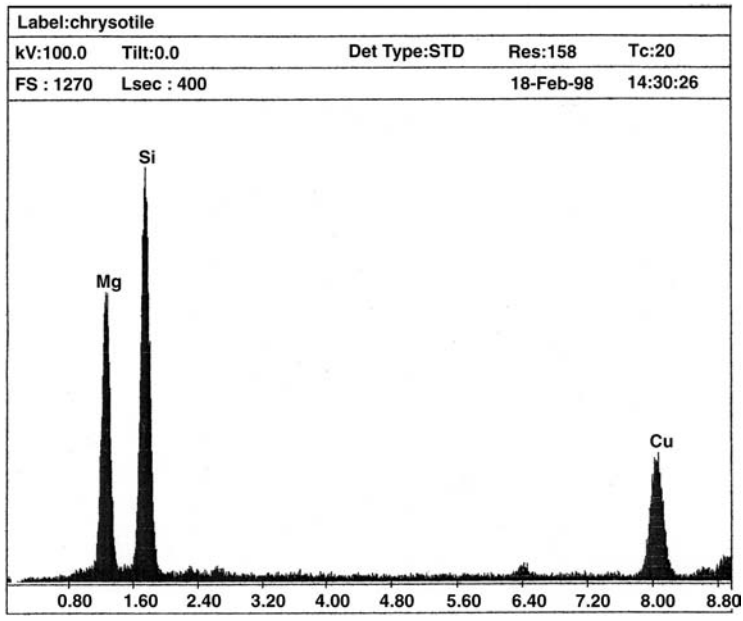

Figure 3.8 This x-ray energy dispersive spectrum (XEDS) illustrates the major elemental components of chrysotile–silicon and magnesium. The copper spike is from the grid that supports the sample preparation.

chrysotile asbestos[48] and is suggested by some investigators to be an important factor in diseases associated with the exposures of Canadian chrysotile.

All types of asbestos have a silicon tetroxide (SiO_4) tetrahedral as backbone of the crystal lattice. Chrysotile is a magnesium silicate (Figure 3.8) that is assembled in nature with the layers of linked silica tetrahedral alternating with the layers of the magnesium oxide–hydroxide octahedral (brucite). The double layering in this type of structure rolls up onto itself to form hollow tubes or scrolls that are characteristic of chrysotile. The impact of this internal organization as reflected in the physical features of the fiber is that the longer the fiber becomes, the more likely it is to coil or curl (Figure 3.9). Thus, the fiber when seen in cross-section displays a true diameter at any one point, which is thinner than the functional diameter of the fiber in an air stream. This greater functional diameter in a potentially air stream results in the reduction of inhalation of longer, more curved, fibers. The amphiboles, on the other hand, contain aggregates of cations (calcium, sodium, iron, and magnesium) between the strips of linked silica tetrahedral in the form of parallel chains (Figure 3.10–Figure 3.12). The variations of the percentage and types of cations determine the type of amphibole asbestos. All amphiboles tend, because of the repeating crystalline units, to be straight even as the fiber (crystal) increases in length (Figure 3.13). Thus, the functional diameter tends to be similar to the actual diameter in an air stream. It is therefore easier to inhale longer fibers of amphiboles than equivalent length longer fibers of chrysotile. This difference

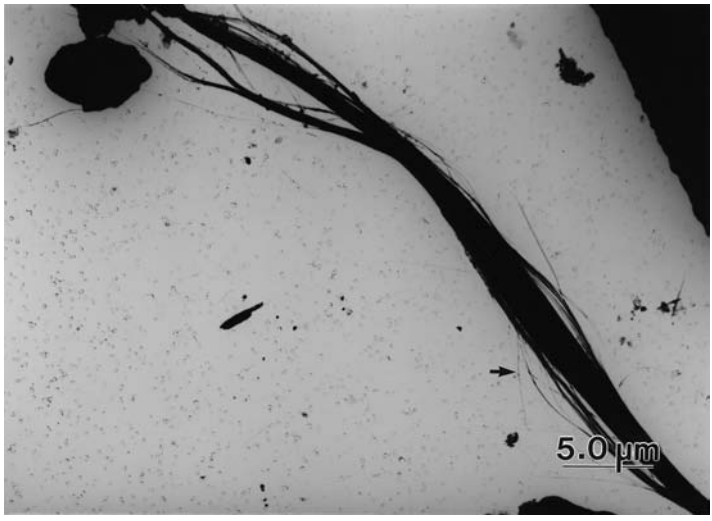

Figure 3.9 The large bundle of chrysotile fibers was obtained from digested lung tissue of a chrysotile miner. The curved morphology of the chrysotile is evident even in this large bundle. There are number of areas on the bundle which show the fraying characteristic that can result in separation into smaller units including separation to the fibrillar level (arrow). (Tissue provided courtesy of Dr. Andrew Churg).

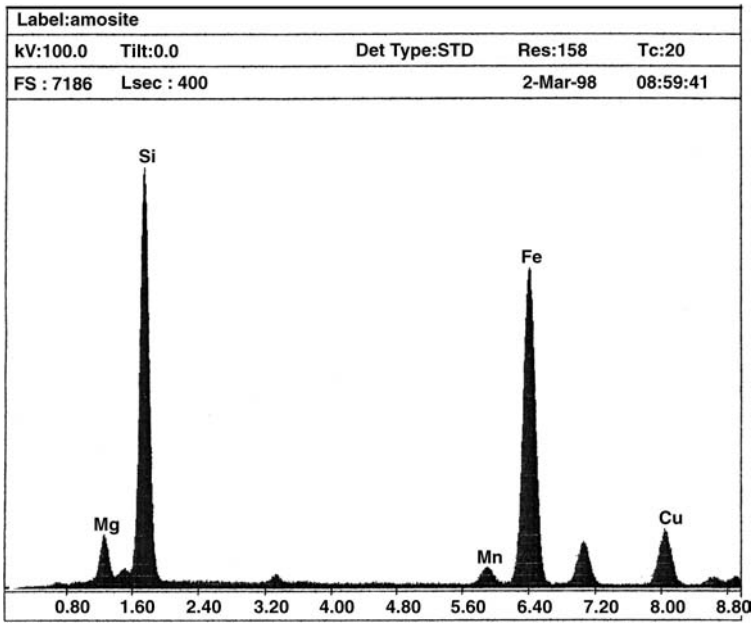

Figure 3.10 This XEDS shows the elemental composition of a major commercial amphibole, amosite asbestos that is a ferromagnesium silicate.

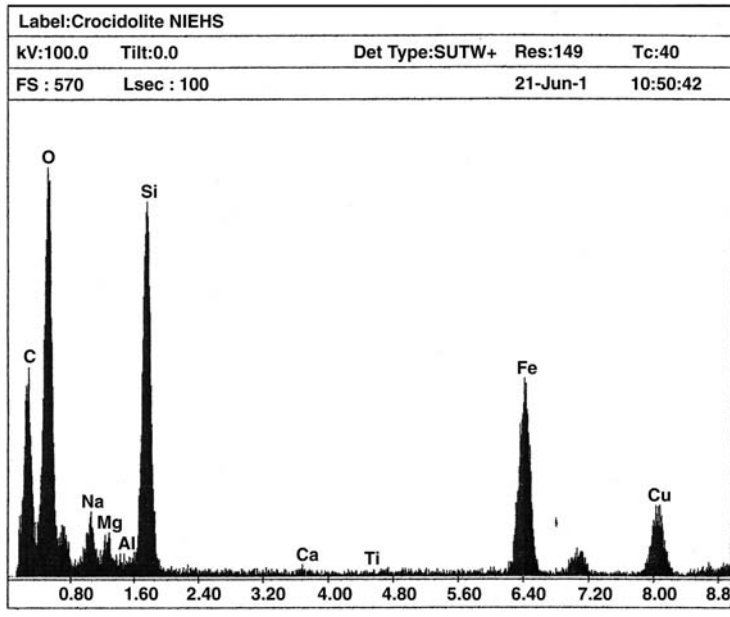

Figure 3.11 This sample of crocidolite (commercially used blue asbestos) was obtained from the National Institute of Environmental Health Sciences and illustrates the usual elemental composition of this type of asbestos as a ferromagnesium silicate with a sodium (Na) component.

alone favors the retention of amphiboles in the lung as short or small entities are more rapidly cleared.[56] There are also important differences in surface charges associated with the differences in composition of the different types of asbestos as has been discussed by Hamilton,[57] Valerio et al.,[58] and Xu et al.[59] Likewise, there are differences in surface cations among the amphibole forms, which result in variations in potential for chemical reactions to occur. Some reactions can produce byproducts including radical formation. These features are discussed in greater detail in the chapter on molecular mechanisms of asbestos interactions with cells and the lung milieu.

The significance of asbestos to become a respirable dust is inherent in that the fibers and bundles can dissociate into shorter or thinner units during traumatic disturbance such as can occur in airflow or exerted physical pressure. The upper limits of respirability in humans has been given for a rounded structure as <10 μm[60,61] and for a fibrous particulate as <3.5 μm.[60] The potential for inhaling fibrils (the thinnest unit structure) is evident when recognizing that the measurement for such structures for the most commonly used commercial types of asbestos are, respectively, chrysotile (0.02–0.08 μm), amosite (0.06–0.35 μm), and crocidolite (0.04–0.15 μm). It is evident that bundles or fibers comprised of multiple fibrils are well within the respirable range for fibrous dust (Figure 3.14). It should be recognized that the filtration and entrapment processes as described earlier results

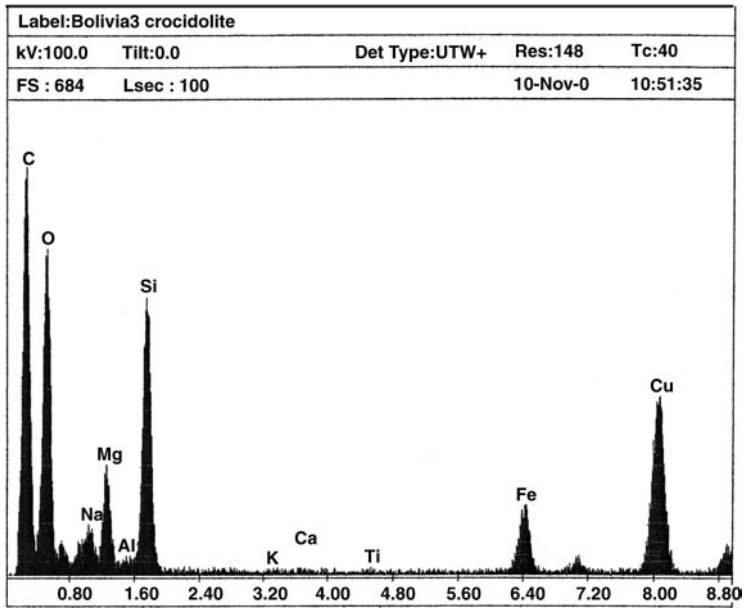

Figure 3.12 The XEDS illustrates the variability of the elemental composition of amphiboles, which can occur in different mineralogical formations. The crocidolite analyzed in this spectrum is referred to as "Bolivian Blue" and illustrates different magnesium to silica ratio when compared with the standard South African crocidolite illustrated in Figure 3.11.

in many of the fibrous particulates being trapped higher up the respiratory system and rapidly eliminated. However, the potential for inhalation is a relative issue based on the overall numbers common in many exposures to fibrous dust as these are distributions in sizes (diameters) that can comprise the aerosolized dust in the individual's breathing zone. Smaller diameter and shorter fibrous particulates are more readily inhaled and to a greater depth in the respiratory system.[62]

3.6 FERRUGINOUS BODIES IN TISSUE

The term ferruginous body means "iron-rich" body. These structures when found in lung tissue are indicators that the defense cells of the lung — the alveolar macrophages, have interacted with a particulate and deposited an iron-rich coating on its surface. If these structures are created on asbestos fibers they are appropriately called "asbestos bodies." The first reports of these golden brown structures in lung tissue was by Marchand in 1906.[63] However, it remained for the relationship of these structures as a result of exposure to asbestos to be first recognized by Cooke in 1929[64] who used the name "curious bodies." In 1931, Gloyne[65] proved the cores of these structures were asbestos fibers by exposing guinea pigs to asbestos dust and after 6 months

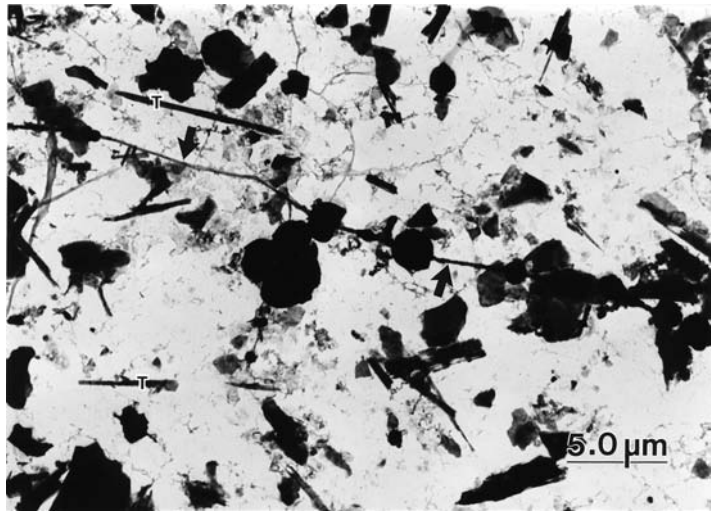

Figure 3.13 The long chrysotile cored asbestos body shown in the center of the photograph (arrow) illustrates tendencies in several areas for a curvature to occur in the fiber. This contrasts with the straight fibers seen as uncoated tremolite asbestos (T) within the field. This sample was from an individual who had been a chrysotile asbestos miner exposed to both chrysotile and tremolite in their work environment. (Material courtesy of Dr. Andrew Churg)

finding varying degrees of maturing bodies in their lungs. He also reported that one such body was found in the lung tissue of a gray rat caught on an asbestos factory premises. There is universal agreement that the coating that forms on asbestos fibers is deposited through interactions with macrophages (Figure 3.15). In 1970, Davis[66] reported in animal models that the "first coating material of the asbestos bodies seems to be some form of acid mucopolysaccharide, but this coating soon becomes impregnated with ferritin or hemosiderin to form the well-known Perls-positive bodies." In 1972, Governa and Rosanda[67] suggested mucopolysaccharides might act as a matrix for iron deposition on the coating (Figure 3.16). Not all animal species readily form asbestos bodies, if at all,[66] while the efficiency of the formation of such bodies in man also vary between individuals.[68–70]

The common link in stimulating the formation of asbestos bodies in tissue is asbestos fibers longer than 8 μm[71] with diameters and surface irregularities also suggested as playing a role because asbestos bodies represent only a portion of the longer fiber burden within the tissue at a given time.[69]

It should be noted that other fibrous and nonfibrous inhaled structures stimulate formation of ferruginous bodies. Gross et al.[72] introduced the term "pseudo-asbestos bodies" or "unusual ferruginous bodies" to designate these structures. Fibrous aluminum silicate, silicon carbide whiskers, cosmetic talc, and glass fibers can stimulate ferruginous body formation in animals.[73] Holmes et al.[74] used sized fiberglass to stimulate "pseudo-asbestos body" formation in hamster lung. In human tissue, Churg and Warnock[75] reported ferruginous bodies were found on

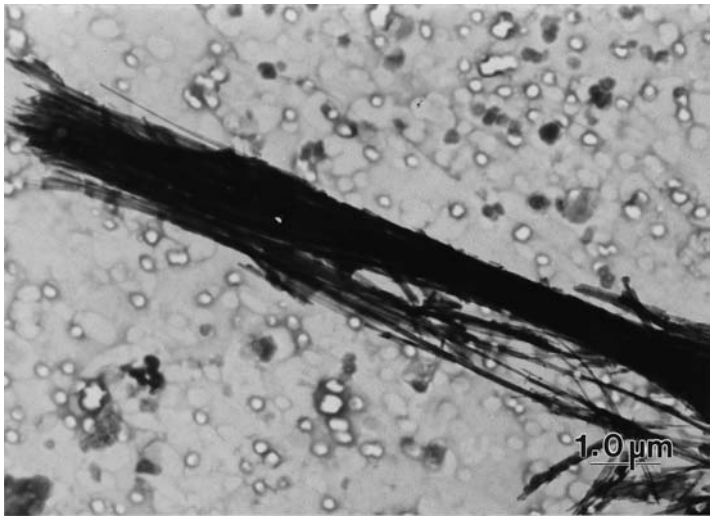

Figure 3.14 This bundle of chrysotile asbestos was isolated by digestion techniques from an occupationally exposed individual. The disassociation of the bundle into smaller units including fibrils is evident in the micrograph.

cores of sheet silicates (talc, mica, or kaolinite) and carbon. Dodson et al.[76–78] demonstrated ferruginous bodies from human material could form on iron-rich fibers, carbon filaments, fibrous talc, and various sheet silicates (Figure 3.17–Figure 3.20). It initially may seem that the previously mentioned types of

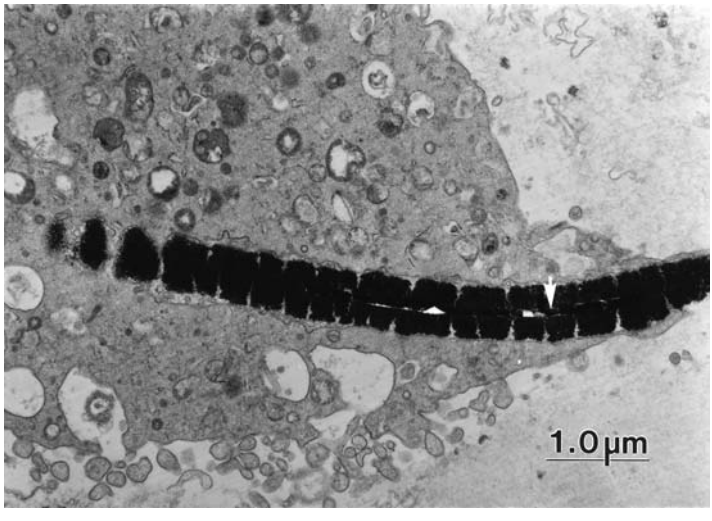

Figure 3.15 The section of the asbestos body seen in this field is surrounded by a macrophage. The asbestos fiber is in the center of the body (arrow) is surrounded by the iron–protein coat deposited through surface interactions with macrophages.

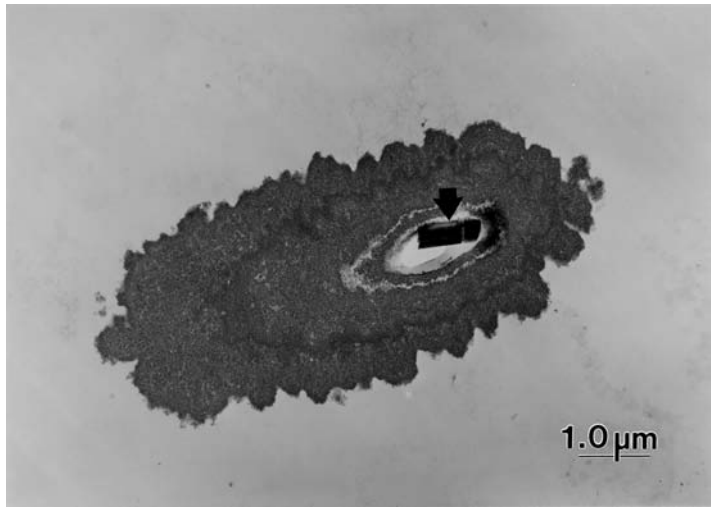

Figure 3.16 This cross-sectional view of an asbestos body reveals the central asbestos core (arrow) as surrounded by layers of iron-rich coating.

ferruginous bodies would make it difficult to differentiate an asbestos body by light microscopy. Churg[70] correctly observed that when a ferruginous body seen light microscopically as a beaded structure formed on a clear, elongated, transparent, usually straight core, that structure is with a high degree of certainty an asbestos body. In fact, a trained reader can easily distinguish the vast majority of nonasbestos ferruginous bodies by use of the light microscope. Asbestos bodies have been found

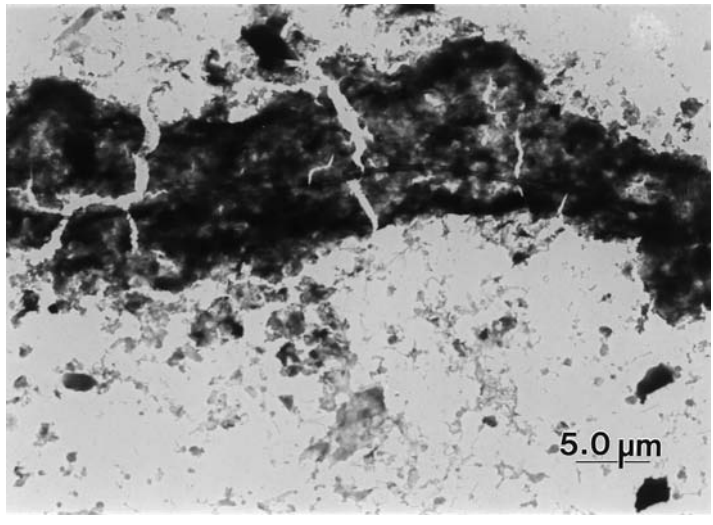

Figure 3.17 The ferruginous body seen in this field is formed on an iron-rich fiber (arrow).

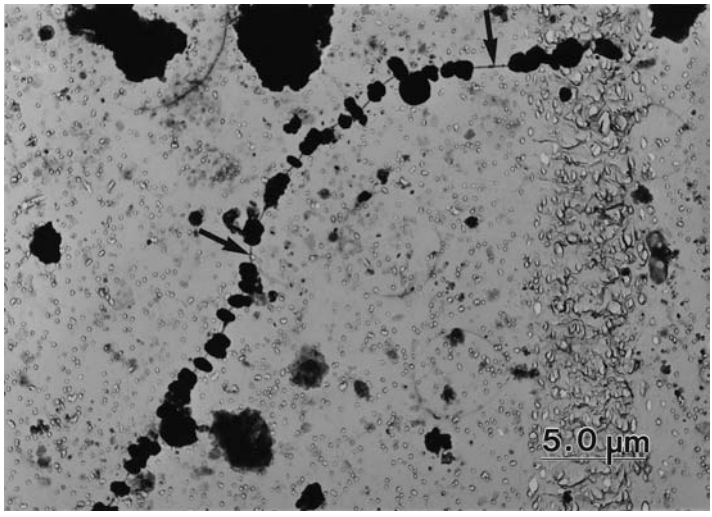

Figure 3.18 The core of this ferruginous body is formed on a graphite (organic) filament (arrow).

in tissue outside of the lung.[79,80] The most common location for such observations has been the lymph nodes.[81–83] The question raised was if asbestos bodies could form in extrapulmonary sites on uncoated asbestos fibers relocated from the lung or were they relocated as mature bodies. In a study from our laboratory, a guinea pig model was used to compare the coating efficiency of fibers introduced into the lung tissue as compared with reactions to fibers from the same preparation

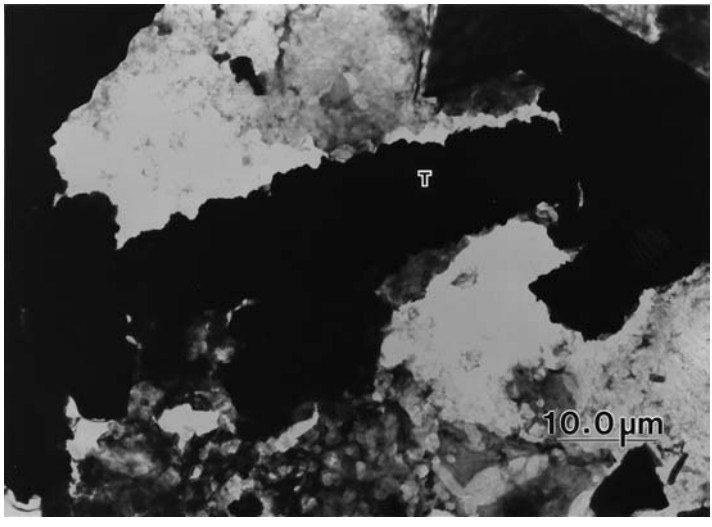

Figure 3.19 A talc fiber (T) forms the core material of this ferruginous body.

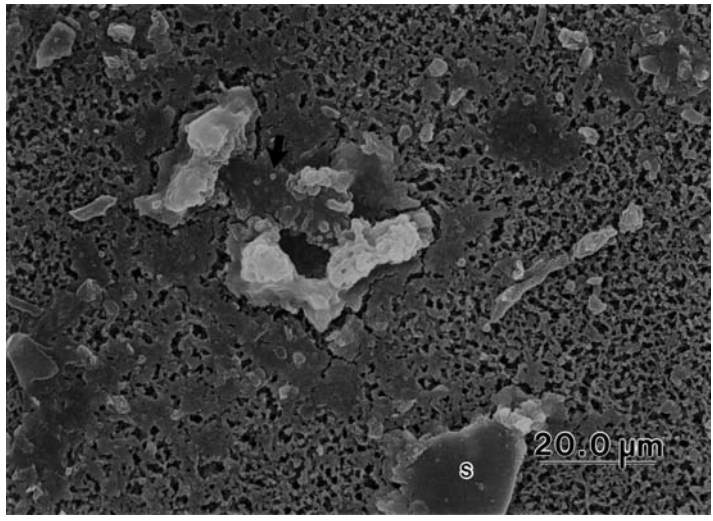

Figure 3.20 The ferruginous bodies seen in this scanning electron micrograph indicate that ferruginous coatings can occur on nonfibrous dusts. One of the bodies was formed on a central core of a thick rectangular dust particle (arrow) while the second ferruginous body was formed on a "plate-like" silicate (S) particle.

injected into the spleen and liver.[84] The liver and spleen were found to independently have the capability to produce ferruginous bodies but at a much less efficient rate than the lung.

The presence of asbestos bodies in a tissue section is an important indicator of past asbestos exposure. The Pneumoconiosis Council of the College of American Pathologists and the National Institute for Occupational Safety and Health stated the "minimal criteria that permitted the diagnosis of asbestosis in tissue were demonstration of discrete foci of fibrosis in the walls of respiratory associated with the accumulations of asbestos bodies."[85] Crouch and Churg[86] in recognizing the relative insensitivity of tissue sections for detection of ferruginous bodies stated, "the demonstration of a single asbestos body on casual inspection of several lung sections implies asbestos exposure many times above background." Compounding the issue of using tissue sections for the identification of asbestos bodies is that the plane of section may only strike one level of the body and not permit visualization of the core material or if the structure is formed on an elongated core.

3.7 OTHER METHODS FOR SAMPLING TISSUE FOR THE ASBESTOS BODIES AND UNCOATED ASBESTOS FIBERS

Although light microscopic evaluation of tissue sections in determination of pathological processes is important, histologic evaluation of tissue sections is a relatively

insensitive method for determining asbestos body and fiber concentrations. Thus, a method that offers an expansion of the amount of tissue sampled involves destruction of relative large amounts of tissue and collection of the particulates from that tissue on a flat surface for analysis. Some techniques used for tissue sampling include sample filtration,[87] low-temperature ashing,[88] and high-temperature ashing.[89] Additional options for tissue destruction include digestion with ozone,[90,91] strong bases,[92,93] and hydrogen peroxide.[94–96] It is important that any tissue preparation where tissue is destroyed avoids inducing sufficient trauma to cause ferruginous bodies to fragment or asbestos bundles to dissociate into smaller units resulting in a falsely elevated asbestos tissue burden.[97–99]

Allowing lung tissue to dry before processing may result in ferruginous body or fiber breakage.[92] To safeguard against this occurrence, it has been recommended that two separate samples are taken from each site (when adequate tissue permits). One sample is completely dried and the other samples pooled and used for the digestion procedure.[97] This approach permits determination of wet to dry ratio as used in determining ferruginous bodies or uncoated asbestos fiber per gram of wet or dry tissue. If there is no adequate tissue, then the sample is maintained in a wet state and data is given as fibers per gram of wet tissue or deparaffinized wet tissue. Clarification of the sampling scheme as well as the tissue status is critical, if comparisons are to be made with the findings of others. When adequate tissue exists multiple sites should be sampled to compensate for variations in asbestos burden within the tissue. The wet samples are weighed and pooled for digestion. Although it is preferable to use multiple samples to help compensate for errors associated with random sampling often single or several small tissue samples are all that is available. Under such conditions, the use of digestion techniques and the screen of digested material for ferruginous bodies by light microscopy and for uncoated asbestos fibers by electron microscopy offers the best evidence of information about past exposure.[100] If a small sample contains asbestos bodies or fibers, there is an excellent chance that similar "hot" areas are present in the lung. If a small sample is negative then the concern is that random sampling error has resulted in the examination of tissue not representative of the general lung burden.

The method for digesting tissue[101] in our laboratory incorporates a modified Smith and Naylor[102] bleach digestion technique. The procedure permits the maximum disruption of tissue but with minimum trauma to particulates obtained from the tissue through the application of the most "direct" mode of sample preparation. This is in contrast with "indirect methods" of preparations that often involve additional manipulations of the sample. These may include the filter being ashed to remove more organic debris and the redispersion of the material collected from the ashed preparation as a suspension into an additional liquid for redispersion. In the direct method, the tissue is digested with the material collected on the filter remaining in place throughout the additional treatment thus avoiding additional manipulations and possible loss or disruption of asbestos bodies or fibers. This is critical because data based on laboratory suspensions of pure chrysotile asbestos indicate fiber size distribution may be greatly affected by indirect preparation procedures with the greatest impact being an increase number of short fibers

below 2.5 μm.[49] These would not be included in a count of fibers longer than 5 μm even though they may have been this length or longer in the tissue prior to the traumatic influence of the preparative procedures. Thus, the indirect method is suspect of splitting and fragmenting chrysotile fibers, bundles, and potentially ferruginous bodies.

The original bleach digestion procedure works well for some tissues but the development of the modified version was deemed necessary to digest tissue with considerable mucus content thus reducing the amount of residual tissue material trapped on the surface of the filter. This procedure also allows digestion of sputum and lavage material to the degree that ferruginous bodies and uncoated asbestos fibers can be quantified.[103,104] The use of a digested aliquot permits sampling of tissue with the least inherent variation in procedures that could contribute to sampling errors. The procedure used in our facility is to sample a portion of the aliquot for ferruginous body content of the tissue by collecting a measured amount of the solution on a mixed cellulose ester filter. This membrane filter is easily cleared by acetone vapor resulting in a transparent film being left on the surface of a glass slide. This preparation can then be screened by light microscopy for identification of ferruginous bodies. It is critical that the core material of the ferruginous bodies be easily seen to distinguish asbestos bodies from nonasbestos ferruginous bodies. The data from this preparation provides the information used for determining ferruginous body numbers per gram of digested tissue.

A second sample of the aliquot is passed through a smooth surfaced polycarbonate filter (0.2 μm pored). The material is prepared for evaluation by analytical transmission electron microscopy (ATEM). The pore size chosen for the collection of material is critical if one desires to include the smaller and shorter fibers in a count as considerable numbers of short- and long-thin fibers in an aqueous solution can pass through a pore size as small as 0.4 μm in diameter.[105] The counter point is that if the digestion procedure selected has not dissolved the majority of the tissue components, the membrane will rapidly occlude even with a 0.4 μm pored filter. This is of concern when the objective of the preparation is to determine uncoated asbestos fiber burden in the tissue as the residue can easily obscure the smaller and thinner fibers. This issue is of much less concern when the collection of material to be assessed is for asbestos body content because asbestos bodies are large compared with uncoated asbestos fibers. Selected filters from each polycarbonate lot should be screened for inherent contamination by transmission electron microscopy (TEM). This data is used as part of the basis for establishment of laboratory background levels for asbestos in a laboratory. Each solution used in the preparation of the tissue should be prefiltered prior to use to further protect against introduction of asbestos from nontissue sources.

3.8 INSTRUMENTATION USE IN TISSUE ANALYSIS FOR ASBESTOS

A discussion regarding the use of the light microscope in determining asbestos burden in tissue involves two applications. The first is the screening of tissue

sections cut from paraffin blocks mounted on glass slides. As discussed this is an insensitive method and the evaluation of digested material by light microscopy for asbestos bodies on a filter is more sensitive. The use of light microscopy for determination of uncoated asbestos fibers collected from tissue is of limited to no value. Most inhaled fibers are below the level of resolution of the light microscope and those seen can only be categorized as fibers because distinction between fiber types (asbestos and nonasbestos) cannot be made.[62] The more definitive instruments for asbestos fiber identification are the analytical scanning electron microscope (SEM) and the analytical transmission electron microscope.

As pointed out in the Health Effects Institute (HEI) report on Asbestos in Public and Commercial Buildings,[49] "the scanning electron microscope appears at first review to be a suitable instrument for analysis of fibers collected on a filter (in this case from air samples). SEMs are cheaper than analytical transmission electron microscopes, specimen preparations are relatively simple, and they can be equipped with an x-ray energy dispersive analyzer for determination of elemental compositions of particles. They have an acceptable level of resolution to permit identification of the asbestos particles. It is not possible to provide a better description as to the limits of the SEM than provided in the HEI report as quoted below. Detection of a small asbestos fiber on the surface of an air filter, using any type of microscope, requires that both resolution and contrast be sufficient. When the SEM is operated at high magnification, a compromise must be made between image resolution and the signal presented to the image-forming system. This compromise leads to a routine detectability for small diameter fibers on the viewing screen that is often only slightly better than that achieved in the PCOM (i.e., approximately 0.2 μm).[106–110] The full resolution of the instrument can be achieved; permitting the detection of the smallest asbestos fibers, but only if each field of view is photographed using a time exposure of about 1 min or more. To produce real-time images at the magnification required, the beam current must be increased, and at the required high-beam currents, the resolution is degraded.[111] Real-time operation is required, because each fiber must be identified. The image quality can be improved by using heavy metals, such as gold, to coat the surface of the filter, but this coating compromises the interpretation of the x-ray spectra on which fiber identification is based, and may even obscure objects on the filter. Energy dispersive x-ray analysis (EDXA) is the only technique available in the SEM by which fibers can be identified. Identification of fibers by this technique alone has some serious limitations. The approximate chemical composition, derived from an EDXA spectrum, is frequently not sufficient to discriminate between asbestos varieties and some other relatively common minerals.[112] In addition, when attempts are made to identify a fiber by the use of EDXA, contributions to the EDXA spectrum may be made by other particulates close to the fiber under examination. The composite EDXA spectrum thus obtained can lead to ambiguities in identification. Definitive identification of asbestos fibers can often be achieved only by a combination of chemical and electron diffraction data, and this combination of identification techniques is available only in the analytical TEM."[49]

Thus most accurate instrument for determining asbestos fiber types in a sample and appropriately providing their dimensions is the ATEM. The data derived from fibers collected on a membrane filter from an air sample or from a tissue preparation require the same levels of resolution and analytical interpretation provided only by the ATEM. The Asbestos Hazard Emergency Response Act (AHERA) (Title II of the Toxic Substance Control Act 15, U.S.C. Sections 2641–2654) defines ATEM as the "state of the art" instrument and required the use of ATEM for final clearance in many abatement projects in schools. Laboratories as of August 1, 1990 performing analysis for abatement clearance in U.S. schools were required to be accredited by the National Voluntary Laboratory Accreditation Program (NVLAP). This accreditation includes assurance that analysis by ATEM is done consistently and that other labs likewise use the same magnification for analysis, including the same dimension fibers in any count scheme, analyzing the fibers in the same way, and reporting the data in the same way. Another important part of the NVLAP program is that of quality assurance. Steps were described in the earlier section as to how our laboratory carries out quality assurance to insure analysis of the tissue is not altered due to contamination within the laboratory or from other sources. Once particulates to be analyzed (including asbestos fibers) are collected on a filter, it is irrelevant as to whether they are from air, water, or tissue. The only major difference is that considerable numbers of fibers can be lost (as per the concern of the indirect method of tissue preparation) or obscured on the filter surface by debris thus preventing the analyst from detecting smaller particulates. The count scheme under AHERA includes structures (fibers) that are greater than or equal to 0.5 μm in length, have an aspect ratio of at least 5:1 and parallel sides (in the case of fibers) for most of their length. The analysis includes defining the morphology, the elemental composition (EDXA) and crystalline characteristics (selected area diffraction). This contrasts with the light microscope counting scheme where fibers counted are 5 μm or longer (with parallel sides for most of their length) and where there is no differentiation as to the type of fiber counted. The power of the ATEM to provide the most accurate information as to uncoated asbestos fiber burden in tissue is only as useful as the quality of the preparation permits and the utilization of the instrument at a sufficient magnification to permit detection of short- and long-thin asbestos fibers. The analytical scheme of counting should include fibers below 5 μm, the population of fibers that make up the majority of fibers in human lung and extrapulmonary sites,[62,113] if the overall representation of fiber burden is to be achieved.

3.9 USEFULNESS OF SPUTUM AND LAVAGE AS INDICATORS OF PAST ASBESTOS EXPOSURE

Sputum is collected as phlegm produced as a normal process of clearance from the respiratory system. A marker of sputum as being from the deeper regions of the lung is the presence of pulmonary macrophages. As described in the section on clearance mechanisms, macrophages are capable of reaching the mucocillary escalator and

thus bring associated (in the case of asbestos bodies), or ingested dust particles (smaller fibers), to the back of the throat for elimination via swallowing or expectoration. Sputum generation can be collected via spontaneous or induced methods. In the latter, a mist of salt water triggers a cough reflex to clear more sputum. Smokers produce more sputum while nonsmokers are poor sputum producers. Asbestos bodies formed in the lung can be found in the mucus or macrophage material in the sputum of occupational exposed individuals. Greenberg et al.[114] evaluated asbestos body production in a group of former amosite workers for approximately a year. Sputum was screened cytologically. One third of sputum samples from workers were asbestos bodies that were most numerous in induced sputum samples. Bignon et al.[115] reported an absence of asbestos bodies in sputum when the asbestos body concentration in lung parenchyma was under $1000/cm^3$. McLarty et al.[116] in a further review of the amosite-exposed cohort concluded the presence of asbestos bodies in sputa was related to radiographic findings of interstitial fibrosis (asbestosis) and pleural fibrosis and to spirometric findings of restrictive lung disease. Age and cigarette smoking were also related to the number of asbestos bodies found in sputum samples. Modin et al.[117] reviewed the findings of asbestos bodies in sputa and bronchial washings obtained as screening in a general hospital/clinic setting and concluded finding ferruginous bodies in either sample was highly specific markers for past asbestos exposure and reflect the presence of a significant asbestos load within the lung. Paris et al.[118] reviewed three consecutive sputum samples collected from 270 retired workers in a textile and friction materials factory. In the study, 53% of the samples were positive for ferruginous bodies. Their conclusions were that the prevalence of asbestos bodies in sputa was not related to sex, smoking status, or latency.

Dodson et al.[119] determined asbestos body and uncoated asbestos fiber content in 12 randomly selected sputum samples from former amosite asbestos workers and 12 individuals with no history of exposure to asbestos from the general population. The sputum was digested by the procedure previously described by Williams et al.[101] after which samples were screened by light microscopy for asbestos bodies and evaluated by TEM for asbestos fibers. The inconsistent findings of asbestos bodies in sputa, even from occupational exposed individuals, was reflected in that none of the 12 sputum samples from former amosite workers contained asbestos bodies, nor were any found in samples from the general population. However, ten of 12 samples from the amosite group contained uncoated amosite fibers detected by electron microscopic evaluation. One short chrysotile fiber was found in our sputum sample from the general population group. The finding of uncoated fibers and no asbestos bodies in sputa from exposed individuals was not surprising as asbestos bodies are larger and less easily brought upward by macrophages than uncoated fibers which are more easily carried upward in mucus or are moved upward within macrophages that have ingested the fibers. Screening for uncoated fibers by electron microscopy increased the sensitivity of sputum analysis for identifying past occupational exposure to asbestos.

The technique for bronchoalveolar lavage (BAL) was developed following the development of the fiberoptic bronchoscope in the late 1960s. The technique by

definition is a procedure that recovers cellular and noncellular components from the epithelial surface of the lower respiratory tract and differs from bronchial washings, that typically refer to aspiration of secretions or small amounts of instilled saline from the large airways."[120] BAL technique provided clinicians a new mechanism by which they could sample the lung milieu and the free cells that populated the lower respiratory tract. Begin[121] reviewed the array of diseases about which additional information could be learned via application of the BAL technique including those categorized as inflammatory and interstitial in nature. One particular application is the sampling of lower airway contents for dust particles. de Vuyst et al.[122–125] provided much of our data concerning the usefulness of lavage assessment in asbestos-exposed individuals. A comparison of the asbestos body content of lavage material was made with the content of lung samples from the same individuals most of whom were undergoing thoracotomy procedures for lung cancer.[124] The absence or low asbestos body counts <1 AB/ml BAL fluid) corresponded in about 70% of cases to concentrations of less than 1,000 AB/g of dry lung tissue and in 100% of the cases to tissue concentrations of less than 10,000 AB/g. In subjects with greater than 1 AB/ml of BAL, it was found that 85% of the cases contained more than 1,000 AB/g of dry lung tissue. Those individuals with greater than 10 AB/ml of BAL fluid were all found to contain lung burdens of greater than 10,000 AB/g of dry lung tissue. In an earlier companion study, the sensitivity of BAL fluid analysis for indicating past exposure to asbestos was supported; in the study, 28 of 28 individuals with obvious exposures were found to have AB's in lavage material.[123] Among 40 controls only five were found to have AB's in BAL fluid and the burden was reported to be <1 AB/ml of BAL fluid. de Vuyst et al.[122] in another study that included assessment of BAL fluid from white-collar workers, blue-collar workers, and subjects with definite exposure to asbestos found AB's were a marker of exposure to asbestos and not an asbestos-induced disease. Asbestos bodies were more likely to be found in BAL fluid from "patients presenting with asbestos-related diseases but in whom exposure is not confirmed by the occupational history (65 of 78 cases)." Sebastien et al.[126] studied BAL fluid from 69 patients with suspected asbestos-related diseases who subsequently underwent lung biopsy or autopsy. They concluded that when the BAL fluid "exceeds 1 AB/ml, it can be quite confidently predicted, however, that the parenchymal concentration is in excess of 1,000 AB/g (dry weight) and that the patient has experienced a nontrivial asbestos exposure."

Schwartz et al.[127] concluded asbestos bodies found in lavage are a reproducible assay for exposure but have little utility in most clinical settings to predict disease presence. Similarly, Oriowski et al.[128] found that the extent of pleural plaques neither did not correlate with frequency or duration of exposure nor to the number of asbestos bodies in BAL fluid in subjects free of lung parenchymal abnormalities determined by high-resolution computerized tomography. One must remember when reviewing the correlation of asbestos bodies in BAL fluid that they represent only a population of longer fibers in the lung and tell nothing about the burden of long uncoated or shorter (<8 μm) asbestos fibers. Furthermore, asbestos-related diseases often occur long after first exposure and not infrequently a

considerable time from last exposure. Thus, asbestos bodies in BAL fluid may confirm a level of past exposure to longer fibers but not offer insight to the quantity of the overall fiber burden in the past. Because asbestos bodies form months to years after exposure, their presence can be detected in BAL fluid long before the latency period required for the development of asbestos-induced diseases, e.g., often 15–50 years. Asbestos bodies in BAL fluid through representation of a higher percentage of longer fibers in the lung, indicate an increased likelihood of occupational exposure to asbestos because asbestos fibers found in general populations are usually short and not coated.[129,130]

The information discussed to this point regarding past levels of asbestos exposure as determined from BAL fluid is based on asbestos body content determined by light microscopy. Additional information regarding past exposure can be obtained from BAL samples analyzed by electron microscopy just as the sensitivity of sputum samples is expanded when uncoated fiber composition is included in an analysis. Gellert et al.[131] compared findings by light and electron microscopy of BAL fluid from 15 subjects with exposure to asbestos, three of whom had clinical and radiological evidence of asbestosis compared with asbestos BAL fluid concentrations findings in 13 urban dwelling control subjects. Asbestos fibers were confirmed in BAL fluid from 11 of the 15 exposed persons ranging between 133 and 3700 fibers/ml of lavage fluid with the range of asbestos bodies per milliliter of lavage fluid was 0–333. Five exposed subjects with no asbestos bodies detected by light microscopy were found to have uncoated asbestos fibers by electron microscopy (range: 133–2711 fibers/ml of lavage fluid). No asbestos fibers were found in BAL fluid in the control group. The use of BAL fluid has been shown to be of value for assessment of exposures to particular fiber types including exposures in secondary settings.[132] These include lavage material analyzed from a woman (household contact) with bilateral pleural and diaphragmatic plaques. Her only source of exposure was while washing the clothing of her husband who had been an asbestos sprayer. The second individual had been a coal miner for much of his adult life. The presence of crocidolite fibers in the lavage material was attributed to the individual's daily use of personal protection masks during work in the coal mine. These masks were reported to have been used from 1920–1970 and contained crocidolite as part of the filter matrix. The third case was of a mason who had for 44 yr lived in a region of Turkey where exposure to tremolite, as found in his lavage material, is known to occur as a result of environmental exposures. The final case consisted of an individual who had "all of the possible asbestos-related diseases except lung cancer." These were attributed to a short but intense exposure that had occurred 47–51 yr prior to the diagnosis of the specific diseases. Dodson et al.[77] found ferruginous bodies formed on a variety of particulates inhaled by foundry workers. These included fibrous and nonfibrous structures. The most common nonasbestos cores of elongated ferruginous bodies consisted of sheet silicates, graphite (carbon) and iron-rich fibers. Dodson et al.[133] reported the greatest specificity attained is obtained for correlating past exposures to asbestos using a combination of light microscopic quantitation of asbestos bodies correlated with the uncoated asbestos fiber burden as determined by ATEM

evaluation of BAL fluid samples. The lavaged individuals in this study had worked in a cement manufacturing facility that utilized chrysotile and crocidolite as reflected in the content and type of uncoated asbestos fiber burden in the BAL fluid.

Another unique observation was obtained, when analysis of lavage material was carried out by light and electron microscopic assessment of samples, from 15 brake lining workers (considered to be only exposed to chrysotile) and 44 asbestos cement workers exposed extensively to amphiboles.[134] As indicated by the authors, the literature is replete with references that chrysotile does not readily stimulate the formation of asbestos bodies (Figure 3.21).[134] However, analysis of BAL fluid indicated an exposure to asbestos among brake lining factory workers occurred to longer fibers of chrysotile as 95.6% of the cores of asbestos bodies were chrysotile. This contrasted with 93.1% of cores of asbestos bodies analyzed from BAL fluid from asbestos cement workers were formed on amphiboles. A similar observation of chrysotile cored ferruginous bodies in BAL fluid was found in our laboratory. The individual's unique asbestos exposure during work as a clutch rebuilder to longer fibers of chrysotile resulted in the majority of asbestos bodies found in a lung tissue sample (77.2%) being formed on chrysotile asbestos cores.[135]

Recent publications[136–139] emphasized that brake dust contained predominately short chrysotile fibers with most fibers being less than 5 μm. This would suggest that exposure to brake dust would not be expected to result in asbestos body formation

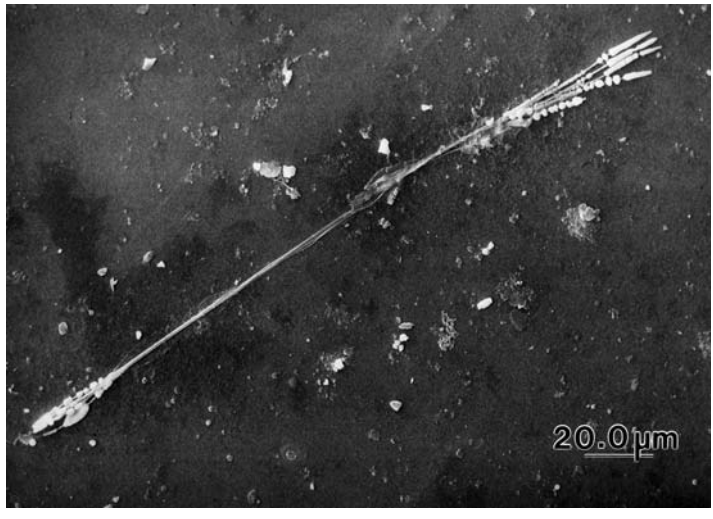

Figure 3.21 Although chrysotile cored ferruginous bodies are less common than those formed on amphibole cores, when longer fibers of chrysotile are inhaled the formation on such cores can occur as indicated in this micrograph. The beaded material representing the ferruginous coating is primarily located on the frayed ends of the fibers.

because, as previously stated, asbestos bodies form on longer fibers usually greater than 8 μm.

Although Dumortier et al.[134] stated longer fibers of chrysotile were inhaled in such a work setting, Sartorelli et al.[140] offered an appropriate synopsis regarding assessment of asbestos body and fiber burdens in BAL fluid stating "fiber concentration in BALF can be considered as a reliable biomarker of past asbestos exposure, even many years after the end of exposure."

3.10 ASBESTOS BODY BURDEN IN EXPOSED AND GENERAL POPULATIONS

The asbestos body as a marker of past exposure to asbestos has been discussed in the context of its presence in tissue sections. A more sensitive method of assessing tissue samples for asbestos bodies is by sampling larger amounts of tissue via digestion techniques. The digested material is collected on a thin membrane (filter) and following clearance, as previously described, can be subjected to screening by light microscopy. The numbers of asbestos bodies found can be extrapolated to the numbers per gram of wet or dry tissue. Some of the earlier works combining light and electron microscopy for determining the numbers of asbestos bodies per gram of tissue and core identification were carried out by Churg and Warnock.[75,94,141,142] Their observations in individuals from the general population from larger cities was that individuals with less than 100 asbestos bodies per gram of wet tissue represented environmental rather than occupational exposures, although one could argue that several persons evaluated had occupational or bystander exposure to asbestos,[94] with the range of asbestos bodies being from 2 to 84 (mean: 33) per gram of wet lung. If one chooses to use a multiplier of 10 to approximate asbestos bodies per gram of dry weight, then the number would be 1000 per gram dry weight for nonoccupational exposures. These two numbers have been referenced as a "break point" that separates occupational from nonoccupational levels of exposure to asbestos as defined by tissue burdens.[94,143,144] Data from our own experience indicates the number of asbestos bodies in the nonoccupationally exposed general population per gram of wet tissue is 0–20 asbestos bodies[129,130,145] which is more in keeping with reference levels reported by Breedin and Buss[146] and by Roggli et al.[147]

Churg and Warnock[141] analyzed core material of ferruginous bodies by ATEM in 23 autopsy and surgical patients, none of them had occupational asbestos exposure. Of the 328 bodies examined, 264 (80%) had diffraction patterns consistent with amphibole asbestos whereas only six had chrysotile cores. In a separate study of 144 asbestos bodies isolated from 29 persons with fewer than 100 asbestos bodies per gram of wet lung tissue (below occupational levels)[142] analyzed by electron diffraction, 143 were found to be formed on amphiboles while only one was formed on a chrysotile core. Chemical analysis by XEDA was used to further define the types of amphiboles. Twenty-one were determined to be formed on amosite or crocidolite cores, 13 on anthophyllite asbestos cores, and one on a tremolite asbestos core.

Commercial amphiboles were the dominant cores of asbestos bodies in men, while asbestos bodies found in women were likely to be formed on anthophyllite or tremolite cores. Cosmetic talc was suggested as the source of the longer asbestos fibers in the females within the study.[75]

Moulin et al.[148] analyzed cores of ferruginous bodies in 19 asbestos-exposed individuals and 25 nonexposed urban dwellers from the Belgium urban population. Of the 319 bodies analyzed, 315 were formed on asbestos. The nonasbestos cores were on talc and crystalline silica. Eighty-two percent of the asbestos cores were commercial amphiboles (amosite/crocidolite) and 7% were formed on chrysotile cores. The remaining 3.8% were formed on noncommercial amphiboles (anthophyllite/temolite). In each study, some ferruginous bodies were totally coated and not capable of being analyzed by XEDA or selected area diffraction.

Roggli et al.[147] studied asbestos body concentrations as related to types of asbestos-induced diseases. The highest numbers of asbestos bodies per gram of tissue were in individuals with asbestosis (greater than or equal to 2000 ABs/g wet tissue). Intermediate levels were found in individuals with malignant mesothelioma and the lowest in patients with pleural plaques. As in other studies, the majority of the cores of the asbestos bodies were on amphiboles. The explanation of why amphibole cores were most common is that amphiboles being straight fibers tend to be more readily inhaled in a longer form than chrysotile. However, when longer fibers of chrysotile are readily available and inhaled, chrysotile cores of asbestos bodies are not uncommon. As stated previously, appreciable numbers of chrysotile cored asbestos bodies were reported in BAL fluid from brake lining workers.[134] Holden and Churg[149] examined ferruginous body content from lungs of chrysotile miners and found that 64% of the cores were formed on chrysotile and with 29% being formed on amphiboles even though the amphiboles, tremolite, and actinolite constituted the majority of the uncoated fibers in these cases. Levin et al.[150] reported a case of a clutch refabricator where 72% of the ferruginous bodies were formed on chrysotile asbestos cores (Figure 3.21).

An ideal model for determining tissue burden of asbestos fibers would be to develop a multiplier of the number of more easily seen ferruginous bodies (as determined by light microscopy), and extrapolate the concentration of uncoated asbestos fibers from this number. Such an effort is an exercise in futility as the ratio varies widely.[69,83,151,152]

However, asbestos body burden is elevated in many occupationally exposed individuals given the longer fibers in lung tissue that provide a stimulus for coating as described data from our laboratory. In a group of 55 occupationally exposed asbestos individuals with mesothelioma, 46 had concentrations of asbestos bodies above 1000/g dry weight of lung tissue.[153] Of 841 ferruginous bodies analyzed, 781 (92.9%) were formed on amosite, 24 (2.9%) on crocidolite, 8 (1%) on tremolite, 3 (0.4%) on anthophyllite, 3 (0.4%) on actinolite, and 1 (0.1%) on chrysotile cores. Eleven (1.3%) of the ferruginous bodies were formed on nonasbestos cores and 10 (1.2%) were totally coated or successful analysis of the core material could not be achieved. Seven of 15 cases of females with mesotheliomas evaluated had over 1000 asbestos bodies per gram.[152]

Ferruginous body quantitation was carried out in 19 cases of individuals with a prior history of occupational asbestos exposure and lung cancer. The ferruginous body content in 11 cases was found to be over 1000 asbestos bodies per gram of dry tissue.[154] In three individuals lung tissue did not contain asbestos bodies (within limits of detectability of the study), and two were found to have concentrations at general population levels. One individual did not have detectable levels of asbestos fibers although lung tissue from the remaining four contained asbestos fibers.

As mentioned earlier, asbestos bodies are not readily formed in some individuals even though their lung tissue contains elevated numbers of longer asbestos fibers[151,153,155] suitable for iron–protein coating. This finding suggests the number of uncoated asbestos fibers found in tissue is independently important as an indicator of causation of asbestos-induced disease.[156] In reality asbestos body burden represents only a portion of the longer fibers in the tissue sample and thus tells only a part of the story about tissue burden. It remains for the uncoated asbestos burden to be established before the story is complete.

3.11 UNCOATED ASBESTOS FIBERS IN OCCUPATIONALLY EXPOSED INDIVIDUALS AND IN LUNG TISSUE FROM THE GENERAL POPULATION

To evaluate uncoated asbestos fiber concentrations in tissue, it is imperative that there is a clear understanding of what techniques were used to obtain asbestos concentration data. The resolution of the light microscope coupled with its lack of ability to distinguish fiber type, greatly limits it usefulness in assessing fiber concentration in tissue. Even in the most ideal settings where tissue has been destroyed and thus there is minimal obstruction of fibers from view, only a small percent are detectable by light microscopic examination. Morgan and Holmes[157] reported approximately only one half of uncoated fibers would have been detected by light microscopy. Ashcroft and Heppleston[92] reported that only 12–30% of uncoated asbestos fibers from tissue samples in their study were light microscopically visible. Rood and Streeter[158] compared the detection capabilities of light microscopy versus those of scanning and TEM for chrysotile fibers collected on a filter. All fibers would have been counted and analyzed by the transmission electron microscope, 60% with the SEM, and only 25% of fibers greater than 5 μm long would have been identified with the light microscope (Figure 3.22 and Figure 3.23). The data from our publications[80,151,152] generally agrees with the range for optically detectable fibers reported by Ashcroft and Heppleston[92] and by Rood and Streeter[158] except when the population of asbestos fibers in a tissue sample is predominantly short- and long-thin fibers.[83,113,129,159] In such cases when the fiber burden is represented by chrysotile and crocidolite the numbers of fibers detected by light microscopy is often 0%. Pooley and Ranson[160] correctly stated, “it is possible, using the electron microscope, to predict the asbestos fibre count that would be obtained by light microscopy, the reverse prediction cannot

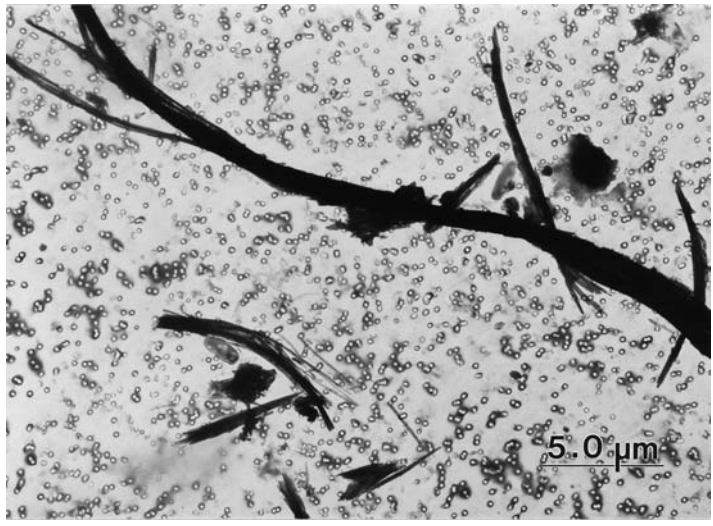

Figure 3.22 Bundles of chrysotile asbestos obtained from new brake components are shown in this field. The tendency is evident for the bundles to disassociate into smaller and smaller units, which indicate the potential that many of these units would be below the level of detection in the light microscope analysis of air samples.

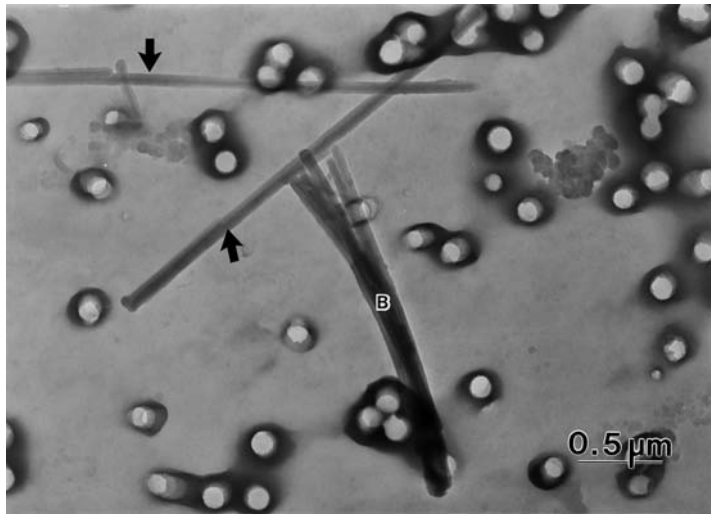

Figure 3.23 Neither the fibrils (arrows) of chrysotile asbestos seen in this field nor the bundle (B) would have been counted in a typical polarized light microscopy counting scheme. The former due to the fact that it is shorter than the 5 μm length included in a count scheme and the latter due to the fact that they cannot be resolved by light microscopy. This provides an example of the problems of interpreting environmental exposures or tissue burdens when large populations of fibers are excluded due to the count scheme or the resolution of the instrument.

be made: it is impossible to determine the proportion of the various asbestos minerals types using the light microscope."

In discussing uncoated fiber burden in tissue it seems reasonable, based on the aforementioned reasons, to compare data obtained by TEM to that generated via similar techniques. It is important to compare data generated at sufficient magnification and with a count scheme that includes "short" and long/thin asbestos fibers as this population makes up the vast majority of asbestos fibers in lung tissue and extrapulmonary sites. Some of the earliest contributions using ATEM for analysis of tissue digestion from "control populations" were contributed by Churg and colleagues. In a study of individuals from the San Francisco area, Churg and Warnock[94] reported 80% of uncoated fibers were chrysotile (mean: 130×10^3) with a range of 12×10^3 to 680×10^3 fibers/g wet lung and 90% of chrysotile fibers less than 5 μm long. Total amphiboles had a mean of 25×10^3 and ranged from 1.3×10^3 to 75×10^3 fibers/g wet lung tissue. Ninety-five percent were noncommercial amphiboles and two thirds were less than 5 μm long. Approximately, 20% of amosite, crocidolite, and anthophyllite fibers identified, were longer than 10 μm. In a subsequent tissue study of individuals residing in Vancouver, British Columbia, Churg and Wiggs[14] reported the mean chrysotile burden to be "only" 0.2×10^6 g of dry lung when compared with approximately 1.0×10^6 g of dry lung in the San Francisco. The difference was possibly explained by the lack of known outcrops containing chrysotile asbestos in the San Francisco Bay area that might contribute to environmental exposures. However, the conclusion offered was that the majority of fiber types are "more or less the same in both cities." Langer et al.[161] in a study involving 28 individuals who had resided in New York City found chrysotile to be present in all 28 cases.

Data from our own laboratory tends in many ways to agree with the early studies of Churg and Warnock.[94] The definition of a member of the general population used in our laboratory is that the individual has not been involved in a known asbestos-related work activity, has no disease conditions which may have been caused by asbestos, and has 20 or less (our background number) asbestos bodies per gram of wet lung tissue. In a study by Dodson et al., 35% of uncoated asbestos fibers involving 33 individuals from the general population, were chrysotile and 86% were <5 μm long.[129] Also, 83% of amphiboles in this study were noncommercial amphiboles and 73% of these were <5 μm long. The most commonly found asbestos fiber was chrysotile observed in 14 cases with anthophyllite being found in 12 cases. Of the 33 cases, 26 cases had no ferruginous bodies found in the light microscope scan. Of the 33 individuals, 10 were not found to have asbestos fibers in their lung tissue (within the limit of detection in the procedure). The geometric mean of fiber length for each asbestos type found was less than 3 μm. An additional study of lung samples from 15 individuals considered as representing the general population[130] confirmed the findings from the earlier study. Only four individuals were found to contain asbestos bodies and only two individuals' lung tissue contained an asbestos fiber in their lung digest (within limits of detection used in the study). In conclusion, lung tissue from the general population contains low numbers of asbestos fibers. If detected, these fibers will likely be short chrysotile or noncommercial amphibole

fibers. When commercial amphiboles are found, the fibers are short (<5 μm) and few in numbers. When a lung tissue sample contains appreciable numbers of asbestos fibers, long fibers and commercial amphiboles (amosite or crocidolite), the suggestion is that the individual has had an occupational or occupational-like exposure to asbestos.

Additional data exists regarding asbestos burden in tissue from occupationally exposed individuals. As mentioned earlier, the chrysotile form of asbestos constituted 90–95% of asbestos used in commercial applications in the United States. However, chrysotile veins have been reported to be "contaminated" with amphiboles particularly actinolite, anthophyllite, tremolite and more recently crocidolite.[162] Quebec chrysotile that constituted the majority of chrysotile used in the United States has been stated to have between 1and 6.9% amphibole asbestos.[163,164] Tremolite has been suggested by McDonald et al.[165] as a "valid marker" for exposure to chrysotile asbestos. This same suggestion was made in a study by Churg[166] of nine chrysotile miners with "asbestos airway disease" (so-called "early asbestosis") but with no evidence of classic asbestosis (interstitial fibrosis) on pathological examination. The findings indicated a strong correlation between the amount of chrysotile and amphibole suggesting the amphibole (tremolite) component was a good measure of original (but no longer) chrysotile burden due to more rapid clearance of the latter. In 1988, Churg[167] reviewed the literature on chrysotile, tremolite, and mesothelioma in man. His opinion was the "induction of mesothelioma by chrysotile requires, on average, as great a lung fiber burden as induction of asbestosis by chrysotile, whereas amphibole (amosite or crocidolite)-induced mesotheliomas appear at several hundred fold smaller lung burden."

In an additional study, Churg et al.[168] found high tremolite fiber concentration was strongly associated with mesothelioma, airway fibrosis and asbestosis in a study involving chrysotile miners and millers from the Thetford Mines in Quebec. Pleural plaques and carcinoma of the lung were reported to show no relationship to tremolite burden. Churg et al.[169] measured tissue burden by ATEM from 20 shipyard and insulation workers. The findings in this study indicated, "amosite concentration, like chrysotile and tremolite concentration, is closely and directly related to fibrosis at the local lung level." They also raised an important issue often ignored by those using counting schemes where only longer fibers (>5 μm) are counted, in the "possibility that short fibers may be more important than is commonly believed in the genesis of fibrosis in man." They also expressed their belief that an amosite fiber was more fibrogenic than a chrysotile or tremolite fiber and that tremolite was more fibrogenic than is chrysotile.

An additional study from Churg's laboratory involved a cohort consisting of 144 shipyard workers and insulators from the Pacific Northwest. The major residual fiber type in the lungs from these individuals was amosite and that lung tissue in most cases contained tremolite and chrysotile fibers.[170] Interestingly, the authors reported that "crocidolite fibers were found in only a very few cases, usually in quite small numbers, and have been excluded from all analysis." This indicates the exposure to the second most commonly used form of "commercial amphibole" crocidolite, was minimal as reflected in the tissue burden of shipyard workers and insulators.

The conclusion from the study was that mesothelioma occurred at much lower lung tissue amosite concentration than did asbestosis, which was in contrast to their conclusion for chrysotile-induced mesothelioma.

A study of lung tissue from former asbestos miners and millers from the Thetford-Mines and Asbestos regions were carried out by Nayebzadeh et al.[171] There were higher concentrations of tremolite asbestos in lung tissues from the Thetford-Mines workers compared with workers from the Asbestos region. Fiber burden was categorized in three sizes: (1) those less than 5 μm long; (2) those greater than 5 μm and less than 10 μm long; and (3) those greater than 10 μm long. The conclusion from review of data was that "no consistent and biologically important difference was found for fiber dimension; therefore, fiber dimension does not seem to be a factor that accounts for the difference in incidence of respiratory diseases between the two groups." "The greater incidence of respiratory diseases among workers of Thetford-Mines can be explained by the fact that they had greater exposure to fibers than did workers at the Asbestos region. Among the mineral fibers studied, retention of tremolite fibers was most apparent."

Langer and Nolan[172] reviewed lung tissue from 53 asbestos-exposed workers and one person with secondary exposure. They concluded amosite was the most prevalent fiber, occurring in 74% of the specimens, with amosite always being found in the lungs of insulators and chrysotile found in only 50% of this group. Crocidolite was found in 24% of this group and increased to 40% of the workers with shipyard exposure.

One early study from our laboratory emphasized the importance in some cases of not only assessing the asbestos body burden when defining past levels of asbestos exposure but also the uncoated asbestos fiber burden.[155] Analysis of lung tissue from 12 former amosite workers showed 10 with over a 1,000 ferruginous bodies per gram of dry tissue where no ferruginous bodies were detected in the digest of the other two samples. This was an unexpected finding in that amosite can be readily inhaled in a longer form and as described previously, is often found as the core of asbestos bodies in occupational exposed individuals. The initial explanation was that individuals had relatively short exposure (0.5 and 3.3 months) although that exposure was known to be in very dusty jobs. Two samples from the individual's tissue when analyzed by electron microscopy retained 1.2 and 2.1 million fibers/g of tissue, respectively. Thus, even with the proper length (>8 μm) and considerable numbers of fibers being present in the lung, the individuals' lungs were apparently not efficient in coating the fibers. The importance of combining data for asbestos body content and uncoated asbestos fiber content is further supported in the evaluation of an individual from a group of shipyard workers[83] who was not found to have chrysotile in his lung tissue. When tissue from his lymph node and pleural plaque was analyzed by ATEM, there were 21,000,000 chrysotile fibers per gram of dry tissue in the pleural plaque and 5,500,000 chrysotile fibers per gram of dry tissue in the lymph node. This finding suggests the efficiency of chrysotile clearance from lung tissue.

Amosite asbestos was found in lung tissue from 53 of 55 persons with mesothelioma whose tissue was evaluated by ATEM[153] with 39 patients having greater than

200,000 amosite fibers per gram dry of tissue. The geometric mean length of the amosite fibers was 13 μm that contrasted with that found in lung tissue samples from the general population where amosite fibers are usually less than 5 μm. Forty-three percent of patient's lung tissue contained chrysotile asbestos and 40% contained crocidolite asbestos. Tremolite was the most commonly found "non-commercial" amphiboles (33 cases) while actinolite and anthophyllite were each found in 21 cases. There was no evidence chrysotile was the source of tremolite in that 11 of the patients had both, but 13 persons whose lungs contained tremolite had no detected chrysotile. These findings contrast with the suggestion of Srebro and Roggli[173] that tremolite is "nearly ubiquitous and represents the most common amphibole fiber in the lungs of urbanites." The link statistically could be more easily made for chrysotile accounting for the amosite compared with the relationship of chrysotile to temolite. Only a small percent of each type of asbestos would have been detected by light microscopy even of longer fiber asbestos (based on diameter). In the study, 26 of 59 patients did not have pathologic asbestosis even though most had appreciable ferruginous body and uncoated fiber burden.

In a series of 15 mesothelioma cases in women the most commonly found fiber was amosite and the second most commonly found fiber was tremolite.[152] The common link in both groups is that fiber burden is often of mixed types of asbestos and contains a population of asbestos fibers longer than 5 μm while these are infrequently seen in tissues from the general population. It would be helpful if a specific concentration of asbestos tissue burden could be linked to it causing a specific disease. Such an objective could only be met in populations with heavier tissue burden in each group as there is a wide number from thousands to millions of asbestos fibers in each disease category. At the time a tissue sample is obtained it is reflective of the dust concentration in the tissue at that time and does not indicate the number of fibers, particularly short fibers, that may have been in the lung and cleared via the mucocillary escalator or to other sites within the body. The question is why should not these cleared fibers have played a role in tissue response as well as creating the setting for permanent pathological changes to occur before their departure? This is particularly an important question relative to chrysotile as repeated exposures would be expected to stimulate continued inflammatory responses and changes leading to neoplasia as the clearance of chrysotile is considerably more rapid from the lung than amphiboles[174] potentially resulting in most chrysotile being eliminated from lung tissue depending on the time of sampling from first exposure.

3.12 EXPOSURE FROM ASBESTOS AS A COMPONENT OF OTHER MINERALS

There is potential asbestos exposure from products that are made from minerals that contain asbestos. This is often referred to as contamination although contamination may not be the proper word as asbestos naturally occurs as a component of these minerals. While many of these products are presented as not containing asbestos, the reality is that miners/millers and consumers have potential asbestos exposures

from their use. Vermiculite, mined in Libby, Montana, as an example, has been distributed to numerous processing facilities in the United States and used in products ranging from garden products, e.g., potting soil component, to insulation products. McDonald et al.[175] as early as 1986 stated tremolite in vermiculite could cause asbestos-related diseases. Wright et al.[176] reported lung burdens of tremolite asbestos from exposure to asbestos-containing vermiculite of over 8,000,000 asbestos fibers per gram dry lung had resulted from a brief summer job exposure 50 yr prior in a vermiculite expansion plant. Sixty-eight percent of the fibers were tremolite asbestos.

Another widely used mineral that can contain asbestos is talc. Kleinfeld et al.[177] and Rohl et al.[178] reported certain talc formations contained tremolite and anthophyllite asbestos that can occur in consumer talc products. Asbestos bodies and fibers have been reported in lung tissue from workers with asbestos-related diseases who worked in New York State talc mines.[179] The fibers in the lungs consisted of fibrous talc, tremolite, and related mineral series. A considerable burden of asbestos fibers and bodies were identified by Scancarello et al.[180] in individuals with respiratory diseases and bilateral pleural plaques following talc inhalation and as found in BAL fluid and tissue samples. These are additional examples where determining asbestos burden in tissue samples can offer potentially important information in settings where exposures occurred to products not thought to contain asbestos.

3.13 ASBESTOS IN EXTRAPULMONARY SITES

The majority of the world's literature regarding asbestos in extrapulmonary sites is based on observations of a few asbestos bodies seen by light microscopy. These sites include the stomach,[181] the liver,[182] the kidney,[79,182] the spleen,[79,81,182] lymph nodes,[81–83,184] and pleural plaques.[185] The limited occurrence of such observations in pleural samples was reviewed in 1988 by Churg.[186] His conclusions were that "as a rule asbestos bodies are not seen in pleural plaques, although Rosen et al.[185] claim to have extracted a few bodies in some cases. As mentioned earlier, the asbestos content of plaques and pleurae appears to be quite different from that of the lung, and these sites are not useful for mineral analysis."[186] With respect to asbestos bodies Dr. Churg was correct in that our laboratory has yet to find an asbestos body in digests of pleural plaques or pleural fibrous tissue. However, the presence of asbestos fibers in uncoated extrapulmonary sites, including pleura, are important indicators of asbestos relocation from the original site of deposition in lung tissue.

The inhalation of asbestos can result in the occurrence of pathological responses in sites considerably removed from the lung (the original site of deposition) has long been appreciated.[85] That particulates can relocate through the lymphatic system to the hilar lymph nodes and to more distant lymph nodes is well recognized.[2] In fact Schlesinger[44] described lymph nodes as "reservoirs of retained material." Gross and Detreville[8] noted lymph nodes were "repositories for dust" and in heavy dust exposures over time become "densely mineralized and stony hard." In cases of more toxic dust such as silica, lymph nodes may show necrosis, fibrosis, and calcification.[45]

As proposed by Becklake[46] and Hillerdal[47] the lymphatic route offers a mechanism for relocation of asbestos from the lung to other parts of the body. Knudson[187] stated the "transport of the fibers to these surfaces (pleural and peritoneal) can lead to mesothelial proliferation, and after many years, to malignant mesotheliomas." Confirmation of relocation to extrapulmonary sites required the application of the ATEM for identification of the type and size of asbestos fibers that reach extrapulmonary tissues. One of the first quantitative studies using ATEM was carried out by Sebastien et al.[188] They analyzed fiber content of lung samples and parietal pleural tissue from 29 cases sent to them for confirmation of diagnosis. The majority of patients had histories of asbestos exposure. In the study, 16 of 29 samples of parietal pleural tissue contained asbestos (within the detection limit of the study) and 27 lung tissue samples were positive. The pleural samples identified to have asbestos in them contained "almost all chrysotile." The reason light microscopic evaluation of extrapulmonary sites for asbestos is usually negative is evident by fiber size as reported by Sebastien. The mean length of fiber in the lung was 4.9 μm whereas the average length in the pleura was 2.3 μm. These asbestos fibers were not long enough to trigger asbestos body formation. Likewise, an assessment by light microscopy would not detect short or longer/thinner asbestos fibers.

A comparative study was carried out by Dodson et al.[83] on samples of lung tissue, lymph nodes and pleural plaques obtained from eight former shipyard workers from Italy. No asbestos bodies were found in the pleural plaques while all but one sample of lymph node contained asbestos bodies. This suggests either a relocation of mature bodies from the lungs to the lymph nodes, a selective segregation based on the size of fibers that reach the two sites (a predictor of asbestos body formation), or differences in coating efficiency between these extrapulmonary sites.

Amphiboles and chrysotile fibers were found at various concentrations in different sites with total concentrations often ranging into the millions of fibers per gram of dry tissue. The average length of chrysotile and amphibole asbestos fibers found in the lung was longer than lengths for the same type of fibers found in the lymph node and pleural plaques. Fibers in all three sites were represented by a majority that were less than 5 μm long with only 4% of the chrysotile in the lung being >10 μm and no chrysotile fiber >10 μm being detected in pleural plaques and lymph nodes. The amphibole content consisted of 20% being longer than 10 μm in the lung with 8% of the fibers in the pleural plaques and 2.5% in the lymph nodes being >10 μm. The importance of including short fibers in a count scheme is illustrated in one individual. The lung tissue from this individual was not determined to have chrysotile (within the limits of detectability). Thus if this parameter alone was used one could extrapolate this to mean no or low exposure. However, the pleural plaque tissue contained 21,000,000 fibers of chrysotile per gram of dry tissue and lymph node contained 5,500,000 million fibers of chrysotile per gram of dry tissue. If only fibers longer than 5 μm were counted only 3.1% of the total chrysotile from the plaques of this individual and none in the lymph nodes would have been counted (given sufficient magnification had been used to "see" the thin fibers). These findings indicated a past exposure to chrysotile and also emphasized the

lung's capability to clear short fibers following succession of exposure whereas the extrapulmonary sites have less efficient mechanisms to rid their tissue of asbestos.

Recently, Suzuki and Yuen[189,190] analyzed asbestos content in lung and mesothelial tissue from individuals with mesothelioma a cancer of the serosal membranes of the body and considered an asbestos marker disease. Concerning mesothelioma, Knudson[187] stated that "in the absence of asbestos, mesothelioma is so rare that it might never be studied." Using ATEM, Suzuki and Yuen[189,190] found the majority of fibers in the lung and the mesothelial tumor tissue were less than 5 μ m in length. They also found the majority of the short fibers were chrysotile. Only 4% of the fibers fit the Stanton model for a more pathogenically active population of fiber of >8 μm long and thinner than 0.25 μm in diameter.

Approximately 10–15% of mesotheliomas occur in the peritoneal cavity. Therefore, Dodson et al.[80] conducted an analytical analysis of lung tissue omentum and mesentery (fatty tissue in the peritoneal cavity), from 20 mesothelioma cases. Asbestos bodies were found in lung tissue of 18 individuals and in five mesentery and two omentum samples. Uncoated asbestos fibers were found in lung tissue of 19 individuals with 17 individuals having fibers in at least one extrapulmonary site. Ten individuals had over 1.4 million asbestos fibers per gram of dry weight of lung tissue. Fourteen individuals had uncoated asbestos fibers in mesentery and omentum samples. The most common type of asbestos fiber found in omentum and mesentery was amosite that was also the most prevalent asbestos fiber type found in lung tissue. The fiber type and concentration in lung tissue was similar to that found in 55 mesothelioma cases reported in 1997[153] with regards to there being a mixture of asbestos types. Different asbestos fiber types were seen in omentum/mesentery in several individuals. Predictors from lung data for fiber presence in omentum and mesentery statistically included asbestos body concentration, uncoated amphibole concentration, fiber length, and aspect ratio. Obviously this study showed asbestos fibers reached the peritoneal cavity where mesotheliomas can develop. In a comparable study of lung, mesentery, and omentum tissue from 15 individuals who conformed to the definition of members of the general population as used in our laboratory, only four lung samples contained asbestos bodies and only two lung samples contained at least one asbestos fiber. The only asbestos found in extrapulmonary sites consisted of one short fiber of chrysotile (3 μm) and one short fiber of tremolite (4 μm) found in two samples of omentum.

An additional assessment of the content of lung and peritracheal lymph node tissue was carried out in 21 individuals who also conformed to the definition of general population.[191] Two lymph nodes were positive for at least one ferruginous body. There were no asbestos fibers detected in the lymph nodes from eight cases. Five of the cases with asbestos fibers in the lung tissue were not determined to have asbestos in the sample of lymph node. Nine of the cases had detectable levels of asbestos in lung and lymph nodes. The most common type of asbestos found in the lymph nodes was anthophyllite (nine cases) with the second most common type being tremolite (six cases). The composition of the asbestos burden (when present) of the tissue and lymph nodes from the general population predominately

reflect past exposures to short fibers (<5 μm) of noncommercial amphiboles or chrysotile.

3.14 FIBER LENGTHS AND THE RELATIONSHIP TO PATHOGENICITY

Asbestos fibers assessed in the work place are counted via reproducible counting schemes by use of phase contrast light microscopy. This system is based on the definition of a "regulated fiber" which physically is sufficiently thick to be observed by light microscopy under the designated magnification, count scheme is 5 μm or longer. This selection criterion was established to permit reproducibility between analysts and provided an inexpensive mode for determining the numbers of fibers in air sampled over a period of time and a certain volume of air. This forms the basis of "action level," "permissible exposure limits," and "excursion levels" which are used to establish levels of exposure for workers in asbestos-containing environments as defined respectfully by OSHA or EPA work practices. As Langer et al.[55] noted the counting guidelines define the physical definition of a fiber to be included in a count, the aspect ratio for fibers to be included, and the definition of asbestos bundles and other structures as applicable to the count scheme. These selection criteria were based on "practicality and theoretical considerations" rather than having a target of a "more toxic" population of fibers. As already stated the predominance of asbestos fibers in lung tissue is short or longer thin fibers that cannot be detected with the light microscope (Figure 3.24).

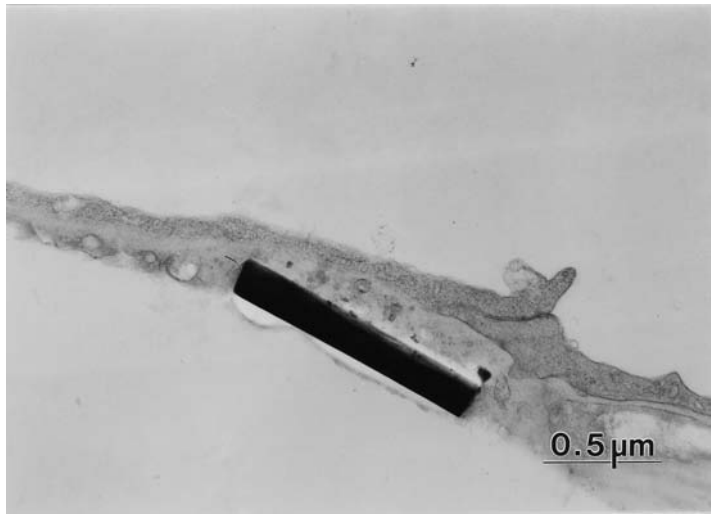

Figure 3.24 The short amosite fiber shown in this field has been phagocytized by a type I pneumocyte. Such "short" fibers in dividing cells create a physical challenge to proper cell division.

What is the scientific basis that long fibers are more likely to cause disease? Simple logic indicates inhalation of longer fibers would result in less likelihood of rapid elimination via lung clearance mechanism than an equivalent number of inhaled shorter fibers. As discussed earlier, it is unlikely that only long fibers are in the breathing zone. There are unique occupational settings where the short fiber grades of chrysotile are used and in these there are fibers longer than 5 μm. The concept of fiber length and potential for disease induction is often referenced to the works of Stanton et al.[192,193] The conclusions from work with pleural implants in rats, was that "the carcinogenicity of fibers depend on dimension and durability rather than on physicochemical properties."[193] As is evident from the chapter on the molecular mechanisms of asbestos-induced disease, the concept of physically based pathogenicity is only partially correct. The entirety of the Stanton publications states "the probability of pleural sarcoma correlated best with numbers of fibers that measured 0.25 μm or less in diameter and more than 8 μm in length, but relative high correlations were noted with fibers in other size categories having diameters up to 1.5 μm and lengths greater than 4 μm."

The second series of studies on fiber length as related to pathogenicity was carried out by Pott et al.[194–196] Various sizes of fibrous dusts were injected intraperitoneally into rats to assess their tumorgenicity. Pott reported asbestos fibers shorter than 10 μm in length could produce tumors.[197] In one experiment milled chrysotile consisting of 99.8% of fibers being less than 5 μm (few longer than 10 μm), produced tumors in 30% of the animals. Fraire et al.[198] injected short fiberglass (mean length of 2.2 μm and width of 0.15 μm) intrapleurally into rats. The histological changes observed included chronic inflammation, fibrosis, foreign body reaction and more proliferative/neoplastic changes of mesothelial hyperplasia and dysplasia. Mesotheliomas developed in three of the 25 rats.

Attempts have been made to extrapolate from tissue burden and animal studies to the risk for developing specific asbestos-related diseases in humans. Lippmann[199] concluded asbestosis was most correlated with the number of fibers longer than 2 μm and thicker than 0.15 μm; mesothelioma to the number of fibers longer than "about" 5 μm and thinner than "about" 0.1 μm; and lung cancer to the number of fibers longer than "about" 10 μm and thicker than "about" 0.15 μm. Churg and Vedal[170] concluded from tissue analysis of individuals heavily exposed to amosite and chrysotile that "except for pleural plaques, the association of fiber size and disease remains uncertain." They further concluded "mesotheliomas are not associated with long fibers and in fact are probably associated with lower-aspect-ratio fibers than found in subjects without asbestos-related disease." McDonald et al.[165] conducted fiber burden analysis in a series of individuals with mesothelioma who were 50 yr or less of age at time of diagnosis. They concluded that "shorter fibers were more abundant than longer fibers, and high concentrations of all fibre lengths tended to occur together." "Short, medium, and long fibres (of amphiboles) were all associated with mesothelioma risk: those longer than 10 μm had the greatest increment in risk per fibre, followed by medium [6–10 μm] and then by short [<6 μm]." Nayebzadeh et al.[171] observed that respiratory disease in a group of former Quebec chrysotile miners and millers was not related to fiber

dimension but to the fiber burden in the tissue, a conclusion which we believe is correct and has general applicability.

Regulation of asbestos in occupational and bystander settings would be much simpler if only the longer fibers visible by light microscopy and scanning electron microscopy were the causative of all asbestos-related diseases. The accurate counting of fiber burdens would not require the more expensive, extensive preparative processes, and time consuming use of ATEM and there would be relief by those who manufacture products whose dust consists of fibers that predominately can only be detected by the ATEM. In reality the majority of asbestos dust that makes up the predominate tissue burden found in the lung and extrapulmonary sites is represented by fibers shorter than 5 μm long and/longer thin fibers not visible by light microscopy or in most preparations by scanning electron microscopy. The short fibers are the ones most readily cleared from the lung. These are often misrepresented in some analyses of tissue samples by their absence as indicating they had never been there and thus excluding them from possible participation in pathological mechanisms in the lung and other tissues. This ability to have short chrysotile cleared over time has lead to the suggestion that occupational histories in some instances may be a better indicator of risk of lung cancer than fiber burden.[151,191] Of additional concern is that short asbestos fibers are the ones more readily transferred to extra pulmonary sites where asbestos-related diseases occur and where short fibers make up the majority of fibers at these sites at any one time.

The primary conclusion from all data presented in this chapter is that inhaled asbestos fibers cause asbestos-related diseases and most frequently consist of a mixture of asbestos types and sizes. Data from any tissue analysis for asbestos must be judged on what is included in the observations and what is excluded. This requires an understanding of preparative techniques and the capabilities of the instruments used in obtaining the information.

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CHAPTER 4

Molecular and Cellular Responses to Asbestos Exposure

Mark A. L. Atkinson

CONTENTS

4.1 INTRODUCTION

The deposition of asbestos in the lower respiratory tract leads to the development of a complex group of interrelated diseases. The physical parameters of what constitutes a respirable fiber will not be discussed in this chapter, since this is discussed in detail in Chapter 3. This chapter discusses short- and long-term cellular and molecular sequellae that occur as the body responds to asbestos once it has been deposited. Responses at the level of the host cells and discussion of the reactions that occur on the fibers themselves will be reviewed. The toxicity and pathogenicity of the various forms of asbestos are a cumulative response to their respective physical, mechanical, and chemical properties, as is discussed later in this chapter. However, once asbestos fibers, or indeed any material, reach the terminal airways and alveoli complex changes occur to the fibers that alter their chemistry, and result in reactions that make the fibers more or less pathogenic.

Specific emphasis will be placed on how resident alveolar macrophages in attempting to remove asbestos from the terminal respiratory tract, initiate a chronic inflammatory reaction. Additionally, a review will be provided as to how the interaction of multiple risk factors and the balance between clearance and persistence might lead to the array of diseases associated with, or believed to be associated with, the inhalation and deposition of asbestos in the terminal bronchioles and alveoli of the lung. The resultant diseases may be relatively benign with little or no impairment of lung function as, for example, with pleural effusions, visceral pleural fibrosis, or parietal pleural plaques. On the other hand, they may be

potentially life threatening as, for example, in instances of asbestosis with a more diffuse fibrosis of the lung parenchyma and lesions in the terminal airways. Finally, they may also be neoplastic, for example, with lung cancers and malignant mesothelioma. It is still unclear as to what level of asbestos exposure lead to a defined sequence of diseases, considering individual variation in susceptibility. The risk and progression of asbestos-induced disease is dependent on factors such as the length of exposure, the total fiber burden, the size of the fiber, and the time between initial and final exposure. However, there has been a suggestion that asbestosis is a predictor of lung cancer risk in both experimental animals[1] and humans.[2] There is some evidence that pleural plaques might be more than benign markers of former asbestos exposure, and could signify dysfunctional areas, indicate an immunological deficiency, or even indicate the site of future malignancies.[3–5] However, it does seem reasonable that many of the cellular and molecular processes that will be discussed underlie each of these disease states, and it is the complex interplay of these interactions that ultimately govern the final physiological outcome. Finally, while there are almost certainly genetic factors that predispose a given individual to a particular endpoint outcome of exposure these will not be discussed in great detail.

4.2 CLEARANCE

Asbestosis appears to be associated with a high level of aggregate exposure, either a very high level over a short period or a low level for an extended period. The level of exposure seems to control the latency period between initial exposure and the development of disease. This appears to be inversely related to the level of exposure ranging up to 40 years (for mesothelioma). The primary pulmonary defense to inspired fibers is their entrapment in the mucous of the upper airways or engulfment (phagocytosis) by alveolar macrophages. In either case, clearance is by way of the muco-cillary escalator and elimination through the gastrointestinal tract. Transmission electron microscopy of sputum samples shows the presence of fibers, coated fibers, and macrophages (Figure 4.1). The confounding effects of cigarette smoking and asbestos exposure probably reflect a number of synergistic effects including the impairment of pulmonary clearance mechanisms by the components of cigarette smoke and the adsorption of nitric oxide (NO) onto the fiber surface.[6] There is some evidence[7] that cigarette smoke stimulates the uptake of asbestos by pulmonary epithelial cells, which in turn causes cytokine release and mechanical damage to the cells. Other mechanisms also affect the balance between clearance and persistence and ultimately the toxicity of fibers. Size is one factor. Shorter fibers may be engulfed entirely by alveolar macrophages, which may facilitate their clearance by way of the muco-cillary escalator. However in instances of heavy exposure this system may become overloaded,[8,9] and the macrophages die in the terminal airways releasing not only the cellular contents but also the fibers. Uptake of fibers by pulmonary epithelial cells may facilitate their translocation to extrapulmonary sites through the lymphatic system. There is some evidence that

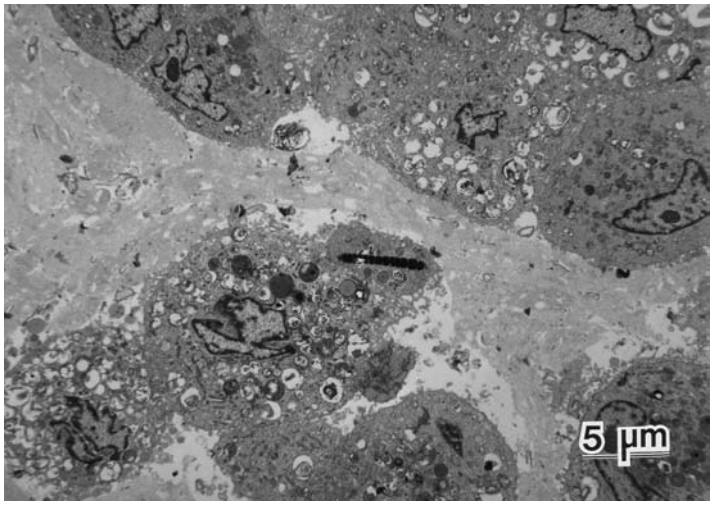

Figure 4.1 Transmission electron microscopy of a sample of sputum showing macrophages (including one with a phagocytozed ferruginous body) and associated mucous material.

alveolar macrophages can also migrate out of the alveolar spaces into the lymphatic system,[10] and thence to the hilar lymph nodes. Equally, fibers cleared from the lungs may be taken up by intestinal epithelial cells during their passage through the gut ultimately resulting in their deposition in the abdominal cavity. Short fibers taken up by dividing cells can interfere with spindle formation and chromosome separation and thus the separation of the daughter cells. The composition of asbestos is another factor. Magnesium can be leached from chrysotile fibers, and consequently they are more readily dissolved than amphibole fibers.[11–13] Fibers longer than approximately 16–20 μm are cleared much less efficiently at least in animals,[13,14] probably reflecting the inability of the alveolar macrophages to phagocytoze these fibers. This prediction of the presence of smaller fibers in extrapulmonary sites compared to pulmonary sites was confirmed by Dodson et al.[15] who also reported recently that the length of the longest fibers found at extrapulmonary sites (omentum and mesentery) in a cohort of mesothelioma patients were shorter than those in pulmonary sites, but that fibers up to 70 and 40 μm were found in omentum and mesentery, respectively. Short fibers are the ones that reach extrapulmonary sites most readily, including sites where mesotheliomas develop.

As discussed by Pezerat,[16] small isometric particles are cleared much more readily through the lymphatics from the pleura and peritonia, than from the lung parenchyma. However, fibers are not cleared efficiently from mesothelial tissue due to their large size compared to the stomata (2–10 μm).

4.3 MOLECULAR PROCESSES

4.3.1 Introduction

The surfaces of minerals may be modified within the lung by processes such as the adsorption of proteins or other molecules or by uptake into cells. Transmission electron microscopy of tissue sections (Figure 4.2a) and either transmission or scanning electron micrographs of digests of lung (Figure 4.2b) show mixtures of uncoated fibers and the characteristic asbestos or ferruginous bodies. Magnesium leached

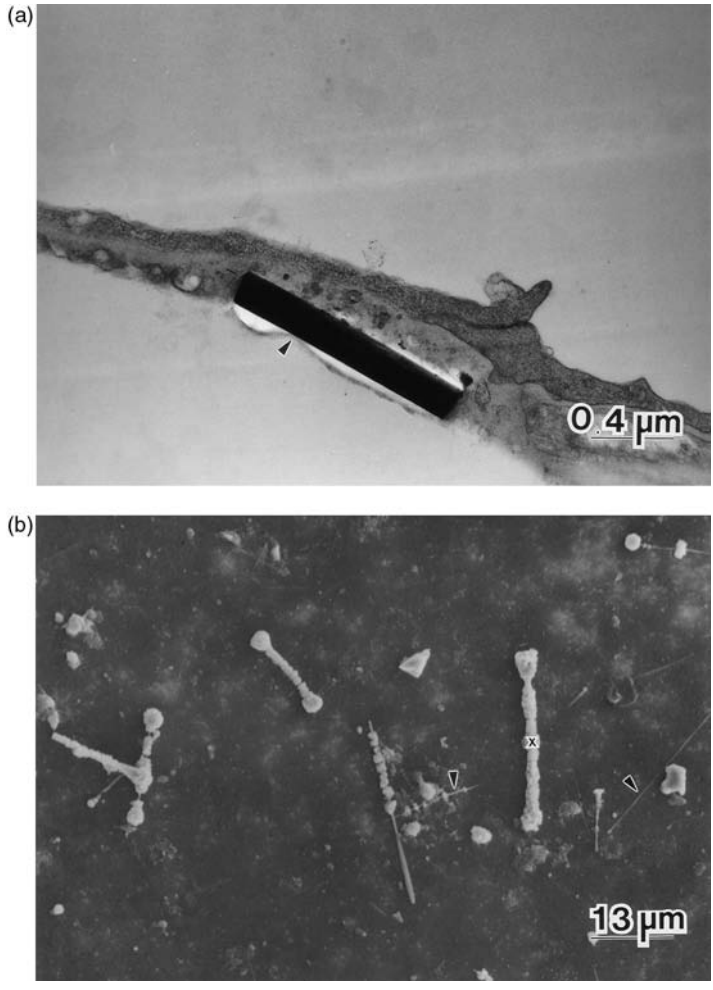

Figure 4.2 (a) Transmission electron micrograph of an amosite asbestos fiber inside a guinea pig type I alveolar cell 2 h after initial exposure. Bar 0.4 μm. (b) Scanning electron micrograph of a mixture of ferruginous bodies and uncoated fibers recovered from a lung digest.

from chrysotile fibers,[17] would change surface charge from positive to negative and affect toxicity.[18] Either surface iron or iron leached from crocidolite or amosite asbestos[19] is able to participate in a range of redox reactions. Ferrous (Fe^{2+}) iron may reduce oxygen, and thereby participate in the generation of a wide range of reactive oxygen species (ROS). In turn ferric (Fe^{3+}) iron may be reduced by superoxide or ascorbate, and thereby participate in redox cycling. The net result is that the hydrogen peroxide and superoxide generated will produce hydroxyl radicals. Nitric oxide produced by lung cells also reacts with superoxide to produce peroxynitrates that are potent in oxidizing and nitrating lipid and protein molecules. Similarly, ROS are injurious to DNA and other macromolecules.

4.3.2 Changes in Fibers in the Lung Milieu

4.3.2.1 Iron

A number of studies have indicated that iron plays a significant role in the pathogenicity of inhaled fibers. Dai et al.[20] showed that loading titanium dioxide fibers with various amounts of Fe^{2+}–Fe^{3+} iron, and then exposing rat tracheal explants to these resulted in increased procollagen gene expression and elevated tissue hydroxyproline (a marker for collagen). The presence of the ROS scavenger, tetramethylthiourea, prevented the activation of transcription factor NF-κB, decrease of total levels of IκB, the cytoplasmic inhibitor of NF-κB, and the increase in proportion of serine- and tyrosine-phosphorylated IκB. Together this suggests that surface iron is the crucial element in the fibrogenic response, and this is mediated through ROS. Similarly, the pathogenicity of air pollution particulate, PM_{10}, has been shown to be mediated through iron-generated hydroxyl radicals.[21] These particles upregulate the PDGF-α receptor in cultured fibroblasts,[22] indicating that the metal component of the particles is central in generating the cellular response.

The surface reactivity of asbestos reflects the amount of bioreactive iron available. This is a function, initially at least, of the chemical composition of the asbestos. However, it is important to note that the chemical composition or the bioavailability of the iron will change with time in the lung. On one hand, iron may be leached from fibers and such soluble iron would be potently pathologic at least briefly until it became sequestered. In a cell-free DNA strand break assay, Lund and Aust[23] demonstrated that the ability of asbestos to induce DNA single-strand breaks was dependent on iron mobilized from the fibers, since the effect was blocked by the addition of desferrioxamine B (a Fe^{3+} iron chelator that makes it redox inactive) and enhanced by the presence of molecules like ascorbate that facilitated redox cycling of the iron. Hydroxyl radical scavengers completely inhibited the DNA damage suggesting that DNA damage is mediated through the hydroxyl radical. Interestingly, the number of breaks reflected the iron content of the various forms of asbestos. Subsequently, Hardy and Aust[24] showed that pretreatment of crocidolite asbestos with the iron chelator desferroxamine attenuated its ability to subsequently induce DNA damage. Presumably this effect is mediated by the removal

of bioavailable surface iron. They also demonstrated that treated and untreated crocidolite asbestos will bind Fe^{2+} iron from solution, and that this restored the DNA nicking activity of the desferroxamine-treated asbestos but did not increase the activity of the untreated asbestos. This suggests that addition of iron from exogenous sources may extend the reactive lifetime of fibers almost indefinitely. It should be noted that even non or low-iron containing asbestos fibers like chrysotile when phagocytozed by macrophages are compartmentalized in the "iron-rich" environment of the sidersome such that an "iron loading" effect may occur.

The importance of exogenous iron binding to respired fibers is illustrated by erionite, a fibrous zeolite that has been reported to be highly carcinogenic yet it contains little or no iron. Zeolites are utilized commercially as supports for transition metal catalysts (e.g., in petroleum manufacturing and in vehicle exhausts catalytic converters). Eborn and Aust[25] have shown that untreated erionite produces no DNA single-strand breaks in a cell-free assay, but it will readily bind iron. If the iron is in the Fe^{2+} state then DNA breaks are induced in their assay in the absence of ascorbate. However, not surprisingly, if it is bound in the Fe^{3+} state ascorbate is required to facilitate redox cycling. This suggests that the uptake of iron following inhalation may be the mechanism through which erionite induces carcinogenesis. We have shown (Atkinson and Dodson, unpublished data) that indeed erionite does acquire iron over time in a guinea pig inhalation model.

In the body, free iron is tightly controlled and there are mechanisms to sequester it with either transport (transferrin) or storage (ferritin) proteins. Iron overload diseases such as hereditary hemochromatosis[26,27] and prophyria cutanea tarda[28,29] are associated with an increased risk of hepatic cancer. Asbestos bodies represent a class of structures in which a coating has been deposited onto an asbestos core. These include ferruginous bodies in which an iron protein coat is present giving them a characteristic yellow-beaded structure under light microscopy (Figure 4.3). The presence of these structures in sputum or in lung parenchyma is indicative of prior exposure to asbestos.[30] However, an analysis of nearly 4000 fibers from human patients suffering from asbestos-related disease indicated that the percentage of fibers that become coated varies substantially from 27% for amosite down to 5% for chrysotile.[31] Light microscopic analysis of ferruginous bodies recovered from guinea pigs 6 months after intratracheal instillation of crocidolite asbestos showed golden yellow beaded structure; energy dispersive x-ray analysis and x-ray photoelectric spectroscopy showed an uptake of iron; and immunolocalization studies using anti-ferritin antibodies localized ferritin to the beaded structures. Despite the increase in chelatable iron, oxidant generation by the asbestos bodies was less than that of uncoated fibers suggesting that the accumulation of nonbioactive iron, presumably associated with ferritin, served as a host-protective mechanism.[32] Amosite asbestos has been shown to bind ferritin in a cell free system and it has been suggested that lysosomal enzymes may partially digest the ferritin molecule during repeated cycles of phagocytosis exposing the iron core and allowing it to participate in ROS generation[33] as Lund and Aust[34,35] have demonstrated for amosite.

Since ferruginous bodies form on longer fibers this phenomenon presumably reflects another manifestation of frustrated phagocytosis by alveolar macrophages.

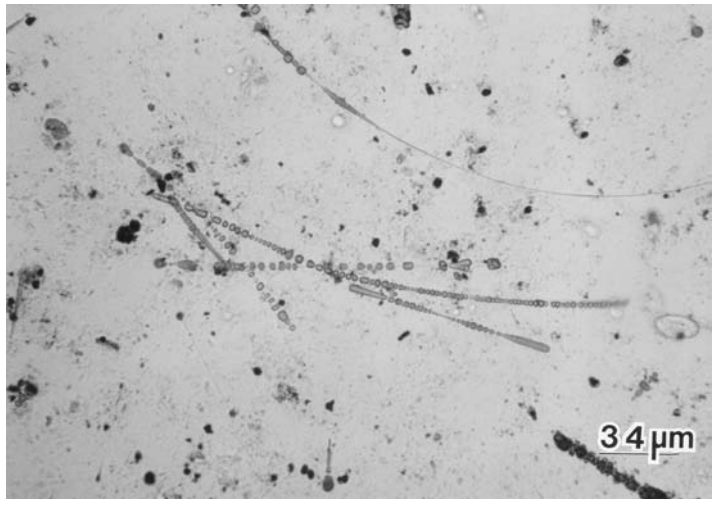

Figure 4.3 Isolated ferruginous bodies as visualized by light microscopy show variable patterns of coating and exposed core material.

There are a number of possible sources of the free iron component. It could be derived from the fibers themselves. And, it might result from the frustrated phagocytes fusing to form giant cells that in turn generate superoxide that reduces surface Fe^{3+} iron to Fe^{2+} iron and solubilizes it,[36] or even by a direct release from ferritin by superoxide.[37] Once oxidized back to Fe^{3+} iron, free iron would become stored in ferritin. Nonfiber sources of iron must exist,[38–40] since ferruginous bodies also form on cores of chrysotile asbestos that contain little or no iron through their interaction with macrophages. This was shown from environmental sources (cigarette smoke, mining), from metal coordinated to low molecular weight chelates such as nucleotides or amino acids, or from sources within the macrophage. It appears that iron bound to either transferrin or lactoferrin cannot be complexed with the fiber.[41]

Aside from the role of fiber bound iron, any iron solubulized from the fibers would play an important role in human pathology. For example, human bronchial epithelial cells have been shown to absorb nontransferrin bound iron as Fe^{2+} iron through the anion exchange protein 2.[42] This process requires reduction of Fe^{3+} iron to Fe^{2+} iron that is mediated by superoxide.

Aside from issues of respirability there remains a misconception that long asbestos fibers are more harmful than short fibers in part since they are less easily removed from the lung than short fibers. Part of this misconception arises from the size of fibers that are "counted" in regulatory count schemes. It should be noted that this definition stems from issues of standardization and instrument limitations rather than ones of potential pathogenicity.[43] Having said that, there are certainly physical and chemical differences between short and long fibers that may affect their relative toxicities. Short fibers are more easily phagocytozed by macrophages and consequently cleared, although, if burdens are heavy the end result may be death

of the macrophage releasing not only ingested fibers but also the cellular contents (Figure 4.4). In the case of longer fibers the phenomenon of frustrated phagocytosis (Figure 4.5) leads to a state of chronic inflammation. Perhaps the most obvious difference between short and long fibers is their surface area per unit mass. Short fibers have a higher surface area, so if surface reactive iron is the mediator of asbestos-related disease one would predict that short fibers would be more bioreactive and therefore more toxic than longer fibers. However, bioreactivity is a function not only of the total amount of iron but, perhaps more critically, of the redox state of the surface iron and its availability to redox cycle and participate in ROS generation (see subsequently). Comparison of the oxidation state and coordination sites of iron on the surface of long and short fibers of amosite asbestos using infrared spectroscopy[44] demonstrated that both types have more Fe^{2+} iron than Fe^{3+} iron, but that long fibers have more iron in the single coordination site, which appears to be more oxidized. This suggests that longer fibers may have surface available iron that is more redox active than short fibers. *In vitro* experiments have demonstrated that increased surface complexed Fe^{3+} iron does increase DNA strand breaks.[41] It should be noted that although chrysotile has little or no surface iron it is still charged.

4.3.2.2 Lipids

The surface of the distal lung is coated with surfactant, a complex mixture of phospholipids and the four surfactant proteins A, B, C, and D, that is also known as the lung lining fluid. This serves to reduce surface tension preventing the lung from collapse and facilitating gas exchange. Surfactant has immune protective properties

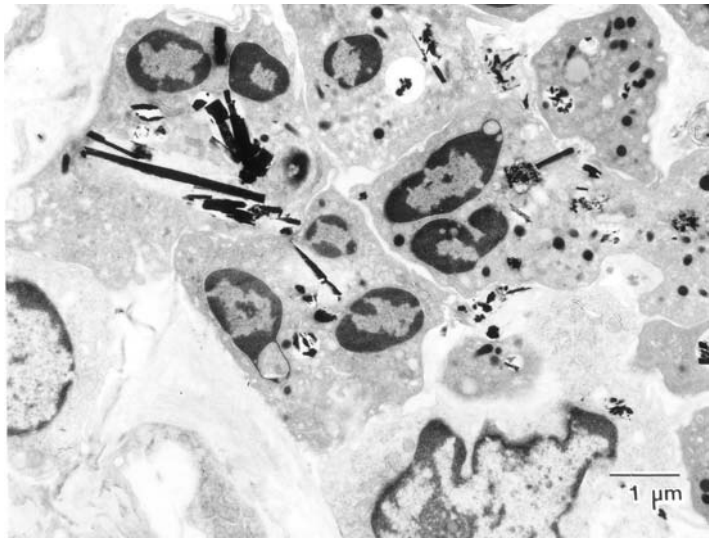

Figure 4.4 Transmission electron micrograph of lung tissue showing the early stages of the reaction of alveolar macrophages to inhaled asbestos.

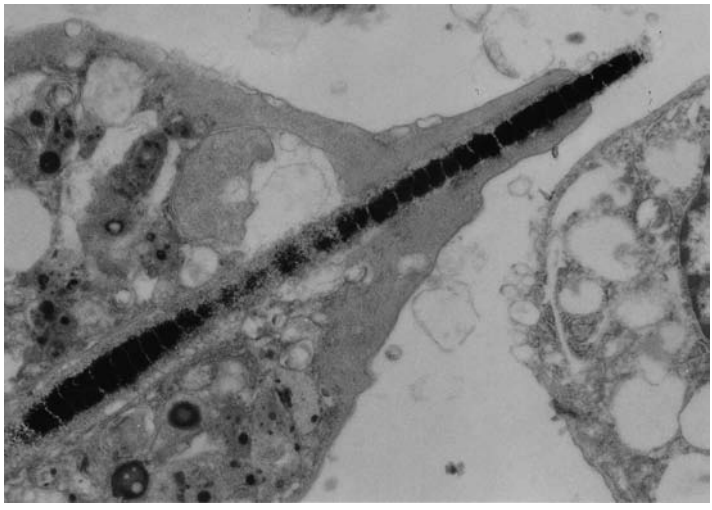

Figure 4.5 Transmission electron micrograph of an alveolar macrophage in the process of attempting to phagocytoze a long asbestos fiber resulting in "frustrated phagocytosis."

and also facilitates the removal of impacted particulates and microorganisms through the muco-cillary escalator. The unidirectional beating of cilia continuously moves the surfactant layer towards the throat over an underlying aqueous layer. In the absence or reduction of the aqueous layer the escalator stalls, for example, in cases of cystic fibrosis, humans with dynein defects that result in abnormal cilia, and heavy cigarette smokers. In all of these instances infection rates increase due to decreased clearance of microorganisms. Experimental studies have also suggested that surfactant- coated fibers release more Fe^{3+} iron than uncoated fibers at the approximately neutral pH of the lung lining fluid.[45] This would result in the increased generation of ROS.

4.3.2.3 Protein Components

Other materials in the lung lining fluid, such as surfactant proteins themselves and a variety of other proteins including immunoglobulins may also coat asbestos fibers and affect the surface reactivity of the fibers. *In vitro* studies have suggested that the adsorptive capacity of asbestos reflects the charge density of the protein.[46] IgG has been shown to specifically enhance superoxide production by alveolar macrophages stimulated with chrysotile or crocidolite asbestos in a dose-dependent fashion.[47,48] Presumably, adsorbed IgG crosslinks macrophage receptors and this activates the cell to produce superoxide. Conversely, inhaled oxidants and ROS derived directly from inflammatory cells as part of the protective respiratory burst or through reactions on asbestos fibers themselves have deleterious effects on surfactant proteins and lipids in the lung lining or epithelial lining fluid (ELF), particularly in the terminal airways where the thickness of the fluid layer, and therefore its antioxidant potential is less.[49] A recent report[50] suggested the presence of oxalate

crystals associated with ferruginous bodies can be explained by the iron mediated oxidation of adsorbed ascorbate. Ascorbic acid is one of the major components of the antioxidant defenses of the lung lining layer. Incubation of crocidolite fibers in an aqueous solution of ascorbic acid consumed ascorbic acid and released 17% of the iron and 6% of the silica in the fiber into the supernatant. This exceeded the surface amount suggesting a partial dissolution of the fiber by ascorbic acid.[51]

Fibronectin, a component of the extracellular matrix that is present in large amounts, has also been shown to bind tightly to asbestos fibers (but not to silica). This in turn facilitates the binding of the fibers to the cell surface through integrin receptors for fibronectin.[52] Vitronectin, the major adhesive protein of serum, has been shown to adsorb to crocidolite asbestos and enhance its phagocytosis by mesothelial cells through binding to the $\alpha V\beta 5$ integrin.[53]

The complement system is an innate immune system that can be activated through three distinct pathways: the classical pathway, the alternative pathway, and the lectin pathway. The classical pathway is triggered by antigen–antibody complexes, the alternative pathway by complex polysaccharides such as those found on yeast cell walls and by dextrans, and the lectin pathway acts through mannose binding protein, a member of the collectin family of proteins that include the classical pathway protein C1q and surfactant protein A (SP-A). These pathways converge and act through the same terminal five components C5–C9 that are activated and assembled to form the membrane attack complex (MAC) on the surface of the target cell. All components of the classical and alternative pathways have been shown to be present in the lung, although, the liver is the major source of the circulating complement proteins isolated alveolar macrophages and alveolar type II cells have been shown to synthesize certain components of the classical and alternative pathways. The alternative pathway Factor B is present in much lower concentrations in the lung lining fluid than in serum as is the classical pathway activator C1q. Despite structural similarities between C1q and SP-A, *in vitro* experiments have not demonstrated evidence that SP-A can substitute for C1q in activating the cascade. Asbestos will activate complement within the lung that generates chemoattractants (C5a), which attract inflammatory cells to the sites of fiber deposition.[54] Significant complement is activated in concentrated bronchioalveolar lavage fluids (BAL) and in rat serum by both chrysotile and crocidolite asbestos (and other particles) and this correlates with macrophage accumulation in a rat inhalation model.[55] In an *in vitro* system using rat plasma this conversion has been shown to involve an initial oxidation of C5 by Fenton reaction generated hydroxyl radicals catalyzed by the asbestos bound iron.[56,57] Chrysotile and crocidolite fibers activated the proteolytic enzyme kallikrein with the effect of crocidolite being more potent. The kallikrein in turn cleaves the oxidized C5 to produce a C5a-like fragment with the same inflammatory properties as C5a.[57] C5a increases vascular permeability and asbestos increases epithelial permeability. Therefore together the net result would be an increase in alveolar permeability and an accumulation of plasma proteins in the alveolar spaces, which is characteristic of the early stages of asbestosis. It has been suggested that complement activation might then serve to allow pulmonary macrophages to detect inhaled particles.

4.3.3 Generation of Reactive Oxygen Radicals

The presence of mesothelioma is generally accepted as a disease of asbestos exposure in the vast majority of cases although there are reports of an occasional occurrence in which there is no history of asbestos exposure; for example, following radiation therapy,[58,59] chronic pleural inflammation,[60] and chemical carcinogens.[61] Of course these reports may just represent outliers in which a limited exposure produced a tumor that in normal circumstances correlates with both the level of exposure[62] and the type of asbestos.[63] At the same time this may indicate that there is no threshold "safe" level of exposure or that if there is, this varies from person to person based on both their genetic predisposition to develop asbestos-related disease and their ability to clear inhaled fibers. It does appear that exposure to amphibole fibers is much more likely to result in mesothelioma development than the exposure to chrysotile,[63] and it has been suggested by some that mesotheliomas that do result from exposure to chrysotile asbestos may, in fact, be due to the tremolite asbestos that contaminates Canadian chrysotile asbestos. This effect most probably reflects two properties of the amphibole asbestoses; first their greater resistance to dissolution in the lung and second their iron content which facilitates the production of reactive oxygen radicals H_2O_2 (hydrogen peroxide) and $OH^{\bullet}$ (hydroxyl radical) via a Haber–Weiss reaction.

The production of ROS by phagocytic cells will be discussed subsequently but a cell free production mechanism also exists. As described in much more detail elsewhere in this chapter, the various forms of asbestos have a hydrated silicate structure in common. Where they differ is in their metal counterions. The amphiboles, crocidolite and amosite, contain up to 25% of iron. While the iron component of chrysotile is much lower (approximately 5%) it is still significant. Also, as mentioned earlier, short chrysotile fibers are readily phagocytozed by macrophages and pass into the "iron rich" sidersome (Figure 4.6) where they can adsorb iron. Iron is central to radical mediated cellular pathology since it catalyzes the production of the extremely reactive hydroxyl radical from hydrogen peroxide via the Fenton reaction:

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + HO^- + HO^{\bullet}$$

Ferric ions can be reduced back to the Ferrous form by superoxide or other biological molecules:

$$Fe^{3+} + O_2^- \longrightarrow Fe^{2+} + O_2$$

This cycle, which results in the generation of hydroxyl radicals from superoxide and hydrogen peroxide catalyzed by iron is known as the Haber–Weiss reaction:

$$O_2^- + H_2O_2 \longrightarrow HO^- + HO^{\bullet} + O_2$$

Since both superoxide and hydrogen peroxide are generated as part of the response of phagocytic cells to environmental stimulus, including asbestos fibers,

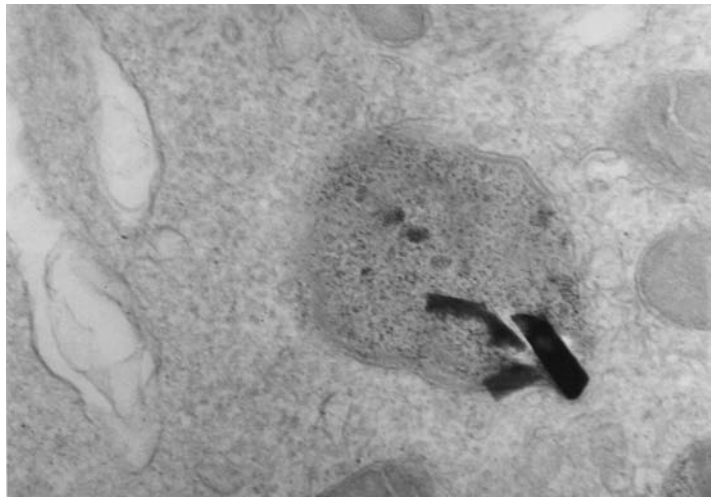

Figure 4.6 Transmission electron micrograph of short amphibole asbestos fibers associated with the iron-rich macrophage sidersome.

it is clear that all of the components are in place in the lungs of asbestos-exposed individuals. Hydrogen peroxide and hydroxyl radicals are generated in mixtures of human neutrophils and a wide range of different mineral fibers.[64] Natural fibers such as asbestos, erionite, and wollatonite produced approximately twice the amount of hydrogen peroxide and three times the amount of hydroxyl radicals as manmade fibers (rock wool, glass wool, and ceramic fibers) in the presence of external iron. In the absence of additional iron the natural fibers still produced considerable hydroxyl radicals indicating that the fibers alone can catalyze the Fenton reaction.

It should be noted that the ability to generate hydroxyl radicals is not the sole factor in determining potential pathogenicity and fibrogenic potential. For example, a careful analysis of the ability of a variety of nonasbestos mineral fibers to generate hydroxyl radicals showed that the amount of iron correlated with hydroxyl radical formation, but cytotoxicity did not. Cytotoxicity correlated with the ability of the mineral to produce lipid peroxidation (albeit through hydroxyl radical formation).[65] Presumably, other factors dictate cytotoxic potential such as the proximity of the hydroxyl radical generating site and the site of potential injury.

Pezerat[16] has proposed that even in an environment where superoxide and hydrogen peroxide are absent, for example, inside an epithelial cell that has phagocytozed an asbestos fiber, the potential exists for the generation of hydroxyl radicals from dissolved molecular oxygen on a reducing surface (such as provided by Fe^{2+} iron):

$$\begin{aligned} O_2 + e &\longrightarrow O_2^- \\ O_2^- + e + H^+ &\longrightarrow H_2O_2 \\ H_2O_2 + e^- &\longrightarrow OH^\bullet + OH^- \end{aligned}$$

Given the inefficient clearance of fibers from mesothelial tissue, the generation of ROS for decades through this mechanism could explain both the rarity and long latency period of mesothelioma. Conversely, the high concentrations of the enzymes superoxide dismutase and catalase in the lung, in addition to more efficient clearance mechanisms, provide a much higher level of protection in lung versus mesothelium against the potentially much higher and more potent ROS generation.

In a comparison of the surface reactivity, cytotoxicity and transforming potential of iron covered against untreated refractory ceramic fibers,[66] it was apparent that the redox state of the iron is critical. Traces of Fe^{2+} iron increased cellular effects, which were attenuated by even large amounts of Fe^{3+} iron. As mentioned earliler the bioavailability of Fe^{2+} iron is the critical factor. Guilianelli[67] has shown that the cytotoxic effects of iron containing minerals (nemalite, chrysotile, and hematite) on primary cultures of rabbit tracheal epithelial cells reflect their content of bioavailable Fe^{2+} iron (nemalite $>$ chrysotile $>$ hematite), and this in turn is manifested in the production of ROS measured using an electron spin resonance (ESR) spin trap. The cytotoxic effect is reduced by the addition of desferroxamine, an iron chelator. Phytic acid another iron chelator has been reported to attenuate pulmonary inflammation and fibrosis in rats following intratracheal instillation of amosite asbestos.[68] In an *in vitro* system Dai and Churg[69] exposed rat tracheal explants to amosite asbestos without any additional iron or after loading with increasing amounts of iron and then measured expression of a number of genes. They showed that expression of procollagen and of the cytokines PDGF-A and transforming growth factor-beta (TGF-β) all increased when the explants were exposed to asbestos and that the level of expression correlated with the amount of iron bound. These effects were suppressed by the addition of either desferroxamine or the ROS scavenger tetramethylthiourea to the media suggesting that the effects on gene expression were mediated through iron generated ROS. Presumably ROS act through either the NFκB path on procollagen expression or the ERK system for PDGF-A and TGF-β expression. No effect was seen on PDGF-B, tumor necrosis factor-alpha (TNF-α), or (TGF-α) expression.

Notwithstanding all these data, there is a school of thought that suggests mesothelioma may have causes other than prior asbestos exposure. This hypothesis is reinforced by the identification of familial clusters of mesothelioma without any obvious asbestos exposure.[70] Prior to 1963, the virus SV40 was a contaminant of the polio vaccine and therefore is present in a large number of adults. Because of this it is not surprising that SV40 DNA sequences have been found in patients diagnosed with mesothelioma both with and without apparent asbestos exposure as well as in patients with other cancers.[70] There are reports that mesothelial cells are particularly sensitive to transformation by SV40 because of the ability of the SV40 large T-cell antigen to inactivate p53.[71,72] However, it appears that the age group with the greatest likelihood of risk through the polio vaccine route has shown a decline in the incidence of mesothelioma while those in age groups outside of this window continue to show an increase. Another possible alternative explanation lies in the physical properties of the fiber itself that may interfere with chromosome segregation during mitosis and could result in malignancy. Mesothelioma cells have been reported

to be aneuploid and to have chromosomal rearrangements; and chromosomal abnormalities have also been associated with the treatment of normal human mesothelial cells with amosite asbestos in culture.[73,74] This is discussed in more detail subsequently.

4.4 CELLULAR INTERACTIONS

4.4.1 Introduction

Asbestosis is a disease associated with occupational levels of exposure to asbestos. It is characterized by a long latency period between the initial exposure and the manifestation of the pathogenic changes in lung architecture associated with the disease. These changes are primarily the deposition of collagen in the interstitium associated diagnostically with the presence of asbestos bodies (ferruginous bodies composed of an iron or protein coat deposited on a central asbestos core) in lung histology sections. These changes are similar to those associated with idiopathic pulmonary fibrosis and are characterized by a chronic inflammatory reaction and the persistent generation of both proinflammatory and profibrotic mediators. IPF and asbestosis are refractory to treatment with corticosteroids and immunosuppressants, and historically asbestosis progresses even after workers are no longer exposed to asbestos dust.

The study of lung pathology following inhalation of asbestos in humans and experimental animals has led to the conclusion that lower levels of exposure[75] result in reversible inflammatory reactions in isolated areas with evidence of alveolar macrophages with heavy fiber burdens but comparatively normal lung histology. In contrast at higher levels of exposure there is a much more extensive and prolonged inflammatory reaction. Mesenchymal cells deposit increased amounts of extracellular matrix including collagen. Alveolar macrophages secrete growth factors and oxidants, while other cells proliferate. Neutrophils, T-cells, and mast cells are recruited and accumulate in the lung interstitium. Interactions between these "defense" cells leads inexorably to damage to specific lung cell populations. Injury to type I epithelial cells is an early event and results in increased proliferation of epithelial cells as a repair mechanism, but if this proliferation is unchecked it can lead ultimately to fibrosis and carcinogenesis. It is not clear if proliferation is initially only at sites of fiber deposition and subsequently occurs at sites of relocation or it is mediated by mitogenic cytokines.

There is data to suggest that the increased proliferation of epithelial cells and fibroblasts may be a consequence of the upregulation of early response proto-oncogenes such as *c-fos*, *c-jun*, and *c-myc*. Fos and Jun proteins dimerize to form the AP-1 transcription factor that in turn binds to the promoter regions of a number of genes that mediate inflammation, cell proliferation, and apoptosis. *In vitro* experiments have shown marked increase in apoptosis of mesothelial cells exposed to asbestos.[76,77] Similarly there is a marked increase in apoptosis of bronchiolar and type II cells in the lungs of rats exposed to a combination of asbestos and cigarette smoke.[78]

Tissue macrophages play a central role in modulating the initiation and maintenance of an inflammatory response. Macrophages in the alveolus, the pleural space, and the peritoneal space may be exposed to asbestos either at the site of primary deposition or following translocation. *In vitro* these cells all produce superoxide, NO, and TNF-α upon activation, but alveolar macrophages produce significantly higher amounts.[79] Treatment of peritoneal macrophages with crocidolite or chrysotile asbestos causes the release of intracellular enzymes lactate dehydrogenase (LDH) and β-glucuronidase (β-Glu),[80] and longer fibers are more potent. The release of cellular contents would not only perpetuate the inflammatory response but also is indicative of the cellular cytotoxicity of the fibers.

4.4.2 Reactive Species

Just as chronic inflammatory responses are becoming increasingly implicated in the progression of a range of chronic diseases, so too a persistent inflammatory response may well be central to the progressive processes of cell injury, proliferation, apoptosis, and fibrogenesis that represent the lung injury in response to asbestos. The generation of ROS is probably critical to this progression. ROS can be formed either directly on the fibers themselves (discussed earlier),[19] in concert with cells growing *in vitro* [81] or may derive from the respiratory burst as a defense mechanism of cells phagocytozing or attempting to phagocytoze fibers.[82] Longer fibers that cannot be completely phagocytozed by alveolar macrophages cause a concomitantly prolonged release of ROS.[83] The ultimate consequence of this "frustrated phagocytosis" is the dissolution of the phagocyte and further generation of ROS. This results in an ongoing recruitment of neutrophils into the alveolar spaces. Neutrophils themselves are short-lived and ultimately release harmful enzymes and reactants. Further credence is given to the idea that phagocytosis of asbestos fibers is a necessary step in asbestosis or asbestos-induced disease pathogenesis from the observation that the phagocytosis of crocidolite asbestos by rabbit pleural mesothelial cells in culture induces oxidative stress, DNA damage, and apoptosis.[84] Fiber phagocytosis is enhanced by coating fibers with vitronectin. The enhancement is probably mediated through binding to cell surface integrins as the effect was blocked by the addition of RGD peptides.

As already discussed the direct generation of ROS on iron-rich asbestos such as amosite and crocidolite is a significant factor in the mechanisms underlying asbestos-related disease. However chrysotile asbestos, the major commercial form of asbestos used in the USA, contains only a few percent elemental iron ($<5\%$ compared to 27–36% in crocidolite). Comparison of the effects of chrysotile with those of crocidolite hence can be used to assess cell mediated radical generation without the compounding effects of direct fiber generated radicals. Mouse macrophage cell lines exposed to crocidolite or chrysotile asbestos (as well as glass wool, rock wool, and ceramic fibers) produced nitric oxide. The cells also produced increased superoxide in response to the asbestos fibers and glass wool, and this appeared to be due to decreased levels of the reduced form of the cellular antioxidant glutathione (GSH)

owing to its nitrosylation to form *S*-nitrosothiol. This may be an indicator of continuous oxidative stress in asbestos exposed cells. NO is also produced in the lung as an inflammatory signaling molecule. Both inducible nitric oxide (iNOS) RNA levels and reactive nitrogen species (RNS) increase in alveolar macrophages exposed to asbestos *in vitro* and in lung homogenates harvested after intratracheal deposition of asbestos fibers.[85,86] Conflicting evidence exists as to whether nitric oxide expresses damaging and inflammatory or antioxidant and anti-inflammatory properties. The majority of published studies suggest that nitric oxide plays a damaging role in pulmonary injury resulting from exposure to asbestos in contrast to an anti-inflammatory role following exposure to lipopolysaccharide (LPS).[87] UV spectrophotometric assays have demonstrated that NO from cigarette smoke or other sources adsorbs to asbestos and other types of fiber.[6] The amount of NO adsorbed as well as how strongly it is absorbed seem to be fiber dependent. NO reacts with superoxide to produce peroxynitrates. Both ROS and RNS are potent in oxidizing DNA, lipid, and protein molecules. RNS may also nitrate macromolecules. Both ROS and RNS cause mutagenic DNA lesions,[86] and other gross chromosomal changes have been reported *in vitro* [88] as a consequence of exposure to large amounts of asbestos. At the cellular level the effects of these macromolecular changes also include blockage of the cell cycle, and the formation of viable aneuploid and polyploidy cells. It is tempting to hypothesize that these events are relevant to the progression of disease in humans although this is unclear.

As has already been mentioned inhaled asbestos translocates to the pleural space[89] and has been shown to be present up to 2 years after a single inhalation.[90] In rat pleural mesothelial cells stimulation with IL-1β in the presence of either chrysotile or crocidolite asbestos causes an upregulation of iNOS mRNA production (assayed by RT–PCR), and the production of both NO and peroxynitrates.[91] Interestingly, the effect of chrysotile asbestos was greater than that of crocidolite. Increases in tyrosine nitration, a consequence of the generation of peroxynitrate radicals have been shown in lung lysates from rats exposed to either crocidolite or chrysotile asbestos and these in turn result in phosphorylation and activation of the ERK1/ERK2 signaling pathways. Increases in ERK phosphorylation have also been demonstrated in BAL cells from asbestos-exposed rats and immunochemically in lung sections.[92]

4.4.3 Growth Factors, Cytokines, and Chemokines

In addition to the direct effects described earlier, reactive species have additional cellular effects mediated through the stimulation of cell-signaling cascades, the release of growth factors, cytokines, and effects on transcription factors. The literature was reviewed in an excellent article by Mossman and Churg[75] in 1998. As they stated, exposure to fibrogenic minerals results in changes in cytokine levels that are readily detected in *in vitro* model systems, in the BAL and lung. However these changes are so numerous that it becomes difficult to determine between cause and effect, or to determine what effect these have on the development of fibrosis or

carcinoma within the lung. As an example, Brody et al.[93] studied the bronchiolar-epithelium of rodents after exposure to chrysotile asbestos. After 3 days of 5 h of exposure per day, lesions developed that persisted for 6 months. Morphologically these showed a rapid proliferation of the epithelium and underlying mesenchymal cells along with deposition of connective tissue. Using *in situ* hybridization to assess gene activation and immunohistochemistry to assess protein levels they demonstrated elevation of TGF-α, TGF-β, PDGF A and B chains. As discussed in more detail subsequently TGF-α is a potent mitogen for epithelial cells and PDGF is for mesenchymal cells. TGF-β slows fibroblast growth but stimulates the deposition of extracellular matrix proteins. More recently Mutsaers et al.[94] have reported that BAL from asbestos-exposed patients was more mitogenic towards fibroblasts in culture than that from control unexposed individuals, but that there was no significant difference between the exposed individuals with asbestosis and those without asbestosis. They also showed that neutralizing antibodies to PDGF, TNF-α, IGF-1 (insulin-like growth factor 1), or IL-1β, did not reduce the differences in mitogenic activity between exposed and nonexposed individuals suggesting that the increased activity was not mediated by these cytokines.

4.4.3.1 Tumor Necrosis Factor-Alpha

Increased TNF-α messenger RNA expression and secretion has been reported by alveolar macrophages in patients after asbestos exposure or during idiopathic pulmonary fibrosis.[95] Using reverse transcription polymerase chain reaction (RT–PCR) assays Tsuda et al.[96] demonstrated that mRNA levels for TNF-α (and for IL-1α) increased in alveolar macrophages isolated from, and in lung tissue in general, rats exposed to chrysotile and crocidolite asbestos. Both cytokines also recruit and activate pleural macrophages in the rat which in turn release NO and TNF-α.[89] Similarly the treatment of rat alveolar macrophages in culture with either crocidolite or chrysotile asbestos[97] resulted in a dose-dependent release of TNF-α. This effect appears to be mediated through iron mediated generation of ROS as it is inhibited by the iron chelator desferroxamine. The hydroxyl radical scavengers tetramethylthiourea and DMSO also inhibited the response indicating that the hydroxyl radical is probably the active intermediary. These effects were mediated at the transcriptional level. TNF-α stimulated both collagen and fibronectin gene expression in fibroblasts *in vitro.* In fact, increased TNF-α production may have a critical role in the initiation of asbestos-related disease and is certainly one of the earliest changes in the pathogenesis of asbestos exposure. Ljungman et al.[98] showed increases in mRNA and in activity of TNF-α in rat alveolar macrophages exposed to crocidolite and chrysotile asbestos, but they noted that a man-made vitreous fiber or rock wool (MMVF 21), RCF1, and a silicon carbide whisker fiber also caused increased mRNA levels and the MMVF 21 increased activity in the time frame studied, arguing against a free radical mediated process. Driscoll et al.[99] have shown increased TNF-α and chemokine levels in experimental animals following exposure to asbestos before any evidence of pathological defects become

apparent. It is particularly interesting that treatment with a soluble human recombinant TNF-α receptor, that blocks the interaction between TNF-α and its cellular receptor, either cures or prevents the development of pulmonary fibrosis in mice exposed to either silica or bleomycin.[100] In contrast, work with rat tracheal explants exposed to amosite asbestos did not show these effects.[69]

4.4.3.2 Transforming Growth Factor-Alpha

Expression of TGF-α has been shown to be upregulated in the bronchiolar–alveolar ducts of rodents experimentally exposed to asbestos.[93,101] TGF-α binds to the epidermal growth factor (EGF) receptor. The extracellular domain of the receptor has been reported to be elevated in the serum of humans with asbestosis and carcinoma.[102] Again no changes were evident in the rat tracheal explants exposed to amosite asbestos.[69]

4.4.3.3 Transforming Growth Factor-Beta

TGF-β is a peptide that inhibits epithelial and mesenchymal cell proliferation and stimulates the synthesis of extracellular matrix components. It is produced as a biologically inactive complex with the latent-associated peptide (LAP). Dissociation of this complex regulates TGF-β activity. TGF-β has been shown by immunohistochemical means to be elevated at the sites of developing asbestos-related disease.[93,103] It acts as a chemoattractant for monocytes and neutrophils, as a mitogenic for mesenchymal cells and upregulates genes involved in the synthesis of collagen and fibronectin. All these events would be central in the development of pulmonary fibrosis and may be mediated through the actions of another cytokine, platelet derived growth factor (PDGF).[104] TGF-β levels were elevated in the rat tracheal explants exposed to amosite asbestos, and this seemed to be mediated by iron produced ROS.[69] Healthy lung contains high levels of latent TGF-β and this is activated by ROS and RNS.[105–107] In a cell free system ROS, generated by the iron in chrysotile or crocidolite asbestos in the presence of ascorbic acid activate the latent TGF-β. In a tissue culture system in which TGF-β was overexpressed in both A549 and mink lung epithelial cell lines it was activated in a concentration-dependant fashion by the addition of asbestos to the cultures. Addition of superoxide dismutase, catalase, or desferoxamine to the culture media reduced this effect. The effect appeared to be mediated by oxidation of LAP that was then unable to bind with TGF-β.

4.4.3.4 Platelet Derived Growth Factor

PDGF is mitogenic for mesenchymal cells, in general, and has been shown to specifically induce chemotaxis of fibroblasts *in vitro*.[108,109] Furthermore chrysotile asbestos has been shown to upregulate PDGF-α receptors on fibroblasts[110] and to stimulate its production[111] *in vitro* providing evidence of an autocrine stimulatory loop. Similar results have been reported for the effects of amosite asbestos on rat

tracheal explants[69] and demonstrated to be mediated through the iron induced production of ROS. Overexpression of PDGF-β from the surfactant protein C promoter in transgenic mice did not stimulate fibrosis in response to a subthreshold dose of aerosolized chrysotile asbestos but did stimulate collagen deposition and vascular smooth muscle hyperplasia.[112] Both wild type and transgenic animals continued to show a persistence of fibrosis 10 months after an 8 week once a week exposure regimen.

4.4.3.5 Interleukin 1 (IL-1)

In addition to the increase in TNF-α production Zhang et al.[95] also reported that IL-1 messenger RNA expression and secretion increased in macrophages from patients after asbestos exposure or during idiopathic pulmonary fibrosis and Simeonova et al.[97] also obtained similar results with rat alveolar macrophages. Also, as mentioned earlier, Tsuda demonstrated that mRNA levels for IL-1α increased along with TNF-α in alveolar macrophages isolated from, and in lung tissue in general, of rats exposed to chrysotile and crocidolite asbestos.[96] IL-1 stimulates collagen and fibronectin gene expression in normal fibroblasts *in vitro*, and fibrosis induced experimentally in mice with either silica or bleomycin can be prevented by treatment with a soluble receptor antagonist.[113]

4.4.3.6 Interleukin 8 (IL-8)

The proinflammatory cytokine IL-8 along with IL-1 and TNF-α may be involved in the earliest initiation of asbestos induced disease.[95,114,115] Early work by Antony showed that rabbit mesothelial cells in culture exposed to crocidolite or chrysotile asbestos release a heat stable protein neutrophil chemoattractant of molecular weight 6000–9000[116] (presumably IL-8) and Griffith et al.[117] showed that asbestos stimulates the release of IL-8 by human mesothelial cells. An approximately two-fold elevation of IL-8 levels have been reported in BAL of nonsmoking asbestos exposed individuals.[118] Alveolar macrophages isolated from these individuals released significantly higher amounts of IL-8 when grown in culture and 2.7-fold higher levels of IL-8 mRNA compared to nonexposed controls as measured by RT–PCR. *In vitro* experiments showed that IL-8 released from mononuclear phagocytes was stimulated by crocidolite and chrysotile asbestos in a dose-dependent fashion. Rosenthal et al.[119] reported that asbestos stimulates the production of IL-8 by lung epithelial A549 cells in culture. More recently Tsuda et al.[52] showed that cyclical mechanical stretching, analogous to normal breathing, in an *in vitro* system using A549 cells, also potentiates the secretion of IL-8 by these cells.

4.4.3.7 Macrophage and Monocyte Chemokines

Monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory proteins-1α and 2 (MIP-1α, MIP-2)—MIP-1α, MIP-2, are also proinflammatory cytokines.

Pleural inflammation involves an influx of leukocytes from the vasculature into the pleural space. Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and chemokines such as MCP-1 and MIP-2 are known to be important in pulmonary inflammation following inhalation of particulate matter.[120] They have also been implicated in asbestos-induced fibrosis.[121] They are produced by a wide range of cells including alveolar macrophages, fibroblasts, and epithelial cells in culture in response to TNF and LPS, and are chemotactic for neutrophils, monocytes, lymphocytes and eosinophils. Increased levels in rat lungs under mineral dust exposure conditions (silica, SiO_2 or titanium dioxide, TiO_2) lead to the accumulation of inflammatory cells. Rat alveolar type II cells *in vitro* upregulate MIP-2 following treatment with asbestos or addition of TNF-α[122] suggesting that pulmonary epithelial cells act as both targets and mediators of inflammation. Cultures of mesothelial cells isolated from rat parietal pleura and adapted for growth in serum-free media showed increased secretion of both MCP-1 and MIP-2 following treatment of confluent cultures with amosite asbestos although these changes were small. Both chemokines were also significantly elevated in pleural lavage samples from rats after 12 weeks of aerosolized asbestos exposure and the MCP-1 remained high after a 12 week recovery period.[120] Similar increases in MCP-1 in pleural lavage fluid has been reported in rats exposed to crocidolite and chrysotile asbestos for 2 weeks.[123] This suggests that secretion of these chemokines by mesothelial cells may play a role in the inflammatory response to mineral fiber exposure in the pleural cavity. Increased levels of ICAM-1 and MCP-1 protein have been measured following 24 or 48 h exposure of cultured rat pleural mesothelial cells to amosite asbestos and have been found in pleural lavage fluid from Fischer-344 rats exposed to amosite asbestos for 1–3 months even after a 3 month recovery period.[120]

4.4.3.8 Adhesion Molecules

In the same experiment described earlier[120] elevated levels of the soluble form of the ICAM-1 adhesion molecule was seen in the medium following exposure of rat mesothelial cells to asbestos although the response was not dose dependent. The increased levels of ICAM-1 in the pleural lavage correlated with the number of cells present suggesting that they might have a role in the recruitment of inflammatory cells from the vasculature. The shedding of adhesion molecules has been reported in some inflammatory situations.[124]

4.4.3.9 Arachidonic Acid Metabolites

Phosphoinositide hydrolysis and signaling through the arachidonic acid pathway have been implicated in the development of asbestos-related diseases.[125] Treatment of isolated rat alveolar macrophages with chrysotile asbestos released a similar panel of arachidonic acid metabolites as treatment of the cells with the calcium ionophore A23187[126] including lipoxygenase metabolites such as leukotriene B_4 (LTB_4) and cyclooxygenase metabolites such as prostoglandin E_2 (PGE_2) and thromboxane

B_2 (TXB_2). The release increased for about an hour and then plateaued. LTB_4 has been reported to have an autoregulatory role in the secretion of TNF-α in response to asbestos.[127] A similar role is indicated in mediating silica induced fibrotic disease where it has been shown the mineral actually stimulates TNF-α production by upregulating the gene promoter.[128] LTB_4 produced by alveolar macrophages is a potent chemoattractant for peripheral blood phagocytes particularly neutrophils.[129] Macrophages have been shown to migrate to sites of asbestos deposition in the lung within 1–2 days of initial exposure and that measurable anatomical lesions (accumulation of macrophages and proliferation of epithelial and interstitial cells) occur within 48 h following a single 1 h exposure to chrysotile asbestos.[126] Thus arachidonic acid metabolites may play a role in the earliest lesions. ROS interact with components of this pathway thereby perturbing signaling.[130]

4.4.3.10 ROS and Redox Signaling

Recent work has clarified that ROS that are discussed in more detail later in this chapter, also act as signaling molecules and turn on a number of processes. These include depletion of reduced GSH leading to epithelial cell apoptosis; the inactivation of protein tyrosine phosphatases by hydrogen peroxide; and the activation of redox sensitive transcription factors such as AP-1 and NF-κB, in which inhibition by I-κB, is released possibly by a direct effect of ROS on NF-κB, itself.[131]

4.4.3.11 Protein Kinase C

PKC activity has been shown to be elevated in hamster tracheal epithelial cells following exposure to crocidolite asbestos.[132] PKC in turn has been shown to activate the transcription factor AP-1 suggesting a plausible signal pathway. Exposure of the alveolar type II cell culture line C10 to crocidolite asbestos increases their PKCδ activity and causes its translocation to mitochondria an event prior to caspase-9 cleavage and apoptosis.[133] The addition of a specific PKCδ inhibitor blocked asbestos induced apoptosis and a dominant negative kinase deficient mutant of PKCδ also did not become apoptotic in response to asbestos. Recently it has been shown that treatment of Beas-2B airway epithelial cells with crocidolite asbestos induced tissue factor (TF) mRNA and TF-dependent procoagulant activity.[134] In this system the phosphatidylinositol 3-kinase (PI3 kinase) inhibitor LY294002 and a selective PKCzeta inhibitory peptide decreased TF mRNA expression in asbestos-treated cells suggesting that the PI3 kinase–PKCzeta signaling pathway may contribute to lung remodeling in response to asbestos exposure.

4.4.3.12 Interferon-γ (IFN-γ)

Cells isolated from BAL of a third of all patients exposed to crocidolite or chrysotile asbestos spontaneously released significantly higher amounts of IFN-γ than

equivalent cells isolated from control subjects. The levels were equivalent to those produced by cells from sarcoidosis patients.[135] These data suggest there is an active cellular immune response in at least some asbestos-exposed individuals. IFN-γ induces iNOS and consequently $NO^{\bullet}$ production. Alveolar macrophages isolated from rats produce NO when exposed to either crocidolite or chrysotile asbestos and this response is synergistic with that of IFN-γ.[136]

4.4.4 Intracellular Signaling

As described earlier signaling pathways may be initialized by asbestos binding to specific cell surface receptors or via oxidants generated as a consequence of phagocytosis or on the mineral fibers themselves. These pathways result in changes in gene expression that in turn lead to cell proliferation or damage. For a recent review see.[137]

4.4.4.1 Nuclear Transcription Factor-κB

NF-κB is a transcription factor that is central in the inflammatory response. In quiescent cells it is in the cytoplasm complexed with its inhibitor I-κB. Activation of inflammatory mediator cells by oxidants, cytokines, ionizing radiation, UV light, and some chemicals results in phosphorylation and degradation of I-κB and the resultant translocation of NF-κB to the nucleus where it activates a number of proinflammatory genes. Using the lung A549 cell line in culture it has been shown[138] that NF-κB translocates to the nucleus in response to an oxidant stress (H_2O_2) and in a dose-dependent fashion in response to exposure to the "carcinogenic" fibers amosite asbestos, silicon carbide, and RCF-1. In contrast "non-carcinogenic" fibers MMVF 10, RCF-4, and glass fiber 100/475 did not have this effect. Addition of the antioxidants curcumin, pyrrolidine dithiocarbamate or nacystelin to the medium reduced the translocation induced by the carcinogenic fibers.

4.4.4.2 ERK1/ERK2

The MAP kinases are widely involved in signal transduction. Upon activation the ERK kinases translocate from the cytoplasm to the nucleus where they phosphorylate nuclear targets. Phosphorylation of ERK2 has been shown to induce dimerization that in turn is essential for nuclear translocation.[139] Increased ERK phosphorylation has been shown in association with proliferative lung alterations following exposure to chrysotile asbestos in mice.[140] Increases in tyrosine nitration, a consequence of the generation of peroxynitrate radicals have also been shown to increase in lung lysates from rats exposed to either crocidolite or chrysotile asbestos and these in turn result in phosphorylation and activation of the ERK1/ERK2 signaling pathway. Low levels of crocidolite asbestos (in low serum) stimulate ERK1/ERK2 phosphorylation and nuclear translocation in mouse alveolar type II cells in culture through an EGF receptor-dependent pathway.[134] This increase is

transitory (2–4 h) and stimulates expression of cyclin D1 and entry into S-phase. At higher concentrations of asbestos the nuclear localization of ERK1/ERK2 is prolonged, S-phase entry is impeded, and apoptosis is induced. Increases in ERK phosphorylation have also been demonstrated in BAL cells from asbestos exposed rats, in lung sections of exposed rats by immunological staining,[92] and in A549 cells exposed to crocidolite.[141]

4.4.4.3 APE-1/Ref-1

APE-1/Ref-1 is a ubiquitous protein that functions as a DNA repair enzyme and as a redox regulator. In this latter role it plays an important function in mediating DNA binding of a number of transcription factors including NF-κB and AP-1. Flaherty et al.[142] have shown that nuclear levels of APE-1/Ref-1 increase within minutes of the exposure of alveolar macrophages to crocidolite asbestos. The effect is inhibited by the NADPH inhibitor diphenyleneiodonium (DPI). The increase is accompanied by increased AP-1 binding that is also inhibited by DPI. They postulate that macrophages respond to fibrogenic stimuli by increasing nuclear levels of APE-1/Ref-1 that in turn stimulate AP-1 binding and targeted gene transcription, which is mediated through ROS.

4.4.5 Direct Cellular Interactions

There is evidence for direct interactions between inhaled asbestos fibers and lung cells. These vary from purely physical interactions that result in mechanical damage to the cells that becomes manifest in problems such as abherrent chromosome separation to more complex phenotypes mediated through receptor-mediated signaling pathways.

4.4.5.1 Charge Mediated Surface Binding

Positively charged particulates interact with cell surfaces through negatively charged sialic acid residues on cell surface glycoproteins.[143]

4.4.5.2 Cellular Receptors and Intracellular Signaling

A direct interaction between asbestos fibers and a range of cellular receptors on different cell types have been reported and postulated to underlie the pathological developments of asbestos-related disease. Barchowsky et al.[144] demonstrated a direct interaction between chrysotile and crocidolite asbestos and porcine aortic endothelial cells in culture that results in changes in cell morphology and motility. These changes are attenuated by the addition of mannosamine (that inhibits the assembly of gylcophosphatidylinositol (GPI) anchored receptors such as the urokinase plasminogen activator receptor or uPAR) and herbimycin A (that inhibits tyrosine

kinase activity) to the culture medium. Exposure of cells to chrysotile changed the pattern of proteins associated with the uPAR and the focal adhesion kinase (FAK). Both crocidolite and chrysotile asbestos increased the activity of FAK. In contrast RCF-1 had no such effects. They suggest that direct interaction of asbestos with uPAR initiates endothelial cell activation, elongation, increased motility, and expression of adhesion molecules for circulating phagocytes. Changes that in turn underlie the pathological markers of asbestosis and tissue remodeling. Increased expression of EGFR has been shown in a number of malignancies and elevated serum levels probably reflect shedding or secretion from these cells. Asbestos fibers induce autophosphorylation of the EGFR that in turn triggers mitogen activated (MAP) kinases and the extracellular signal regulated kinases (ERK) cascades and therefore cell proliferation.[145] Asbestos binds fibronectin that in turn will mediate binding to cell surface integrins.[143] Prior opsonization of amosite asbestos with IgG increased the generation of superoxide by rat macrophages exposed to the fibers in culture.[146] Longer fibers were more effective than short correlating with their higher IgG binding capacity. The effect is presumably mediated through the Fc receptor.

4.4.5.3 Functions of Physical Dimensions

When trying to assess the pathways by which asbestos elicits a cellular response the difficult task is to distinguish which property causes which effect. This is of particular concern because a number of man-made mineral fibers (MMMF) and man-made vitreous fibers (MMVF) have been developed to replace asbestos. To investigate the role of shape Hirano et al.[215] used spherical particles and fibrous titanium dioxide and a differential display method to assess gene expression changes in alveolar macrophages in response to the two physical forms of the same material. The fibrous form was very cytotoxic to rat alveolar macrophages equaling that of crocidolite asbestos at higher concentrations. In contrast the spherical form was much less cytotoxic. In this system *krox/egr-2* was upregulated in response to the fibrous TiO_2 and to crocidolite asbestos and this was confirmed by Northern blots. Since *krox/egr-2* was also transiently upregulated in response to cell adhesion to culture dishes this may reflect a direct consequence of cell adhesion. This gene is upregulated when cells proliferate in the presence of growth factors. Macrophages bind to plastic dishes through scavenger receptors and these have also been shown to bind unopsonized environmental particles.[148] It is certainly plausible that cellular effects may be mediated through these receptors.

4.4.6 Phagocytosis

Whether asbestos fibers mediate their pathophysiological effects through the generation of ROS or through mechanical effects, phagocytosis may be a critical first step. In mesothelial cells exposed to crocidolite asbestos the downstream appearance of oxidative stress, DNA damage, and apoptosis are linked to phagocytosis.[84] If phagocytosis is blocked by inhibiting the process with cytochalasin B or by blocking

the interaction between coated fibers and cell surface integrins the consequent cellular injury is inhibited. Similarly asbestos induced production of RNS by mesothelial cells is also inhibited by cytochalasin B suggesting that phagocytosis of the fibers is involved.[91]

4.4.7 Apoptosis

The process of regulated cell senescence is critical in normal physiology, however like many aspects of asbestos-related disease it has its dark side. As has already been discussed, both ROS and RNS are generated by the interaction of asbestos with a range of cells including alveolar macrophages, but ROS can also be generated directly on the inhaled fiber. Irrespective of how they are generated ROS and RNS both induce DNA damage in lung cells including mesothelial cells[76,77] and DNA damage is in turn a potent stimulus for apoptosis. As discussed PKC has been implicated in asbestos-induced apoptosis and similar downstream events are seen when cells are exposed to hydrogen peroxide as those seen when they are exposed to asbestos. However, it is not simply a case of the asbestos effect being mediated through hydrogen peroxide, as the dominant negative kinase deficient mutant of PKCδ still became apoptotic in response to hydrogen peroxide while it did not in response to exposure to asbestos.[133] Broaddus and co-workers[84] have shown that phagocytosis of asbestos by mesothelial cells in culture induces apoptosis along with oxidative stress and DNA damage.

Perhaps it is not surprising that, at least in tissue culture, the addition of either an antioxidant (catalase) or of an iron chelator, desferroxamine, reduce the proportion of cells that enter apoptosis.[77] Once apoptosis is initiated further sources of ROS are generated during the subsequent cell death process.[149] Apoptosis is a critical mechanism for the body to rid itself of irreparable damaged or pathogen infected cells and to allow their replacement, and mild oxidative stress is recognized as a signal for apoptosis. Lung lining fluid contains high levels of GSH (90–500 μM compared to 1–2 μM in plasma)[149] and these levels decrease substantially in a variety of lung diseases. GSH in turn has been shown to inhibit apoptosis. Hydrogen peroxide causes reductions in[150] GSH that in turn release the inhibition of apoptosis.

Mossman and coworkers[151] have suggested that mitochondria are the initial targets of asbestos-induced DNA damage and apoptosis through an oxidant-related mechanism. They have shown that isolated mesothelial cells show mitochondrial DNA damage as determined by quantitative PCR at fourfold lower concentrations of crocidolite asbestos than those required to cause nuclear DNA damage. DNA damage was preceded by oxidant stress and resulted in changes in levels of a number of apoptotic related markers and increased numbers of apoptotic cells. These changes were blocked by pretreatment of cells with a caspase-9 inhibitor. Apoptosis was also decreased in the presence of catalase. Transfection of HeLa cells with a mitochondrial transport sequence targeting the human DNA repair enzyme 8-oxoguanine DNA glycosylase to mitochondria demonstrated reduced asbestos-induced apoptosis and increased cell survival.

4.4.8 Malignant Transformation

It is not difficult to envision mechanisms to explain the role that respired fibers might play in malignant transformation. Hydrogen peroxide diffuses through the cell and is able to interact with Fe^{2+} iron either in the free form or associated with fibers producing reactive hydroxyl radicals. If these radicals are generated in close proximity to the DNA (Figure 4.7) (because they have a relatively short half life) they cause DNA base damage or DNA strand breaks that could result in either oncogene activation or tumor suppressor gene inactivation, for example, as has been demonstrated for K-*ras* and C-*raf*.[152] Using pulse-field gel electrophoresis Marczynski and colleagues[153] showed double-strand DNA breaks in chromosomal DNA isolated from the nuclei of lung and liver cells of rats 4–16 months after exposure to double doses of crocidolite asbestos that were administered intratracheally and intraperitoneally. Given the prolonged nature of the generation of ROS by asbestos, it is easy to imagine a progressive accumulation of such mutations could ultimately result in malignant transformation. Mutation spectrum analysis of mammalian cells exposed to either H_2O_2 or crocidolite asbestos showed similar patterns indicating that they were through similar ROS mediated pathways.[154] Asbestos and cigarette smoke have been shown to synergistically generate hydroxyl radicals that in turn cause DNA damage in a cell free assay.[61] This mechanism may underlie their synergistic effects in causing pulmonary malignancies.

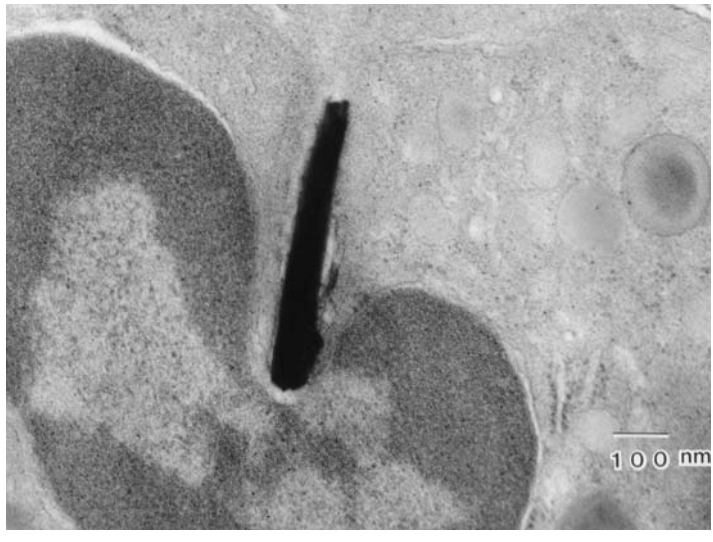

Figure 4.7 Transmission electron micrograph of a phagocytozed asbestos fiber in proximity to the nucleus. The fiber could have a direct physical effect on chromosome segregation and indirect effect by acting as a source for the generation of ROS in close proximity to DNA.

4.4.8.1 Gross Chromosomal Effects

Chrysotile, amosite, and crocidolite asbestos have all been shown to increase the generation of micronuclei in Syrian hamster cells and human amniotic cells in tissue culture[155] indicating gross chromosomal changes including both loss and breakage of chromosomes. The frequency of micronuclei generation seems to correlate with carcinogenicity potential. The effect may be mediated through the generation of ROS, by disturbing chromatin structure and function or by a direct interaction with the chromosomes during mitosis. Given their size and persistence asbestos fibers might also cause effects merely by a physical interference with the normal segregation of the chromosomes during mitosis and resulting aneuploidy or polyploidy.

4.4.8.2 p53

Unfortunately there is a dearth of information about the involvement of tumor suppressor genes or proto-oncogenes in the development of the asbestos induced malignancies, that is, lung cancer or mesothelioma. The transcription factor p53 is important in the cellular response to DNA damage and is a determinant in whether the cell enters apoptosis or cell division is blocked while repair mechanisms are activated. A549 human pulmonary epithelial type II cells express wild-type p53. When exposed to varying doses of either chrysotile or crocidolite asbestos the levels of total p53 and of p53 phosphorylated on Ser15 increased in a dose-dependent fashion. Chrysotile was more potent in inducing phosphorylation and accumulation of p53 protein than crocidolite. Blocking of the ERK pathway with U0126 or inhibition of p38 activity with SB203580 in these cells in culture did not suppress chrysotile-induced Ser15 phosphorylation but treatment with wortmannin, an inhibitor of DNA-activated protein kinase did. As neither catalase nor *N*-acetylcysteine suppressed this effect it does not seem to be mediated by ROS.[156] Disruption of p53 has been linked with the theory for a viral origin of mesothelioma[71,72] and this will be discussed further subsequently. Mesothelial cells with a spontaneous mutation in p53 appear more sensitive to asbestos-induced DNA damage than normal cells.[157] Also $p53^{+/-}$ mice have been shown to have increased numbers and earlier onset of asbestos-induced mesotheliomas supporting the hypothesis that circumvention of p53 surveillance is a prerequisite for mesothelioma development.[158] Kane and coworkers[159] have suggested that repeated exposures of mesothelial cells to asbestos result in changes in key genes like p53 that allows cells to proliferate even in the presence of DNA damage. This would allow the accumulation of additional mutations especially in an environment producing chronic generation of oxidants and ultimately invasive neoplasia. Chrysotile and crocidolite asbestos induce DNA damage in human mesothelial cells in culture after a very short exposure time but without any evidence of the DNA base adduct 8-oxo-guanine. Mesothelioma cells and cells containing the SV40 large T antigen (Tag) showed an increased expression of p53, but no additive genotoxic effects after exposure to asbestos.[160]

The deregulation of the apoptotic pathway may lead to proliferation of genomically damaged cells and ultimately to the development of mesothelioma. Human pleural mesothelial cells exposed to chrysotile or crocidolite asbestos in culture do respond to the oxidant stress by increasing the steady-state mRNA levels of the antioxidant enzymes, manganese superoxide dismutase (MnSOD), and heme oxygenase and slightly up regulating the protein levels.[161] Recently other markers such as the folic acid receptor α, cyclooxygenase 2, and multidrug resistance proteins 1 and 2 in mesothelioma tissue have pointed to possible new therapies for malignant mesothelioma.[162]

4.4.8.3 SV40 Infection

As mentioned earlier in this chapter SV40 infection of mesothelial cells has been proposed to be at least a contributing factor in mesothelioma development.[163,164] Simian virus 40 large T antigen and small t antigen (tag) are largely responsible for the carcinogenicity of the virus, and it is possible that SV40 and asbestos are cocarcinogens.[165] Currently available therapies for malignant mesothelioma prolong survival by only a few months. An SV40 vaccine is being developed for human use and it is hoped that it may reduce the incidence of malignant mesothelioma in asbestos workers. As a word of caution a recent report in Lancet has suggested that the association of SV40 with mesothelioma may be due in large part to contamination of laboratory reagents with plasmids containing SV40 sequences.[166] If the association between SV40 and mesothelioma proves to be artifactual then one is left with the epidemiological association that approximately 80% of patients with malignant pleural mesothelioma have a history of asbestos exposure even though only 10% of those with asbestos exposure acquire malignant mesothelioma.[162] A genetic predisposition component in the progression to mesothelioma however cannot be denied. For example in Anatolia where outcrops of erionite occur 50% of the inhabitants in one village reportedly died of malignant mesothelioma while in an adjacent village there was only one case and that was in a woman who originated in the former village.[167]

4.4.8.4 Oncogenes

As described earlier the c-fos and c-jun proteins dimerize to form the active transcription factor AP-1. Levels of mRNA for *c-jun* and for ornithine decarboxylase (a gene with an AP-1 site in its promoter region) are both increased in lung homogenates from rats following inhalation of asbestos[168] and in lung cells *in vitro* that have been treated with asbestos.[169–171] Both *c-jun* [172] and ornithine decarboxylase[173] overexpression have been linked to *in vitro* cell proliferation and could therefore have a role in both pulmonary fibrosis and lung cancer. Increased expression of the EGFR has been shown in 50–80% of mesotheliomas[174–176] and it acts as a mitogen for mesothelioma cell lines.[177,178] While high serum concentrations of both EGFR and Neu, a related growth factor/oncogene of the erb family, have

been found in patients with asbestosis who subsequently developed cancer[179–181] this appears to be associated with past asbestos exposure rather than with the development of cancer because in a large study of exposed workers 39% had elevated EGFR and 72% elevated Neu.[148] Interestingly, the presence of pleural plaques correlated with lower levels of EGFR but not with Neu suggesting that the secretion of a soluble receptor might protect cells from increased proliferation (and the development of plaques) but also that Neu must have a different mechanism of action.

4.5 DETOXIFICATION

Three strategies spring to mind to protect the exposed individual from the harmful effects of asbestos inhalation. The first is to prevent the conditions that result in exposure and inhalation. The second is to somehow sequester or chelate the iron that is central in the pathogenesis of asbestos-related disease. The third is to somehow protect the functional molecules that are affected by the free radicals produced by the iron.

Obviously the regulation of workplace exposure remains the most effective approach to restrict asbestos-related disease. At the same time the concept that only "regulated" fibers (those greater than 5 μm in length) are harmful is very dangerous. There is adequate evidence in the literature to suggest that all respirable asbestos is potentially harmful to health. Traditionally pulmonary fibrotic diseases have been treated with corticosteroids or immunosuppressants with little result in terms of improved outcome in terms of morbidity or mortality. A compounding factor is the long latent phase between exposure and the onset of disease symptoms so that therapeutic interventions tend to be directed towards treatment of the disease rather than the cause. Based on the work discussed above it is apparent, in animal models at least, that blocking TNF-α and IL-1 at the early stages could be a powerful therapy.

Clearly asbestos-related diseases are, in large part, oxidant mediated diseases as, for obvious reasons, are a number of other pulmonary diseases including acute respiratory distress syndrome (ARDS), xenobiotic induced injury (bleomycin, paraquat), gas inhalation (ozone, nitrogen dioxide), hyperoxia, tobacco smoke, sarcoidosis, beryllium disease, and ischemia-reperfusion injury. To combat these there are a wide range of antioxidant defense mechanisms designed to protect cells against the continuous production of ROS and RNS under normal conditions by preventing the formation of free radicals, converting oxidants to less toxic forms, compartmentalizing reactive species, and repairing molecular injuries. For more detailed reviews see.[182,183] In any potential therapeutic intervention there has to be a balance. Let us assume that iron is the critical element in the toxicity of asbestos. At the same time iron is obviously critical to normal physiology. Approximately 65% of the iron in a human circulates in hemoglobin, another 10% is in myoglobin, cytochrome, and other iron containing enzymes with the rest, 20–30% bound either tightly to the plasma transport protein transferrin or less tightly to the lower affinity but higher

capacity storage protein ferritin or to hemosiderin. Small amounts may be chelated by organic molecules like the siderophores. Only trace amounts exist in a free state. The reason that these mechanisms exist underlines the importance of the metal in biological functions as well as it potential toxicity, however, even the toxic reactive species generated by iron have a dual role. Under normal "controlled" conditions ROS are pivotal in redox signaling, in the activation of certain transcription factors, and in inflammatory responses particular to microorganisms. However, it appears that it is the uncontrolled generation of ROS that overwhelms the body's antioxidant defenses that results in molecular damage to DNA, membranes, and proteins that in turn leads to organ dysfunction through unregulated cellular proliferation or malignant transformation. Thus iron chelation as a possible therapeutic intervention in asbestos disease would, in all probability, be of limited value if not harmful. There is evidence that a small but crucial pool of iron in a low molecular mass form exists in the lung lining fluid.[184] More to the point the persistence of amphibole asbestos and their high iron content would present an almost inexhaustible supply of slowly mobilizing iron. In an experimental rat model of acute and chronic inflammation the subcutaneous delivery of desferroxamine had no effect on the levels of lipid peroxidation.[185]

Cytochrome oxidase forms a crucial role in the reduction of oxygen within the mitochondria. Without this there would be a considerable generation of ROS during normal oxidative phosphorylation. Compartmentalization of transition metals (primarily iron and to some degree copper) is also a critical antioxidant defense as they catalyze the generation of harmful hydroxyl radicals from superoxide and hydrogen peroxide. To avoid this, hemoglobin (which readily loses its iron) is sequestered within erythrocytes, which are rich in antioxidants. Extracellular iron is bound very tightly in the Fe^{3+} state to the transport glycoproteins transferrin or lactoferrin. Bound iron is unable to participate in the Haber–Weiss reaction due to its mode of binding. Both are only partially saturated under normal conditions and so provide a buffer for free iron. Transferrin does have a slightly lower affinity than lactoferrin and can release bound iron at lower pH (<5.6) that may occur during ischemic-reperfusion injury. Ceruloplasmin is a plasma acute phase glycoprotein that acts to oxidize free Fe^{2+} iron to Fe^{3+} iron that will then bind to transferrin. It has a number of other roles in attenuating the production of ROS. Within the cell the majority of iron is present in a redox inactive state bound to ferritin a large molecular weight protein comprising 24 subunits with 4500 iron binding sites. A small pool of free iron does exist within the cell that is used for the synthesis of iron containing proteins but which can also participate in the generation of free radicals. In addition free iron may be mobilized from the ferritin bound form following cell disruption and interaction with ascorbic acid, organic radicals, or superoxide. The excess circulating lactoferrin may serve as a protective mechanism during cellular inflammation, moping up excess iron, and the conversion of ferritin to hemosiderin in lysosomes under iron overload conditions, and may also serve a protective role as hemosiderin iron is less effective than ferritin iron in facilitating lipid peroxidation[186] and hydroxyl radical formation.[187]

The next line of defense in the lung is a complex system of free radical scavengers. These include:

(1) The antioxidant enzyme systems: Catalase (EC 1.11.1.6) that dismutates hydrogen peroxide; superoxide dismutase (EC 1.15.1.11) that dismutates superoxide to hydrogen peroxide; the GHS system comprising GHS (oxidized and reduced) and the enzymes glutathione peroxidase and glutathione reductase.
(2) Lipid soluble antioxidants: Vitamin E that terminates lipid peroxidation chain reactions and also converts superoxide, hydroxyl, and lipid peroxyl radicals to less reactive forms; β-carotene that scavenges superoxide and reacts with peroxyl radicals.
(3) Water soluble antioxidants: A range of water soluble compounds have oxidant scavenging potential to varying degrees including uric acid, glucose, cysteine, reduced GSH, and taurine. While vitamin C can act as an antioxidant it also has pro-oxidant properties. Vitamin C is the sole cellular component aside from superoxide that is able to reduce Fe^{3+} iron to Fe^{2+} iron and facilitate iron mediated redox cycling.
(4) Some proteins present in large amounts such as those present in tracheobronchial mucus and serum albumin may serve as suicide scavengers because they are present in such a large excess that oxidant mediated damage to a small percentage of the molecules does not present any biologically significant consequences.

Finally cellular mechanisms exist to repair oxidant damage. These include identification, excision, and repair of DNA base damage, membrane lipid removal, and whole scale cellular proliferation to replace damaged tissue.

Given the evidence for the role of oxidants in asbestos-related diseases stimulation or augmentation of pulmonary antioxidant systems would seem to hold therapeutic promise. The use of antioxidants to prevent or reduce the generation of free radicals could ameliorate some of the deleterious effects. These can be directed to protect the functional molecules (lipids, proteins, and DNA). Vitamin E is believed to play a critical role in lung antioxidant defense protecting surfactant lipids from oxidative damage.[188] Evidence indicates that even under conditions of high oxidative stress, for example, in smokers, lung levels of vitamin E are maintained (from circulating HDL) presumably at the expense of other tissues. Conversely in cases of vitamin E deficiency there is evidence of concomitant acute and chronic lung injury although this may be the result of a further insult rather than directly caused by the deficiency. There is no direct evidence addressing whether oral vitamin E therapy is protective in asbestos exposed individuals. Moreover, the wide range of different protective mechanisms at work within the lung would it be wise to rely on just one that at high doses could have other potentially deleterious effects? On the other hand there is strong evidence for a protective role for vitamin E in iron overload situations.[189]

The role of vitamin C is much less clear given its capacity to reduce Fe^{3+} iron to Fe^{2+} iron, which could then participate in the generation of reactive hydroxyl radicals. In conditions of potential iron excess it would seem prudent to avoid vitamin C supplementation. Clinical interventions with β-carotene do not seem to reduce the

risk of the progression of lung cancer (defined as the incidence or prevalence of sputum atypia) in asbestos-exposed workers.[190] Flavonoids are a class of plant polyphenols that seem to have beneficial effects on several chronic diseases. They can be incorporated into animals as part of the diet from products such as tea, red wine, purple grape juice, cocoa products, apples, onions, and certain nuts. They participate both in iron chelation, trapping radicals, and even protecting lipids.[189]

Changes in excreted biomarkers of oxidant mediated DNA damage as a result of human interventional studies involving vitamins C and E, β-carotene, coenzyme Q, and various dietary regimens has suggested that these may create a mechanism to assess the overall state of oxidative protection,[191] but it will be of limited value in assessing the value of such therapies in an organ specific manner like asbestos induced lung injury.

Lung lining fluid contains high levels of GSH ($90-500\ \mu M$ compared to $1-2\ \mu M$ in plasma).[150] This provides a strong antioxidant defense but these levels decrease substantially in a variety of lung diseases. Hydrogen peroxide causes reductions in GSH[151] that in turn releases the inhibition of apoptosis by GSH. Brown et al.[192] measured the ability of various fiber preparations to deplete antioxidants GSH and ascorbate from lung lining fluid obtained by lavage of rats. They showed that all fibers tested depleted GSH and ascorbate in a fiber number dependent manner but that there was no correlation between potential carcinogenic fibers (amosite, silicon carbide, and RCF1) and non carcinogenic ones (glass fiber and RCF4).

Elevated mRNA and enzyme activities of antioxidant enzymes in both alveolar type II cells[193] and in lung homogenates[194] of rats exposed to asbestos indicates that the body does mount its own oxidant stress response to respired asbestos. mRNA levels and MnSOD activity increase in rat lungs,[195] and tracheal epithelial cells and pleural mesothelial cells *in vitro*[161,196] following exposure to asbestos. Presumably the oxidants generated by asbestos somehow up-regulate MnSOD. The protective effect of which is illustrated by experiments in which hamster tracheal epithelial cells were transfected to overexpress MnSOD. These cells were refractory to asbestos-induced toxicity.[197] While MnSOD activity appears elevated by immunohistochemical staining in Type II cells and macrophages during the early stages, it appears low in the latter stages of interstitial fibrosis suggesting that the antioxidant defenses may be impaired as fibrosis progresses.[198] Surprisingly, MnSOD activity and mRNA levels appear to be elevated in mesothelioma cell lines compared to control healthy lung and SV40 transformed lung mesothelial cells[199] suggesting that they may have a higher oxidant resistance. This is the opposite of many tumors and could explain the resistance of mesotheliomas to chemotherapeutic drugs that act through redox cycling and the production of free radicals.

It is likely that oxidants moderate gene expression in mammalian cells through sensing the redox equilibrium in the cell in a manner similar to bacterial two component systems. Intracellular levels of reduced GSH are depleted in lung cells in the presence of elevated inflammatory mediators. Perhaps sensor sites in proteins become oxidized and then act as intracellular second messengers activating

transcription factors such as NF-κB, AP-1, and STAT,[183,200] and activating a subset of genes in response to the oxidative stress. I-κB kinase is an oxidative stress activated kinase[201] that phosphorylates I-κB and thereby regulates its degradation and the concomitant nuclear translocation of NF-κB and activation of its target genes. Thus NF-κB genes activation is regulated by redox equilibria.[202,203] Addition of the antioxidants curcumin, pyrrolidine dithiocarbamate, or Nacystelin to the cell culture medium reduced the nuclear translocation of NF-kB in A549 cells induced by amosite asbestos.[139] The availability of gene arrays opens the possibility of identifying these specific genes.

Mossman et al.[204] have tested the efficacy of catalase (coupled to polyethylene glycol to extend its biological half-life) in an animal model of lung fibrosis. Catalase was administered continuously from a subcutaneously implanted osmotic pump while giving the animals a 20-day asbestos inhalation protocol. Both inflammation and fibrosis, as measured by biochemical and morphological end points in lung and in BAL, were reduced in a catalase dose-dependent manner. The potential effectiveness of treatments based on the reduction of free radical generation through iron chelating agents is further underlined by an experiment in which phytic acid, an iron chelator, was used to pretreat amosite asbestos prior to instillation in rats. There was, histologically at least, a marked attenuation in pulmonary inflammation and fibrosis[68] over the 4-week period following the challenge.

Glutathione-S-transferase deficiency has been reported to be a risk factor for the development of asbestosis[205] suggesting that the natural antioxidant GSH may serve a protective role. Along similar lines garlic extracts, which are rich in sulfur compounds and GSH precursors, have been demonstrated as effective in ameliorating the genotoxic sequellae of chrysotile exposure to lymphocytes in culture.[206]

A link between oxidant generation and subsequent TNF-α production has been demonstrated in a number of studies of silica-induced fibrosis suggesting that the generation of ROS may be essential in TNF-α and therefore the primary initiator of fibrosis. For example, pretreatment of rats with *N-tert*-butyl-alpha-phenylnitrone, a free radical scavenger, prior to instillation of silica, inhibits the generation of ROS and the elevation of TNF-α mRNA levels and histological evidence of fibrosis.[207] Acanthoic acid, a diterpene, reduces silica-induced production of IL-1 and TNF-α from alveolar macrophages, oxidant production, and both granuloma formation and fibrosis[208] thus adding further support to the hypothesis that blocking oxidant generation and TNF-α production will be antifibrotic.

Modifying the redox state of the bound iron would have similar effects as was demonstrated in studies using refractory ceramic fibers loaded with iron that were discussed earlier.[66]

4.6 SUMMARY

Inhaled asbestos fibers initiate a chronic inflammatory state mediated through ROS generated by activated macrophages through cycles of frustrated phagocytosis and cell death, by direct catalysis on the particle surface and by direct interactions on

the cell surface. The injured epithelium releases cytokines that initiate macrophage accumulation, which in turn secrete inflammatory and fibrogenic cytokines such as PDGF that cause a proliferation of alveolar type II cells to repair the epithelium, underlying mesenchymal cells, and of TGF-β that causes an increased deposition of extracellular matrix material that leads to the characteristic fibrotic scar.

It seems clear that inflammatory mediators such as TNF-α and IL-1 that seem to have a role in the early stages of the development of asbestos-related fibrosis stimulate a vast array of other inflammatory and immune responses that probably play complex roles in the progression of the disease (for a review see Driscoll[209]). Each of the cell types involved in this process, not only alveolar macrophages, has the potential to play both a role in lung defense or lung injury. Macrophages can clear shorter fibers, but at the same time they can cause epithelial type II cell proliferation and fibrosis. If they become overloaded or are exposed to long fibers that cannot be completely phagocytozed they can die and release their contents into the lung milleu causing lung injury and recruiting another generation of inflammatory cells. The fibers that are released, some of which are now coated with the characteristic iron-rich coating of the ferruginous body, are now available for free radical generation or may be phagocytozed by another generation of macrophages. Mast cells also play a key role[210] as do T-lymphocytes,[211] and neutrophils[212] which may also have either beneficial or injurious effects on the lung.

In the absence of fiber clearance this cycle continues year after year. In circumstances where the fiber load is very high, short fibers may be preferentially relocated to extrapulmonary sites, presumably through the lymphatic system, where events similar to those described here probably continue. Thus while it may be argued that on a one-to-one basis that long (>8 μm) and thin (<0.25 μm) fibers (such as the "Stanton fiber"[213,214]) carry a risk of being a more carcinogenic than a shorter fiber, the fact remains that shorter fibers can also cause pathological events through their multiple interactions between fibers and cells, cells and cells, clearance and retention, retention and relocation that cumulatively lead to the causation of asbestos-related diseases. It should also be realized that shorter fibers are more easily inhaled, relocated to other sites in the body, and when phagocytozed offer a more direct interference with cellular processes such as cell division than longer fibers that do not "fit" inside cells or subcellular compartments.

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CHAPTER 5

The Pathologic Features of Asbestos-Induced Disease

Samuel P. Hammar

CONTENTS

Asbestos causes a variety of diseases that can be grouped into two categories: (1) nonmalignant diseases and (2) malignant diseases. Most nonmalignant diseases are associated with scarring (fibrosis) of some type, whereas malignant diseases primarily occur in the lung and the lining of the body cavities (pleura, peritoneum, and pericardium). Asbestos is also capable of causing pleural effusions.

5.1 NONMALIGNANT DISEASES

5.1.1 Asbestos-Induced Pleural Effusion

Asbestos exposure causes pleural effusions in individuals. Frequently, this occurs many years after an individual was last exposed to asbestos for reasons that are not well understood. In 1982, Epler et al.[1] reported 39 benign effusions in 1135 asbestos-exposed workers and compared them with otherwise unexplained effusions among 717 unexposed control subjects. Asbestos-induced pleural effusions were dose-related with 7, 3.7, and 0.2% associated with severe, indirect, and peripheral asbestos exposure, respectively. Epler et al.[1] found the latency period being shorter for asbestos-induced pleural effusions than for other asbestos-related diseases; and benign effusion was the most commonly found abnormality during the first 20 years of exposure. Incident studies showed 9.2 effusions per 100,000 person-years for level 3 exposure, 3.9 effusions for level 2 exposure, and 0.7 effusions for level 1 exposure. Most effusions identified were small and the majority of patients were asymptomatic. In the Epler et al. study,[1] the effusion was recurrent in 28.6% of the cases and in one case mesothelioma was reported 6 years after the first effusion. Epler et al.[1] concluded that asbestos exposure should be carefully searched for in persons with idiopathic pleural effusions. In 1971, Gaensler and Kaplan[2] found that 91 out of 4077 patients had pleural effusions. Of the 4077 patients, 57 had asbestos exposure and 24 of these had a pleural effusion. Twelve of these were excluded because of the possible association with mesothelioma, carcinoma of the lung, or congestive heart failure. The remaining 12 (21.1%) were thought to have an asbestos-induced effusion.

Collins[3] described two patients with pulmonary fibrosis who developed an effusion, and concluded that the changes were caused by asbestos. Mattson and Ringqvist[4] reported seven cases of exudative pleural effusion in patients without signs or symptoms of other disease. They also reported 42 men with pleural plaques who had been exposed to asbestos. In 1975 Mattson[5] reported 25 persons with monosymptomatic exudative pleural effusions of unknown etiology and found that 11 of these patients had been exposed to asbestos. No other cause of the pleural effusions was noted in 11 of these men during an observation period of 4–8 years. Diffuse pleural fibrosis was developed in 9 out of 11 patients during a 4–8 period. However, one patient developed asbestosis.

Eisenstadt[6] reported an asbestos-induced pleural effusion in a 54-year-old individual who had been suffering from acute hemithorax chest pain. This person subsequently developed a pleural effusion on the right side and over a period of time

developed diffuse pleural thickening requiring decortication. Eisenstadt[6] concluded that benign asbestos pleurisy resembled tuberculosis and was a self-limited disease but could progress to fibrosis. Eisenstadt[6] also concluded that the correct diagnosis required a pleural pulmonary biopsy for the demonstration of asbestos bodies.

The incidence of signs and symptoms in persons with asbestos-induced pleural effusion has varied from one series of patients to another. In the Gaensler and Kaplan report,[2] all patients were symptomatic with pleuritic chest pain being the most frequent symptom. Several patients had dyspnea, which may have been, in part, related to underlying asbestosis. One patient developed arthritic symptoms and had lumps on the elbows, while another patient developed fatigue. In the Gaensler and Kaplan series,[2] the fluid was sanguinous or serosanguinous in 6 out of 12 patients and was straw colored in five patients. In contrast with the report by Epler et al.,[1] 66% of their patients were asymptomatic. In the Hillerdal and Ozesmi series[7] of 60 patients with benign asbestos-induced pleural effusions, 47% had no symptoms, 34% had chest pain, 6% had dyspnea, and the remainder had a variety of other symptoms.

In most instances, the pleural fluid from patients with asbestos-induced pleural effusion is an exudate that is either serous or serosanguinous. Pleural fluid usually contains an elevated number of white blood cells, most of which are either polymorphonuclear leukocytes or lymphocytes. An increased number of eosinophils is often seen in asbestos-induced pleural effusion and sometimes is thought to be characteristic of an asbestos-induced effusion, although this occurs in other types of conditions. In the report by Mattson,[5] more than 50% of the white blood cells were eosinophils in 5 out of 11 effusions evaluated; and 15–17% of the cells were eosinophils in two additional effusions. In most instances, the pleural fluid had high protein content, high concentration of lactic dehydrogenase, and a low glucose content.

The pathogenesis of asbestos-induced pleural effusions is not well understood, but could relate to the presence of asbestos fibers in the pleural space or pleural tissue, which causes inflammation and irritation of the pleural surface. As described in other chapters of this book, asbestos has the capability of inducing a variety of inflammatory conditions through a variety of pathways that are probably important in the development of the effusion. Why the effusions occur in any individual patient at a given time is not understood, especially in older patients who develop pleural effusion caused by asbestos sometimes 15–20 years after they were last exposed to asbestos.

Lung tissue obtained by performing video-assisted thoracoscopic biopsies or open thoracotomies, generally shows markedly thickened visceral pleura with an increased number of vessels and inflammatory cells (Figure 5.1 and Figure 5.2). Fibrin is frequently seen on the visceral pleural surface. In some patients, hyaline pleural plaque (see subsequently) is also identified and, in some instances, the patients may have asbestosis (Figure 5.3).

5.1.2 Hyaline Pleural Plaques

Hyaline pleural plaques are yellow-white, discrete, irregularly shaped structures that most frequently occur on the parietal pleura (Figure 5.4). They occur

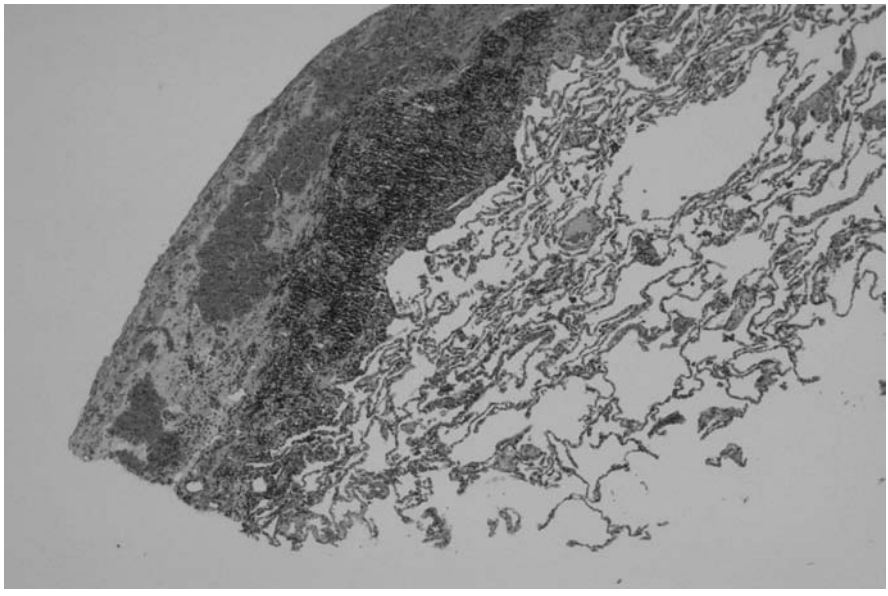

Figure 5.1 This open lung biopsy from an asbestos-exposed patient with a pleural effusion shows marked thickening of the visceral pleura (H&E 100×).

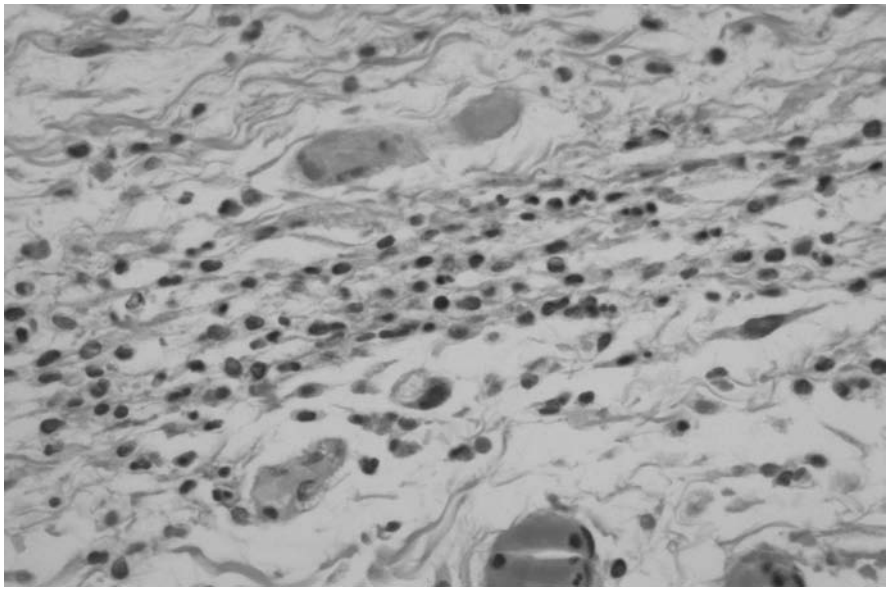

Figure 5.2 At greater magnification, the thickened visceral pleura shows edema, early fibrosis, an increased number of blood vessels, and occasional inflammatory cells (H&E 400×).

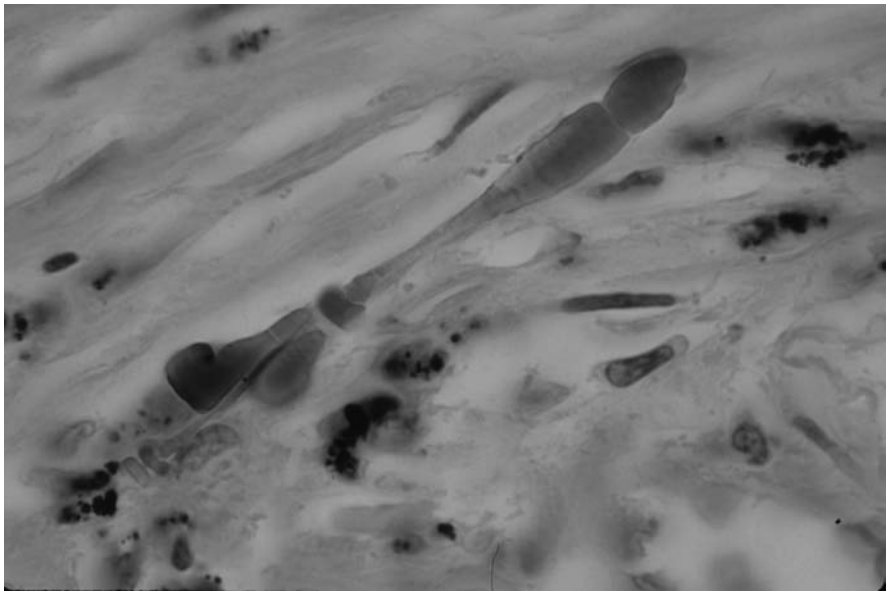

Figure 5.3 Lung tissue from this asbestos-exposed patient showed interstitial fibrosis in association with asbestos bodies, the findings being diagnostic of asbestosis (H&E 400×).

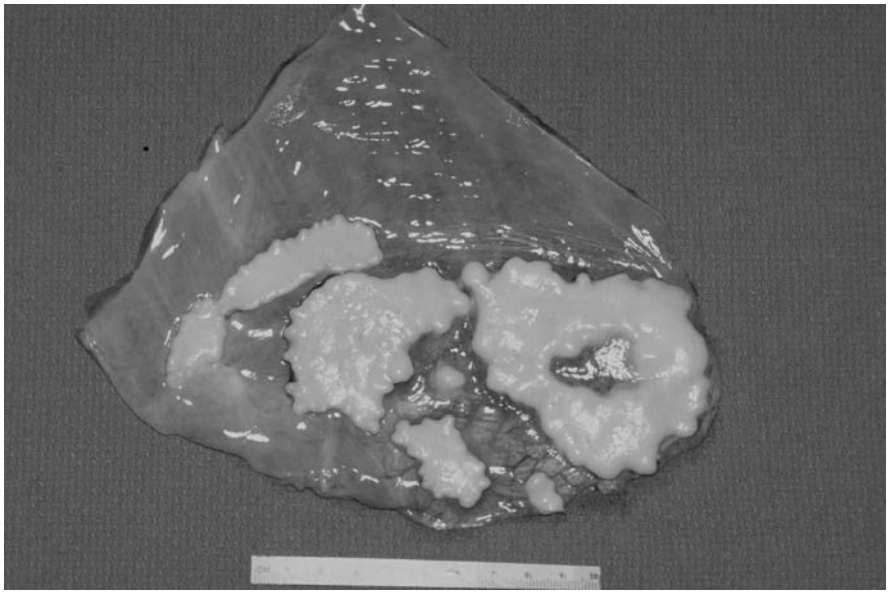

Figure 5.4 This diaphragmatic hyaline pleural plaque is composed of dense fibrous tissue.

most frequently on the diaphragmatic surface and between the fifth and eighth ribs in posterolateral portions of the chest cavity, characteristically sparing the apices in the costophrenic angles. Uncommonly, pleural plaques occur on the visceral pleura, parietal pericardium, and adventitia of the aorta. Plaques identical to pleural plaques occur within the peritoneal cavity, usually on the surface of the spleen or liver. They are frequently calcified and can have small nodules at the periphery. Histologically, hyaline pleural plaques are composed of dense hypocellular collagenous tissue exhibiting a basket weave pattern (Figure 5.5) and can be associated with chronic inflammation (Figure 5.6). Schwartz[8] reviewed 16 separate autopsy studies and noted that pleural plaques were found in 857 out of 7085 routine autopsies (12.2%); range (0.5–30.3%). Wain et al.[9] found 25 pleural plaques in 434 autopsies performed over a 2.5-year period. More than 80% of persons occupationally exposed to asbestos have hyaline pleural plaque at autopsy, most frequently occurring on the diaphragmatic surfaces. From author's view, all persons with pleural plaques have elevated numbers of asbestos bodies or fibers in their lung tissue.

Others have shown an association between asbestos exposure and pleural plaque development. In the study by Wain et al.,[9] asbestos bodies were identified in lung digests from 25 patients with pleural plaques and exceeded their normal range in 14 cases.

Hourihane et al.[10] evaluated the autopsies performed at the Department of Forensic Medicine between January and March 1965 and found 15 cases of pleural plaque in 134 autopsies, many of which were associated with metastatic lung neoplasms or diffuse malignant pleural mesothelioma. In 115 routine autopsies, classical asbestos bodies were found in 28 cases. In contrast, asbestos bodies were

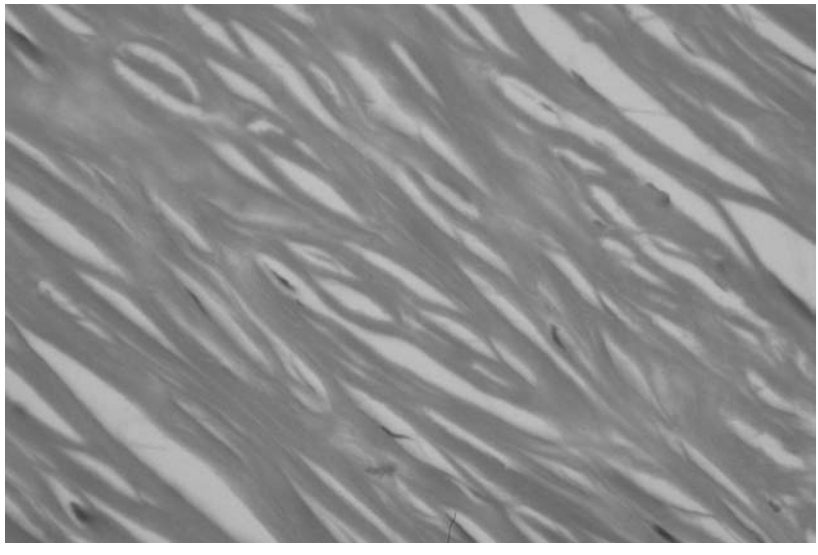

Figure 5.5 Microscopically, hyaline pleural plaques are composed of dense hypocellular collagenous tissue exhibiting a basket weave pattern (H&E 200×).

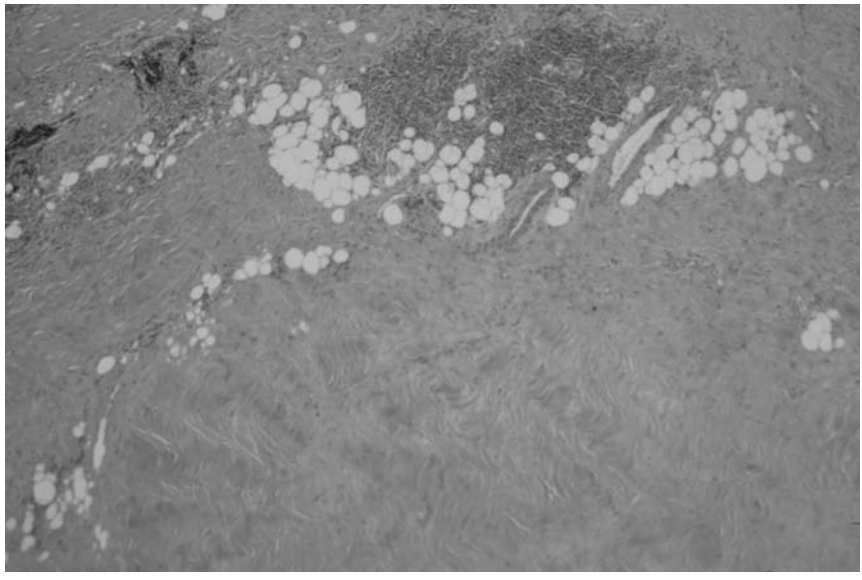

Figure 5.6 Not infrequently, hyaline pleural plaques are associated with chronic inflammation (H&E 200×).

found in all patients with hyaline pleural plaques. The authors stated the association between plaques and asbestos bodies in the lung was statistically significant at a p value of <0.1. Warnock et al.[11] reviewed epidemiologic studies and found that all types of asbestos were involved in the development of pleural plaques. Plaques also developed in persons who were exposed to talc, which was most likely due to tremolite contamination.[12] Warnock et al.[11] found that plaques occurred most frequently in persons 60–80 years old and had a latency in the range of 20 years, although some plaque cases that had a reported latency as short as 5 or 6 years after initial exposure.[13] Warnock et al.[11] found a significantly higher concentration of amosite and crocidolite in lung tissue of persons with plaques as compared to a control group. They found three cases of mild or minimal asbestosis in patients with plaques.

Sebastien et al.[14] analyzed lung tissue from two groups of patients with pleural plaques and found 10^7 and 10^6 asbestos fibers/cm^3 in patients with and without asbestosis, respectively. Whitwell et al.[15] found more than 20,000 asbestos fibers/g of dry lung tissue in 55% of the subjects with pleural plaques. Only 5.5% of those with fewer than 20,000 fibers/g of dry lung tissue had pleural plaques.

Churg[16] studied pulmonary asbestos burden in 29 patients identified as having pleural plaques at autopsy, and compared the concentration of asbestos in those patients with 25 persons who had no history of occupational exposure to asbestos. He found the average number of asbestos bodies in the plaque and control group was 1732 and 42 per g of wet lung tissue, respectively. Churg[16] found a history of fairly certain asbestos exposure in 16 out of 29 plaque patients and concluded

that about half of the patients in the general population who developed plaques had a history of asbestos exposure, while the etiology of plaques in the other half was unclear. Churg concluded that the presence of pleural plaques correlated with a 50-fold increase in the number of high aspect ratio commercial amphiboles in the lung tissue, but was not correlated with the number of chrysotile fibers, noncommercial amphiboles, or the total number of asbestos fibers. However, Churg and dePaoli[17] identified four men more than 70 years old in the chrysotile mining town of Thetford Mines, Quebec, who had never been employed in the chrysotile mining or milling industry, with pleural plaques. The lung asbestos content of these persons was compared with persons living in the same vicinity who did not have plaques. They found an equal concentration of chrysotile in lung tissue in the plaque persons versus the nonplaque persons but found a fourfold elevation in the median tremolite concentration of the plaque persons' lung tissue versus the lung tissue in persons without plaques. They concluded from this evaluation that environmental pleural plaques in this region of Quebec were possibly caused by tremolite derived from local soils or rocks and by titanium oxide of environmental origin. Kishimoto et al.[18] determined the concentration of asbestos bodies in 400 autopsy lungs and found 71 cases in which asbestos bodies were significantly elevated. In all 71 cases, hyaline pleural plaques were identified.

Most studies have found no asbestos bodies in pleural plaques,[19] although asbestos bodies were identified by Rosen et al.,[20] Roberts,[21] and Sebastien et al.[14] This author has seen asbestos bodies in pleural plaques in only one case of over several thousand examined.

LeBouffant et al.[22] studied pleural plaques by electron microscopy and found that chrysotile was the cause of plaques. Warnock et al.[11] also identified chrysotile in several plaques, but not in the majority of plaques.

The pathogenesis of hyaline pleural plaques is not well understood. Kiviluoto[23] and Meurman[19] suggested that hyaline pleural plaques were formed as a direct result of local inflammation of the parietal pleura caused by asbestos fibers that protruded from the visceral pleura, which directly irritated the parietal pleura. No pathologic evidence has been found to support this theory, and therefore it has not gained wide acceptance. Asbestos fibers have been identified in pleural fluid by Hillerdal.[24] Wang[25] described prelymphatic stomata on the surface of the mesothelium of the parietal pleura connecting the pleural cavity and the lymphatics of the parietal pleura. Wang[25] also stated that it was possible for the fibers to gain access to the parietal pleura through the lymphatic route. This theory has been supported by a study concerning the pathogenesis of mesothelioma.[26] Taskinen et al.[27] suggested asbestos fibers could reach the parietal pleura by retrograde lymphatic flow from mediastinal lymph nodes through retrosternal intercostal lymphatic channels.

5.1.3 Diffuse Pleural Fibrosis

Diffuse pleural fibrosis is relatively common in persons exposed to asbestos. The exact incidence of this condition is not well documented, although from this

author's experience it is significantly less frequent than hyaline pleural plaques. As with most asbestos-related diseases, there is a dose–response relationship and the latency period is usually >15 years.

The severity and extent of visceral pleural fibrosis in persons exposed to asbestos is highly variable. Visceral pleural fibrosis frequently involves the costophrenic angles and may be relatively diffuse (Figure 5.7). Diffuse pleural fibrosis may involve the parietal pleura and, in rare instances, there is fusion of fibrotic visceral and parietal pleura to form a condition referred to as "fibrothorax" in which the pleural cavity is obliterated by dense fibrous tissue and macroscopically somewhat resembles a mesothelioma (Figure 5.8). The pathogenesis of diffuse visceral pleural fibrosis is poorly understood and was reviewed by Schwartz.[8] Visceral pleural fibrosis may be a direct extension of parenchymal fibrosis. Both probably begin as an inflammatory-type process initiated by asbestos with progressive scarring by a variety of mechanisms. This author has observed several cases of diffuse visceral pleural fibrosis that have been diagnosed radiographically as asbestosis. However, many, if not most, of these cases show some degree of subpleural parenchymal fibrosis, which fulfills the pathologic criteria of asbestosis. As discussed by this author in 1992,[28] this remains an area of controversy. Stephens et al.[29] evaluated the pathological and mineralogical features of seven cases of diffuse pleural fibrosis in persons known to be exposed to asbestos. All individuals had a significant asbestos exposure history ranging from 2 to 25 years. In the seven cases described, the histologic features were those of a basket weave pattern of thickened pleural

Figure 5.7 The visceral pleura of this portion of lung is mildly opacified due to scarring caused by asbestos.

Figure 5.8 The visceral and parietal pleura are markedly thickened due to scarring. They are fused to produce a condition referred to as "fibrothorax" that resemble a sarcomatoid (fibrous) mesothelioma.

tissue and dense subpleural parenchymal interstitial fibrosis with fine honeycombing extending to a depth of 1 cm in the underlying lung tissue. Crocidolite and amosite concentrations were elevated in 6 out of 7 patients, whereas chrysotile concentrations were elevated in four cases. Stephens et al.[29] concluded that diffuse visceral fibrosis was a specific asbestos entity of uncertain pathogenesis with lung tissue asbestos burden concentrations being between those found in persons with plaque and with minimal asbestosis ($2.4-28 \times 10^6$ fibers of amosite or crocidolite per g of dry lung tissue). In their laboratory, individuals not exposed to asbestos had asbestos fiber counts of $<20{,}000$ fibers/g of dry lung tissue and persons with pleural plaques had $10{,}000-50{,}000$ fibers/g of dry lung tissue.

Gibbs et al.[30] studied lung tissue from 13 patients with a known history of asbestos exposure and diffuse pleural fibrosis. In their study, samples of tissue were taken from the visceral pleura and the central and subpleural zones of the lung for histopathological and mineralogical studies. They found an increased concentration of amphibole fiber counts, which was similar to that seen in cases of pleural plaques, mild asbestosis, and mesothelioma. However, they found a wide case-to-case variation and there was no significant difference between the central and subpleural zones, whereas the pleura had low asbestos counts, and asbestos in the visceral pleura consisted mostly of short chrysotile fibers. In the lung tissue, more than 45% of the asbestos was amphibole fibers longer than 4 μm and thinner than 0.25 μm. They interpreted this to suggest that the thinner fibers were important in

the pathogenesis of asbestos-related disease, including pleural fibrosis. Once again, it might be inappropriate to determine the significance of pleural fibrosis based on the concentration of asbestos in lung tissue.[31] As recently shown by Suzuki et al.,[32–34] chrysotile is the dominant type of asbestos found in pleural tissue. Also, short fibers are found much more frequently than long fibers in pleural tissue. Warnock et al.'s[11] statement that one must be extremely careful in interpreting low concentrations of chrysotile in the lungs of persons occupationally exposed to asbestos, because it may not rule out the possibility that chrysotile was responsible for the disease, should be remembered. This is due primarily to the short half-life of chrysotile asbestos, which is stated to be in the neighborhood of about 90–120 days.

As reviewed by Schwartz,[8] Cugell and Kamp,[35] and Kilburn and Warshaw,[36] diffuse pleural fibrosis may be associated with signs and symptoms of respiratory disease and also with abnormal pulmonary function tests.

5.1.4 Round (Rounded) Atelectasis

Most cases of round atelectasis are identified radiographically in persons occupationally exposed to asbestos.[8,35] These individuals are usually asymptomatic, and radiographically have a unilateral round peripheral density most frequently in the right middle and right lower lobe with one or more curvilinear shadows that radiate from this density toward the hilum of the lung that may be misinterpreted as a neoplasm.

In 1928, Loeschke[37] observed localized atelectasis due to pleural effusion. Hanke[38] reported a similar condition, which he called "round atelectasis." In 1966, Blesovsky[39] described the condition in the English literature as "folded lung." Dernevik et al.[40] reported on 28 patients with similar radiographic and histologic features and termed it as "shrinking pleuritis with atelectasis." Round atelectasis has been referred to as Blesovsky's syndrome,[41] pleuroma,[42] and pulmonary pseudotumor.[43] The pathologic features of round atelectasis were described in the German literature by Schummelfeder[44] and Giese,[45] and in the English literature by Dernevik et al.,[40] Mark,[46] and, more recently, by Menzies and Fraser[47] and by Chung-Park et al.[48] Macroscopically, the visceral pleura shows irregular fibrosis and may be fused with a thickened parietal pleura. Below the area of pleural fibrosis there is an infolding of the visceral pleura causing one or more areas of invagination. Histologically, the pleural fibrosis is superficial to the outer layer of visceral pleural elastic tissue and the portion of the visceral pleura consisting of the internal and external layers of elastic tissue that are thrown into variably sized and complex wrinkles, which extend downward into the underlying lung tissue for a variable distance. This is best shown by using Movat Pentachrome stain (Figure 5.9). The lung tissue under the area of invagination of the visceral pleura may be normal or show compressive atelectasis and interstitial fibrosis.

As reviewed by Chung-Park et al.,[48] 61 out of 107 cases of round atelectasis (57%) had a history of exposure to asbestos. The remaining 46 had no history of exposure to asbestos or evidence of asbestosis, but developed localized atelectasis apparently due to other factors such as tuberculosis, exudative pleural effusion

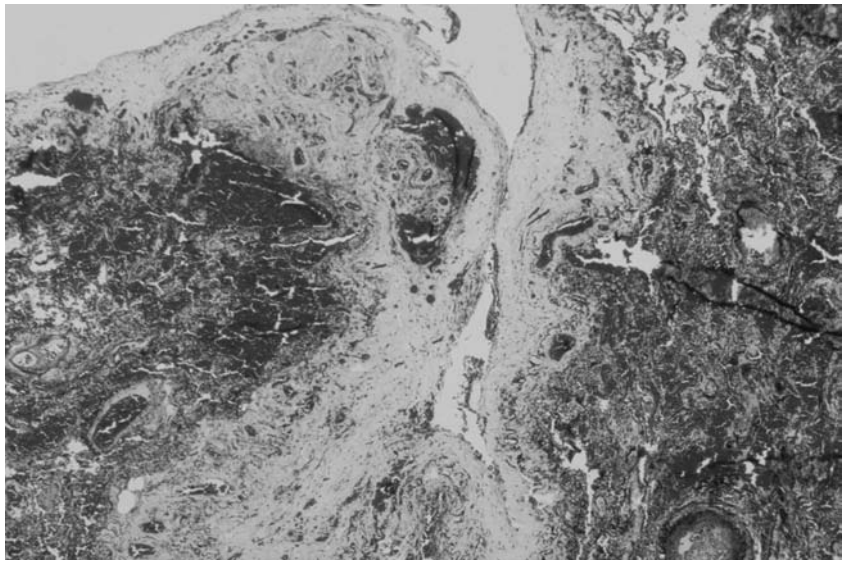

Figure 5.9 This region of round atelectasis is characterized by invagination of the visceral pleura and compressive atelectasis of the surrounding lung parenchyma (Movat Pentachrome 100×).

due to infection, congestive heart failure, myocardial infarction, or trauma. With respect to the pathogenesis of round atelectasis, Loeschke,[37] Hanke,[38] and Kretzschmar[43] suggested round atelectasis began with a pleural effusion large enough to result in a separation of the visceral pleura-covered lung from the parietal pleura. According to their theory, focal collapse of lung parenchyma occurred because the effusion formed a groove or a cleft in the lung tissue with infolding of lung tissue upon itself causing an area of invagination. Organization of the fibrinous exudate of the pleural surface resulted in mature fibrous tissue being formed, which then fixed the area of folds and maintained the underlying atelectasis. An alternative theory proposed by Blesovsky[39] and Dernevik et al.[40] was that the visceral pleural fibrous tissue, matured and contracted, pulling the underlying pleura with it. Because the pleura could only be minimally compressed, there was no alternative other than for it to fold into the underlying lung tissue, which led to collapse of the lung parenchyma with the associated thickened pleura. Chung-Park et al.[48] referred to this as shrinking pleuritis and proposed it was related to pleural fibrosis and pleural effusion with the understanding that the pleural fibrosis may have been due to a consequence of organization of pleural fluid.

5.1.5 Asbestosis

The history of asbestosis has been extensively described elsewhere in this book and will not be repeated. The most comprehensive pathologic description of asbestosis is

that by Craighead et al.[49] More recent reviews have been published by Roggli and Shelburne,[50] Roggli,[51] and Roggli et al.[52,53]

As discussed by Warnock and Isenberg[54] concerning the development of lung cancer and asbestosis, the degree of fibrosis in a person's lung with similar concentrations of asbestos varies significantly. Cigarette smoke may influence the development of asbestosis, although the relationship between asbestosis and cigarette smoking is not clear.

The macroscopic morphology of asbestosis depends on the severity of the disease. Persons with histologic CAP–NIOSH grade 1–2 asbestosis usually show no macroscopic abnormalities. As asbestosis becomes more severe, there are streaks and foci of grayish-white fibrous tissue in the parenchyma, usually in a subpleural location and are more observable at the base of the lung than in the upper lobes. With progression, additional deposits of fibrous tissue occur with the development of honeycombing (Figure 5.10). Although asbestosis often appears radiographically to first develop in the lower lobes, it is frequent to find significant asbestosis in the middle and upper lobes of individuals occupationally exposed to asbestos. As reported by Churg et al.[55] and Dodson et al.,[56] the concentration of asbestos in the lungs of persons occupationally exposed to asbestos is just as great in the upper lobes as it is in the lower lobes.

The panel commissioned by the College of American Pathologists and the National Institutes for Occupational Safety and Health headed by Craighead[49] graded asbestos into four categories according to the location of the fibrosis and its severity (Table 5.1). The simplest definition of pathologic asbestosis is the

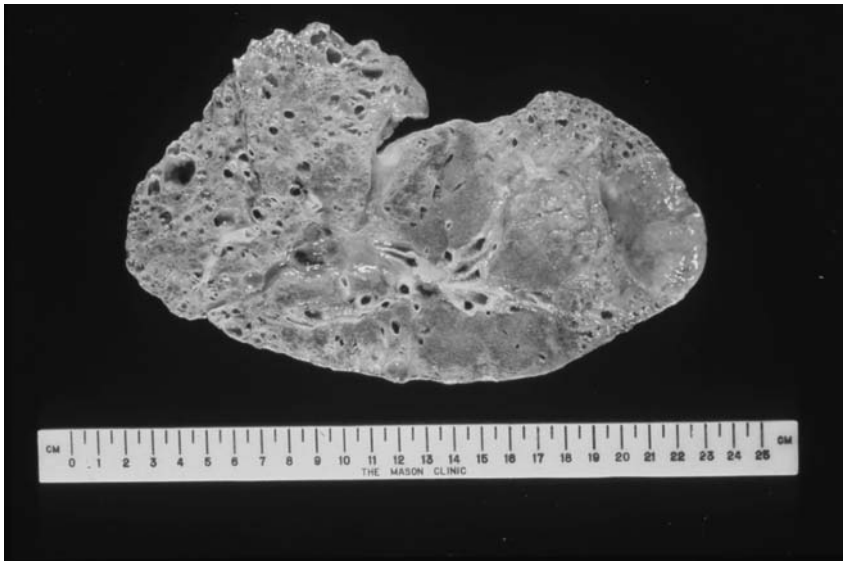

Figure 5.10 An example of grade 4 asbestosis. The lung parenchyma shows diffuse grayish-white scarring most severe in the subvisceral pleural area with cyst formation referred to as "honeycombing."

Table 5.1 Asbestosis Grading Schema

Grade 0	No fibrosis is associated with bronchioles
Grade 1	Fibrosis involves wall of at least one respiratory bronchiole with or without extension into septa of the immediately adjacent layer of alveoli; no fibrosis is present in more distant alveoli
Grade 2	Fibrosis appears as in grade 1, plus involvement of alveolar ducts or two or more layers of adjacent alveoli; there still must be a zone of nonfibrotic alveolar septa between adjacent bronchioles
Grade 3	Fibrosis appears as in grade 2, but with coalescence of fibrotic change such that all alveoli between at least two adjacent bronchioles have thickened, fibrotic septa; some alveoli may be obliterated completely
Grade 4	Fibrosis appears as in grade 3, but with formation of new spaces of a size larger than alveoli, ranging up to as much as 1 cm; this lesion has been termed *honeycombing*; spaces may or may not be lined by epithelium

presence of fibrosis in association with an increased number of asbestos bodies or asbestos fibers. CAP–NIOSH histologic grade 1 asbestosis is characterized by peribronchiolar fibrosis with possible focal extension into the septa of adjacent alveoli but with no fibrosis in the more distant alveoli (Figure 5.11); CAP–NIOSH histologic grade 2 asbestosis is characterized by involvement of alveolar ducts of two or more layers of adjacent alveoli with a zone of nonfibrotic alveolar tissue between adjacent bronchioles (Figure 5.12); CAP–NIOSH histologic grade 3 asbestosis is characterized by a coalescence of the fibrotic lung tissue of alveoli between at least two adjacent bronchioles showing interstitial fibrosis in addition

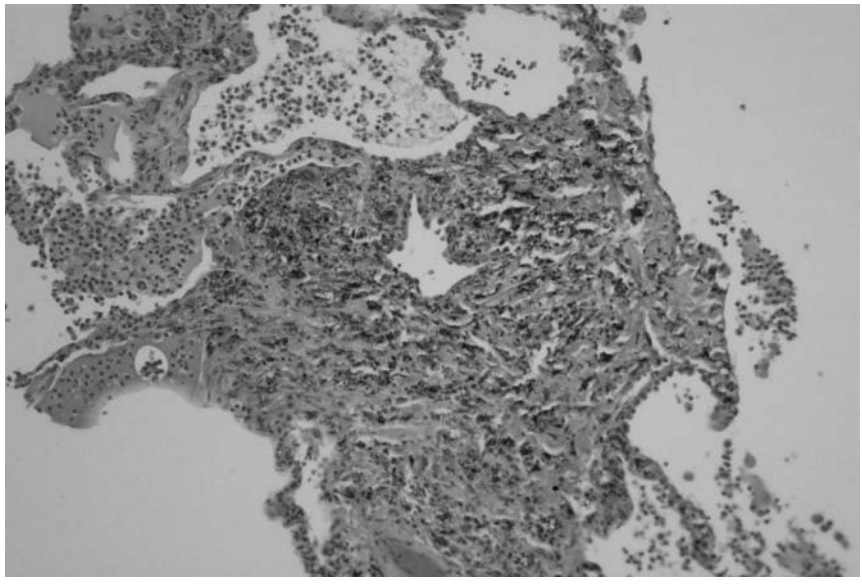

Figure 5.11 CAP–NIOSH grade 1 asbestosis is characterized by peribronchiolar scarring in association with asbestos bodies (H&E 200×).

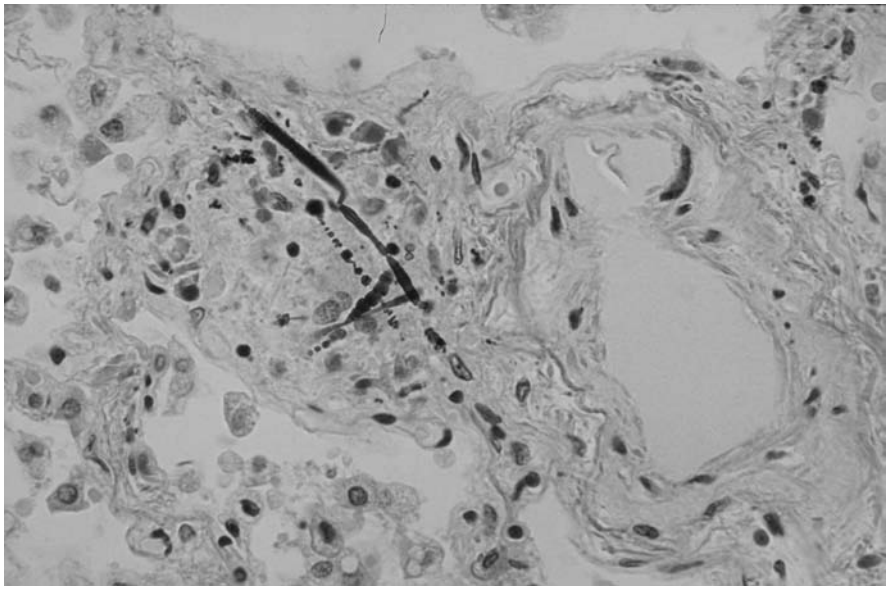

Figure 5.12 CAP–NIOSH grade 2 asbestosis shows scarring in two or more layers of adjacent alveoli (H&E 200×).

to peribronchiolar fibrosis (Figure 5.13); and CAP–NIOSH histologic grade 4 asbestosis is characterized by diffuse interstitial fibrosis with honeycombing (Figure 5.14). The morphology of grade 4 asbestosis is essentially identical to that of usual interstitial pneumonia with the two exceptions that asbestos bodies or asbestos fibers are identified in the tissue, and there probably is more chronic inflammation in usual interstitial pneumonia than asbestosis and more fibroblastic foci in usual interstitial pneumonia than asbestosis.

Frequently, lung tissue from individuals exposed to asbestos shows patchy irregular fibrosis that is difficult to grade according to CAP–NIOSH criteria.

Occasionally, it can be difficult to find asbestos bodies in cases of diffuse interstitial pulmonary fibrosis consistent with grade 4 asbestosis. This may be due to clearance of asbestos over time or breakdown of asbestos bodies. There is significant variation in the number of asbestos bodies in cases with grade 4 asbestosis. From author's view, in some cases of grade 4 asbestosis (diffuse interstitial fibrosis with honeycombing in association with at least two asbestos bodies), asbestos bodies can rarely be identified histologically in the lung tissue in association with multinucleated histiocytic giant cells (Figure 5.15). Multifocal areas of ossification are not uncommonly seen in persons with grade 3–4 asbestosis (Figure 5.16). Roggli has tabulated the histologic changes in 100 cases of asbestosis (Table 5.2).

Several controversies exist concerning the pathologic features and diagnosis of asbestosis.[28] For example, Churg[57] defined asbestosis as "bilateral diffuse interstitial fibrosis of the lungs caused by exposure to asbestos" and states that "diffuse

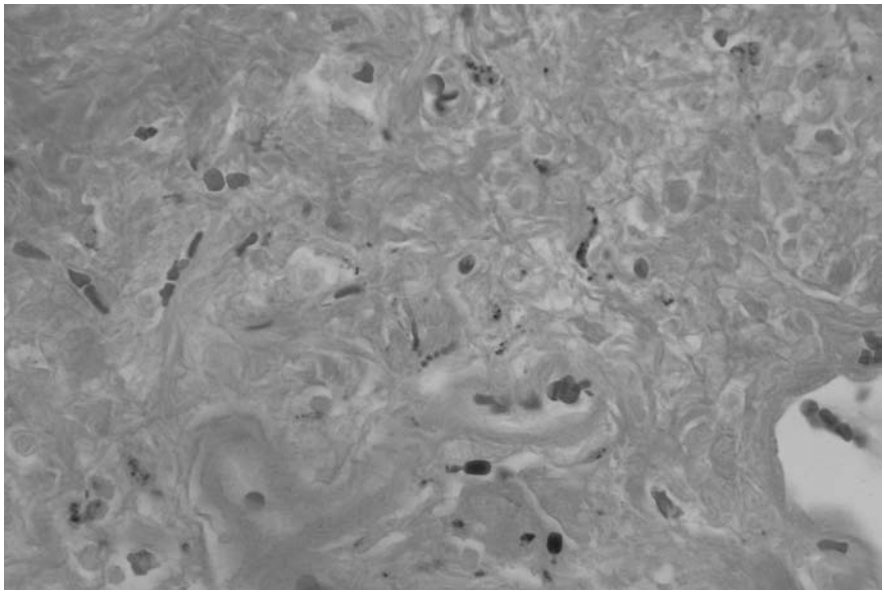

Figure 5.13 CAP–NIOSH grade 3 asbestosis is characterized by diffuse interstitial fibrosis of most lung parenchyma without honeycombing (H&E 200×).

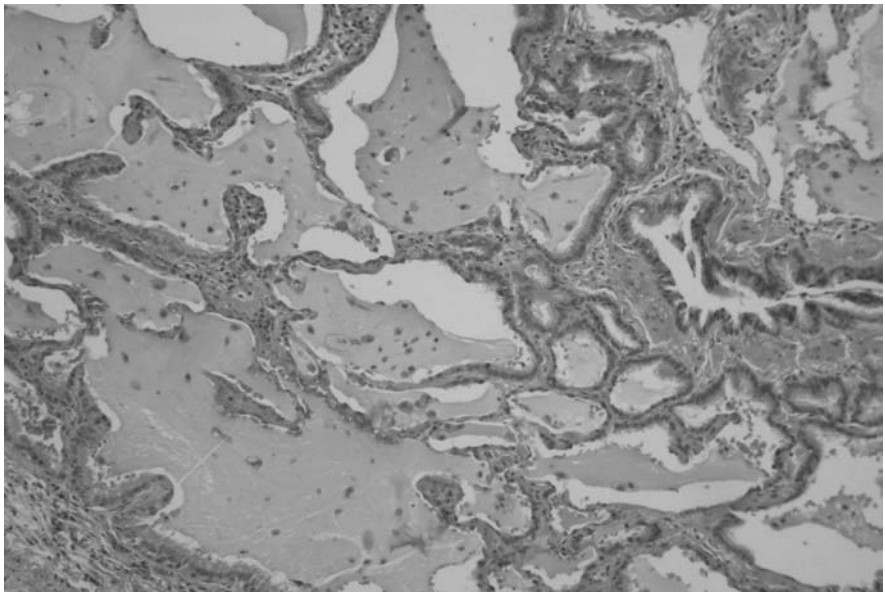

Figure 5.14 CAP–NIOSH grade 4 asbestosis is characterized by diffuse, predominantly subpleural interstitial fibrosis with honeycombing (H&E 200×).

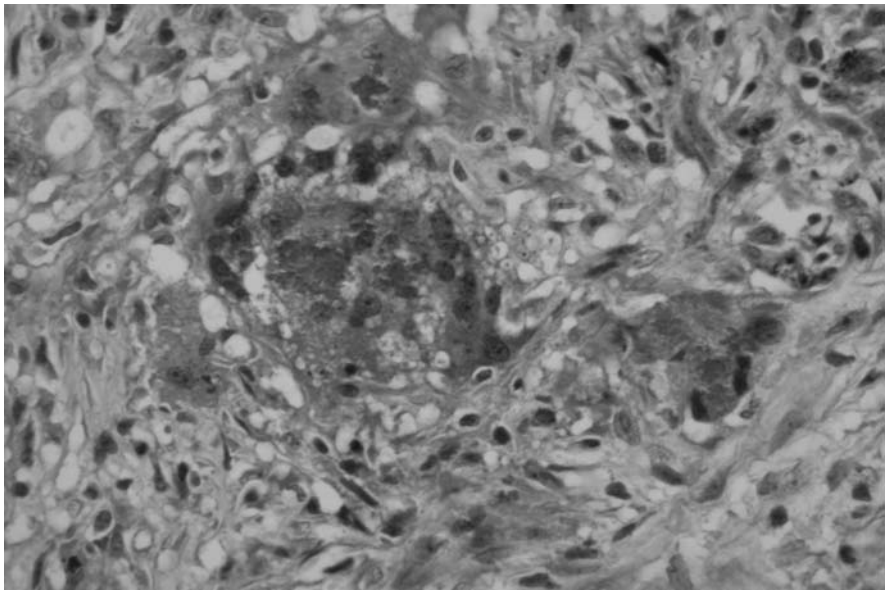

Figure 5.15 In this case of diffuse interstitial pulmonary fibrosis with honeycombing, asbestos bodies were rare and were only seen in multinucleated macrophage giant cells (H&E 400×).

interstitial fibrosis is the only process to which the term asbestosis should be applied." This definition may in part relate to Churg's concept of whether the lesion referred to as grade 1 asbestosis (peribronchiolar fibrosis in association with asbestos) should be called asbestosis. As discussed by Churg and Wright[58] and Wright et al.,[59] a variety of mineral dusts, including coal, talc, mica, silica, aluminum oxide, and iron oxide, as well as chrysotile and amphibole asbestos, can induce small airways disease consisting of fibrotic thickening of the membranous and respiratory bronchioles. They suggested the generic term "mineral dust-induced airways disease" be used to describe these lesions. As reviewed by Wright et al.,[59] part of the problem is that many persons exposed to mineral dust are also cigarette smokers and cigarette smoke can produce a similar type of lesion (although not identical) called respiratory bronchiolitis. However, Wright et al.[59] found that only 4% of nondust-exposed smokers showed fibrosis in the region of respiratory bronchioles, whereas 48% of respiratory bronchioles from smoking workers with asbestos exposure and 35% of the alveolar ducts from such workers showed fibrosis. Similar types of changes were seen in 31% of respiratory bronchioles and 14% of the alveolar ducts from subjects with other types of dust exposure. The latter findings suggest that asbestos is the more potent agent in inducing respiratory bronchiolar or alveolar duct fibrosis than other agents.

Like other asbestos-induced diseases, asbestosis has a dose–response relationship and, in general, relatively high concentrations of asbestos are needed to

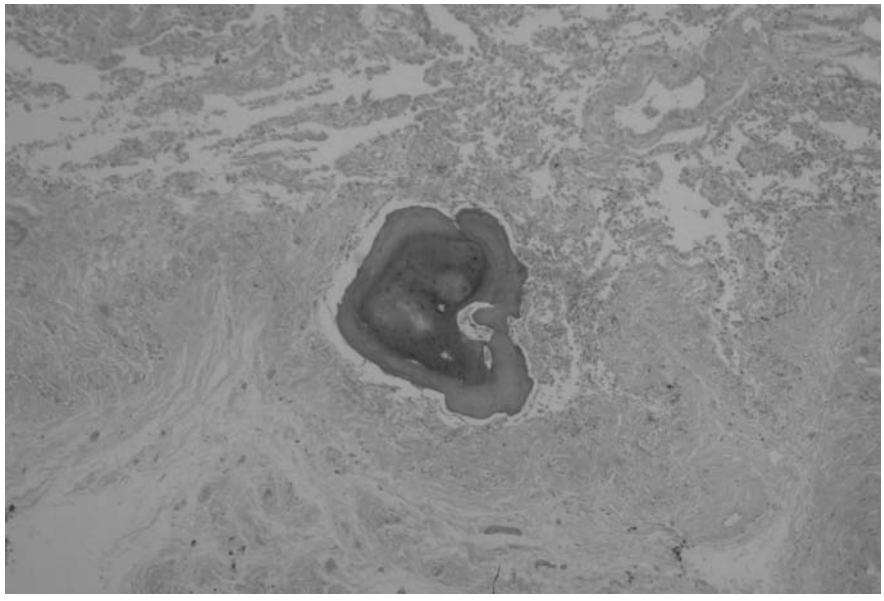

Figure 5.16 Multifocal areas of ossification (bone formation) are frequently seen in CAP–NIOSH grade 3–4 asbestosis.

cause asbestosis, specifically grade 3–4 asbestosis. In industrial hygiene terms, this is often greater than 25 fiber/cc-years.[60]

A report in 1988[61] suggested that chrysotile asbestos did not cause asbestosis. Most experimental and clinical studies have convincingly shown that chrysotile asbestos causes asbestosis. A number of experimental studies suggested that short fiber chrysotile asbestos (<5 μm long) is nonfibrogenic.[62–69] However, there is

Table 5.2 Histologic Features of Asbestosis

Histologic Features	Percent
Always present	
Asbestos bodies	100
Peribronchiolar fibrosis	100
Often present	
Alveolar septal fibrosis	82
Occasionally present	
Honeycomb changes	15
Foreign-body giant cells	15
Pulmonary adenomatosis	10
Cytoplasmic hyaline	7
Desquamative interstitial pneumonitis-like areas	6
Rarely present	
Osseous metaplasia (dendriform pulmonary ossification)	2
Pulmonary blue bodies	1

no doubt that long fiber chrysotile asbestos causes asbestosis in asbestos miners and millers and in asbestos textile workers.[70,71]

The short fiber–long fiber controversy is discussed in Chapter 3 by Dr. Dodson.

Asbestos is found in the lungs of most adults over the age of 30 in industrialized nations and, therefore, by itself is not a specific marker for asbestosis. In general, the concentration of asbestos in dry lung is 10 times greater than that in wet lung because the wet weight:dry weight ratio is usually about 10:1. As reported by Gylseth,[72] there is often a significant variation in asbestos body or fiber concentration as determined by different laboratories.

Roggli[51] reviewed the asbestos content of lung tissue in four reported series of patients with asbestosis and reported the asbestos body count in the lungs of 76 patients with histologically confirmed asbestosis (grade 4 asbestosis). The median asbestos body count for patients with asbestosis was 37,800 per g of wet lung tissue, whereas the median values for patients with idiopathic pulmonary fibrosis (usual interstitial pneumonia) was 16 asbestos bodies per g of wet lung tissue. For controls, the median was 0.4 asbestos bodies per g of wet lung tissue. Roggli found that the asbestos body count in 95% of cases of asbestosis was 1700 asbestos bodies per g of wet lung tissue or greater. Roggli pointed out that when this concentration of asbestos is present in the peripheral lung tissue, one can usually, but not always, see several asbestos bodies in a 2 cm × 2 cm iron-stained section. In 1983 Roggli and Pratt[73] pointed out that finding one asbestos body in a 2 cm × 2 cm, 5 μm thick section of lung tissue stained with hematoxylin and eosin, or in an iron-stained section on casual inspection (moving slide with one's finger rather than a mechanical stage), was equivalent to approximately 1000 asbestos bodies per g of wet lung tissue by digestion analysis.

While asbestos bodies are a marker of asbestos exposure, uncoated asbestos fibers are most likely responsible for causing asbestosis. Roggli[51] found that very few patients with alveolar septal fibrosis had uncoated fibers counts of $<100{,}000$ per g of dry lung tissue. However, as reported by Churg[74] and Bellis et al.,[75] it takes considerably less asbestos to cause grade 1 asbestosis than higher grades of asbestosis. For example, Bellis et al.[75] found grade 1 asbestosis in some patients with fiber counts as low as 1000–10,000 fibers/g of dry lung tissue. In 15 patients reported with grade 1 asbestosis, 13 had fibers <1000–10,000 per g of dry lung tissue. Roggli[51] correlated the histologic grade of asbestosis with tissue asbestos content and other parameters, and found that only uncoated fibers >5 μm long as determined by scanning electron microscopy in the total fibers per g of lung tissue (coated and uncoated) had the highest correlation coefficients and were statistically significant. Asbestos bodies per g of lung tissue, smoking history, age, and duration of exposure to asbestos had correlation coefficients between 0.26 and 0.06 and were not statistically significant. However, as stated elsewhere in this book, when one limits asbestos fiber counting schemes to only those fibers >5 μm in length or greater, a substantial concentration of asbestos fiber burden in the lung tissue will be missed.

The pathogenesis of asbestosis is not well understood, although the molecular basis has been discussed by Rom et al.,[76] Mossman and Churg,[77] and Kamp and

Weitzman.[78] These reviews stated asbestos is first deposited in the region of the respiratory bronchioles and alveolar ducts, and incites a fibroinflammatory response that eventually leads to the development of scarring (please see Chapter 4 by Atkinson and the review articles[76–78] for further descriptions). As reported by Hansen and Mossman[79] and Timbrell et al.,[80] the most important factor for asbestos to cause asbestosis was the total surface area of the asbestos fibers rather than their concentration in lung tissue.

Bellis et al.[75] studied the minimal pathologic changes in the lungs of humans exposed to asbestos and concluded that minimal bronchioloalveolar fibrotic changes with concomitant asbestos bodies could be considered as a mild pneumoconiotic lesion referred to as grade 1 asbestosis. Interestingly, lesions referred to as "small airways disease" in which no asbestos bodies were identified could also be regarded as an additional indicator of asbestos exposure because the concentration of asbestos present in the lung tissue from the two groups was similar.

As reported by Begin et al.,[81] who studied the experimental delivery of asbestos in sheep whose pulmonary anatomy most closely resembles humans, the initial asbestotic lesion in sheep caused by experimental administration of asbestos was scarring around the respiratory bronchioles and alveolar ducts. Of interest, Harless et al.[82] reported relatively acute onset obstructive airway disease in 17 out of 23 construction workers who suffered an intense 5-month exposure to chrysotile asbestos, and referred to a paper published by Jodoin et al.[83] that indicated asbestos-induced obstructive disease. Harless et al.[82] reported no other possible cause than asbestos for airway obstruction. That asbestos can cause larger airways disease, including cylindrical bronchiectasis and fibrotic narrowing, was reported by Jacob and Bohling[84] in 1960. Becklake[85] cited studies suggesting that autoimmune mechanisms may be responsible for the development of fibrosis in that there was a higher incidence of antinuclear antibodies in persons with asbestosis compared to that found in the general population.

With respect to asbestos airways disease and parenchymal lung disease, a study by Pinkerton et al.[86] suggested deposition of asbestos in lung tissue was related to the length of the airway from the hilum to the periphery of the lung and the degree of branching of the airways. Lung tissue that had the shortest distance from the hilum and the straightest airways was stated to have the highest concentration of asbestos. This observation was challenged by Delfino et al.[87] who studied 178 construction insulators and found no association of pleural abnormalities with airways geometry or length of airways.

Asbestosis and cigarette smoking has been discussed elsewhere in this book. With respect to the pathologic changes, there are instances in which there are changes of both asbestosis and cigarette smoke-induced interstitial lung disease. These include more severe interstitial fibrosis, areas of desquamative interstitial pneumonia (DIP) or respiratory bronchiolitis, and asbestos bodies in peripheral lung tissue.

With respect to the pathologic diagnosis, asbestosis is defined as the presence of fibrosis in association with asbestos bodies or fibers. The CAP–NIOSH Committee required two asbestos bodies in association with fibrosis.[49] In our experience, there are cases of asbestosis in which asbestos bodies are not easily identified. A situation

in which there is a strong history of occupational exposure to asbestos in association with pulmonary fibrosis, but no observable asbestos bodies in H&E and iron-stained sections, one should attempt to do asbestos digestion fiber analysis on the tissue. Examples of asbestosis have been reported in which asbestos bodies have not been recognized in lung tissue, but asbestos fibers have been found in great enough concentration to cause asbestosis.[85,88,89]

In the proper clinical context, specifically in patients with the clinical features of asbestosis, analysis of bronchoalveolar lavage fluid can suggest the diagnosis of asbestos by showing an increased number of neutrophils and eosinophils in the fluid.[90] In some instances, asbestos bodies can be identified in BAL fluid, either alone or in the cytoplasm of macrophages (Figure 5.17). Likewise, identification of asbestos bodies in sputum or in transbronchial biopsy specimens can strongly suggest the diagnosis of asbestosis in the proper clinical setting. The primary pathologic differential diagnosis of grade 3–4 asbestosis is primarily idiopathic pulmonary fibrosis (usual interstitial pneumonia). Pathologic features of usual interstitial pneumonia and grade 3–4 asbestosis are similar with the exception that, in asbestosis, one can identify an increased concentration of asbestos bodies or fibers. As stated earlier, there are cases of grade 3–4 asbestosis where asbestos bodies are not identified, but shows significantly elevated concentrations of asbestos fibers.

Persons who are occupationally exposed to asbestos are sometimes exposed to other dusts that can cause pulmonary fibrosis, including silica, talc, and welding fumes. In some instances, the pattern of fibrosis, for example silicosis, allows for

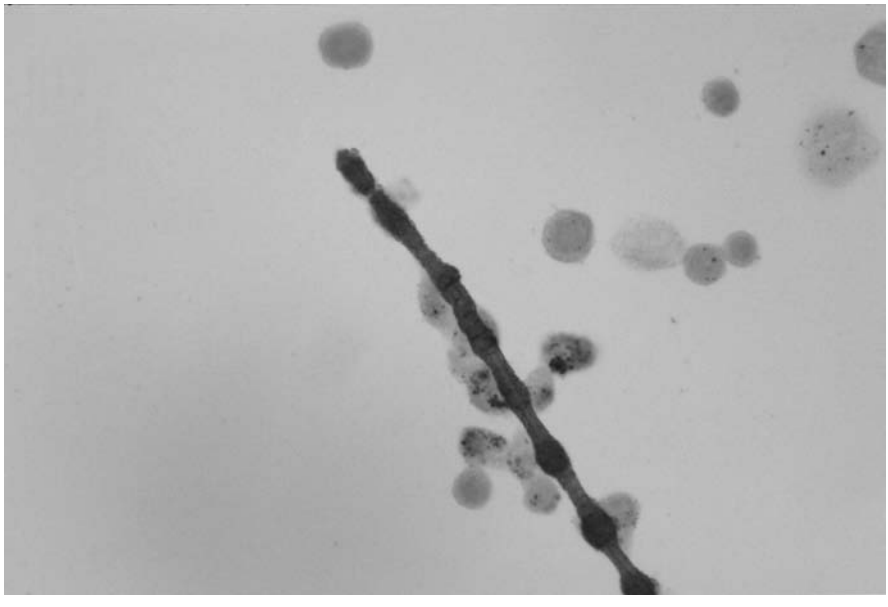

Figure 5.17 This cytologic preparation of BAL fluid shows an asbestos body within the cytoplasm of a macrophage (PAP stain 400×).

an easy differentiation. Sometimes, pseudoasbestos bodies can be seen in lung tissue (ferruginous body in which the core is something other than asbestos, which would suggest a nonasbestos cause for the fibrosis).

5.1.6 Localized and Unusual Nonneoplastic Pulmonary Diseases in Persons Occupationally Exposed to Asbestos

There are a variety of other pathologic conditions that are occasionally seen in individuals exposed to asbestos that do not fall into the usual categories. These include organizing pneumonia–bronchiolitis obliterans-type change, desquamative interstitial pneumonitis-like change, *Aspergillus* infection, granulomatous inflammatory changes, and lymphocytic interstitial pneumonitis.

5.1.7 Organizing Pneumonia — Bronchiolitis Obliterans-Type Change

Although asbestos is usually not thought of as producing localized parenchymal lung masses, Hillerdal and Hemmingson[91] reported ten patients with localized visceral pleural fibrosis and fibrosis of the underlying lung parenchyma that caused a pseudotumor. Lynch et al.[92] identified 16 localized masses (nine intraparenchymal and seven subpleural) in 260 asbestos-exposed individuals evaluated radiographically. In 1961, in the Case Records of the Massachusetts General Hospital, a case was reported that suggested asbestos caused localized bronchiolitis obliterans-organizing pneumonia.[93] The case concerned a 61-year-old man who developed a localized consolidation in his left upper lobe that histologically showed the changes of an organizing pneumonia in which numerous asbestos bodies were identified. A secondary infection was suggested to be the cause of this reaction, although was never proven. In 1981 Saldana[94] described four men whose chest radiographs showed localized infiltrates in the absence of diffuse changes. These masses had the histologic features of organizing pneumonia–bronchiolitis obliterans in which asbestos bodies were identified in the organizing granulation-like tissue that were occluding bronchi. The organizing pneumonia part of the lesion consisted of a large number of histiocytes and confluent giant cell granulomata, lymphocytic angiitis and lymphoplasmocytic cellular infiltrate. Because no other etiology could be identified, Saldana[94] referred to this lesion as "localized asbestos pneumonia."

Spencer[95] described organizing pneumonia as a primary pathologic feature of asbestosis. Roggli[51] reported organizing pneumonia in several asbestos-exposed patients who underwent thoracotomy for suspected malignancy. In 1993 Hammar and Hallman[96] reported four cases of organizing pneumonia with focal bronchiolitis obliterans in patients occupationally exposed to asbestos, who had significantly elevated concentrations of asbestos in their lung tissue and in which no other cause was identified.

Keith et al.[97] studied rats that were intratracheally injected with UICC Canadian chrysotile-B asbestos and observed alveolar and interstitial edema at 1, 3, and

6 months after treatment and found bronchiolitis obliterans in 33–45% of the bronchioles examined. In the cases reported by Hammar and Hallman,[96] the patients were usually asymptomatic and presented with nodular masses radiographically. In most instances, these masses were thought to most likely represent primary lung cancers. Histologically, the masses showed the pathologic features of bronchiolitis obliterans-organizing pneumonia (Figure 5.18) consisting of nodular masses of loose myxomatous granulation tissue that filled alveolar spaces and bronchioles associated with frequent asbestos bodies (Figure 5.19).

5.1.8 Desquamative Interstitial Pneumonitis-Like Change

Corrin and Price[98] reported a case of desquamative interstitial pneumonitis in a 53-year-old man who had smoked 10 cigarettes a day until 1 year before his illness. Asbestos bodies were identified in the intra-alveolar macrophages. Freed et al.[99] reported a case of DIP in a 32-year-old man who had a history of working in the drywall construction industry and smoked 3-pack of cigarettes per day. A single asbestos body was identified in a frozen section specimen and asbestos digestion analysis showed 4666 asbestos bodies per g of wet lung tissue. Asbestos fiber analysis showed 819 and 20 million chrysotile and tremolite fibers per g dry lung tissue, respectively. In the report by Hammar and Hallman,[96] one patient had a desquamative interstitial pneumonitis pattern in which asbestos bodies were easily identified in the tissue, specifically in the macrophages that filled alveolar spaces (Figure 5.20).

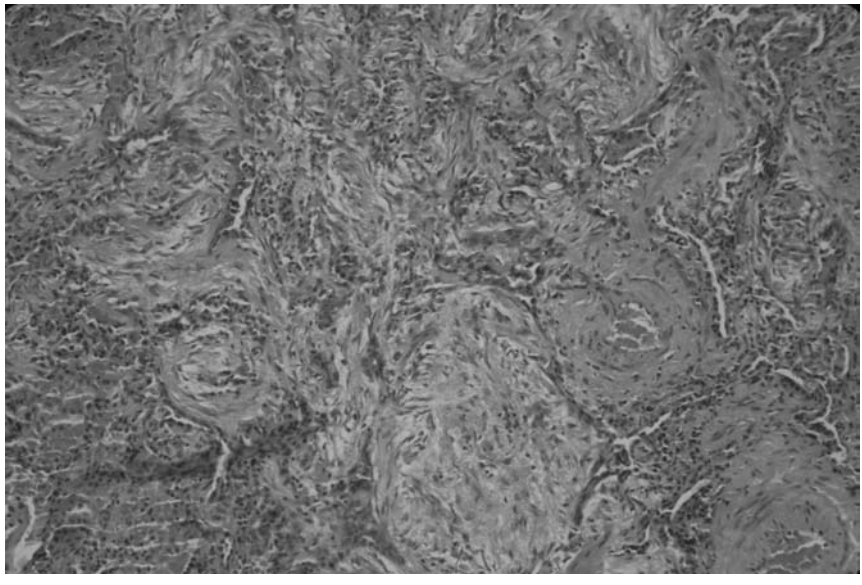

Figure 5.18 This region of lung tissue shows an organizing pneumonia–bronchiolitis obliterans pattern characterized by loose myxomatous tissue in alveoli and bronchial lumens (H&E 100×).

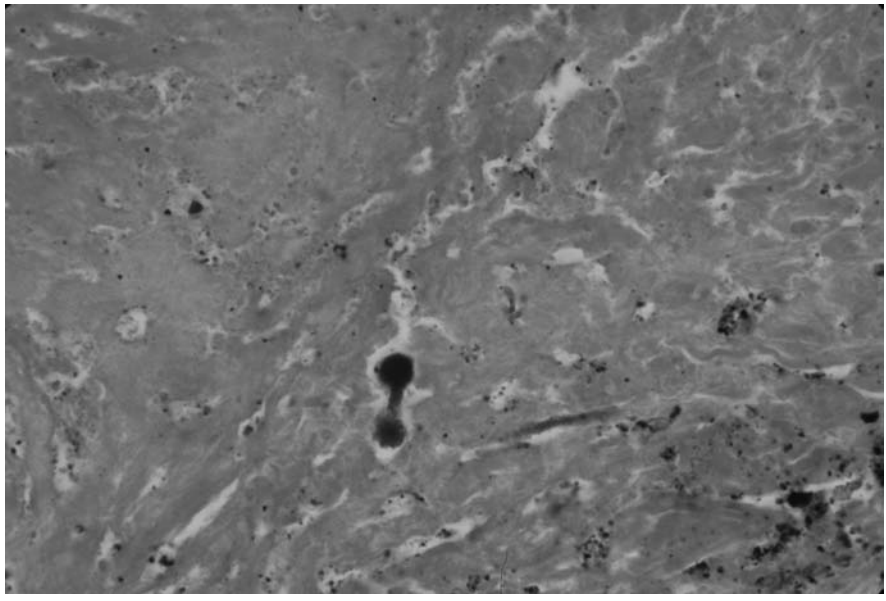

Figure 5.19 Asbestos bodies are seen in this area of organizing pneumonia–bronchiolitis obliterans (H&E 400×).

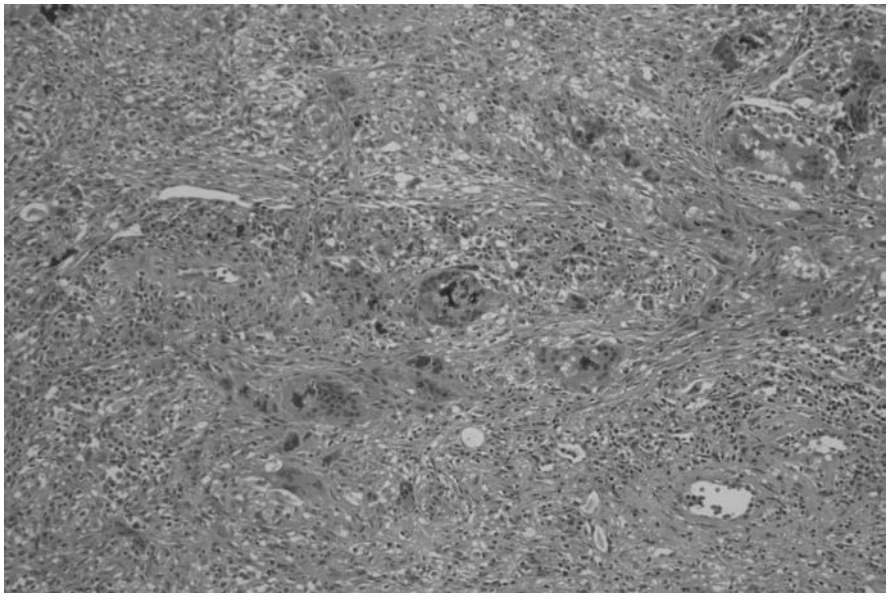

Figure 5.20 In this lung tissue showing a DIP pattern, asbestos bodies are seen in the cytoplasm of macrophages that are filling alveoli (Iron Stain 400×).

The significance of finding a DIP pattern is uncertain, because the primary cause of desquamative interstitial pneumonitis is cigarette smoke. It is possible that all cases reported were due to cigarette smoke-induced DIP in which the individuals were also exposed to asbestos. However, asbestos does cause the accumulation of macrophages in tissue specimens, even in nonsmokers, so it is possible that these changes were caused by the combined effect of cigarette smoke and asbestos or by asbestos alone.

5.1.9 *Aspergillus* Infection in Exposed Individuals

In 1982 Hillerdal and Hecksher[100] reported *Aspergillus* infection in the lungs of four asbestos-exposed persons, two of whom reportedly had localized lung masses. Another case of aspergillosis in association with asbestosis was reported by Hinson et al.,[101] and they suggested asbestos could cause cylindric bronchiectasis and fibrotic narrowing of the bronchi. Roggli et al.[102] described five cases in which *Aspergillus* was identified in the lungs of persons occupationally exposed to asbestos. In the study by Hammar and Hallman[96] of eight patients with localized masses, one case showed a focal area of *Aspergillus* infection (Figure 5.21) in which ferruginous bodies characteristic of asbestos bodies were identified. This patient worked at the Puget Sound Naval Shipyard in Bremerton, Washington and had a history of occupational exposure to asbestos. There was no evidence of allergic bronchopulmonary aspergillosis and the patient was not asthmatic. One has to be

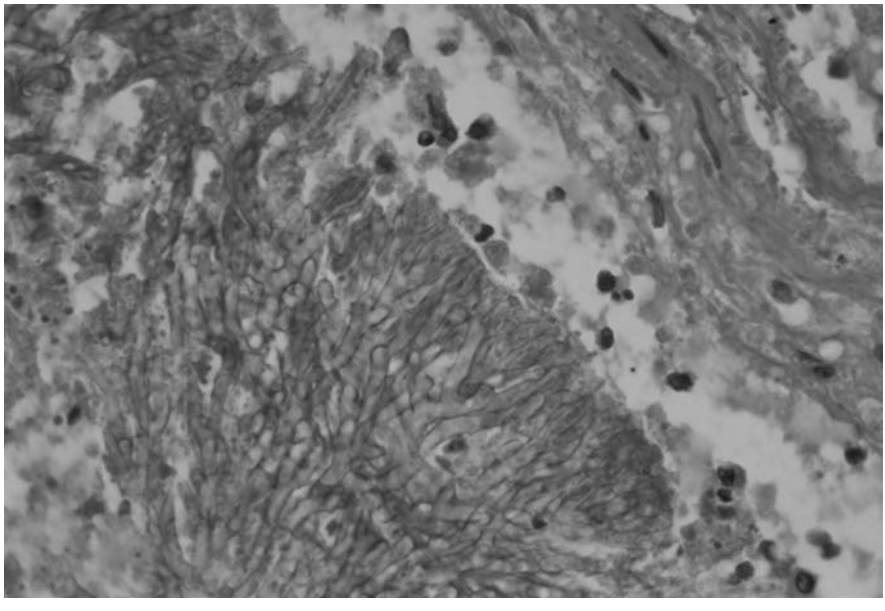

Figure 5.21 In this region of lung tissue are focal areas of *Aspergillus* proliferation. Asbestos bodies were identified elsewhere in the lung tissue (PAS 400×).

cautious in interpreting this finding because *Aspergillus* involvement of lung tissue can occur in many settings.

5.1.10 Granulomatous Inflammatory Changes

As previously stated in this chapter, histiocytic (macrophage) giant cells can contain asbestos bodies or fibers and are seen in the lungs of persons occupationally exposed to asbestos. Occasionally, small nodular aggregates of histiocytes and multinucleated macrophage giant cells form nonnecrotizing granulomata. As reported in one case,[96] there was a striking granulomatous inflammation localized in the lung in which asbestos bodies were identified in giant cells forming the granulomata (Figure 5.22). The patient who had this change, however, had a history of rheumatoid arthritis, although had a negative rheumatoid factor. This patient had no clinical or laboratory evidence of sarcoidosis. Of interest, Monseur et al.[103] reported a granulomatous inflammatory reaction in the urinary bladder of a patient who worked in an asbestos factory and in whom asbestos fibers were identified in prostate tissue.

5.1.11 Lymphocytic Interstitial Pneumonitis

Rom and Travis[104] reported a lymphocyte–macrophage alveolitis in open lung biopsies of two nonsmoking patients occupationally exposed to asbestos. The pathologic

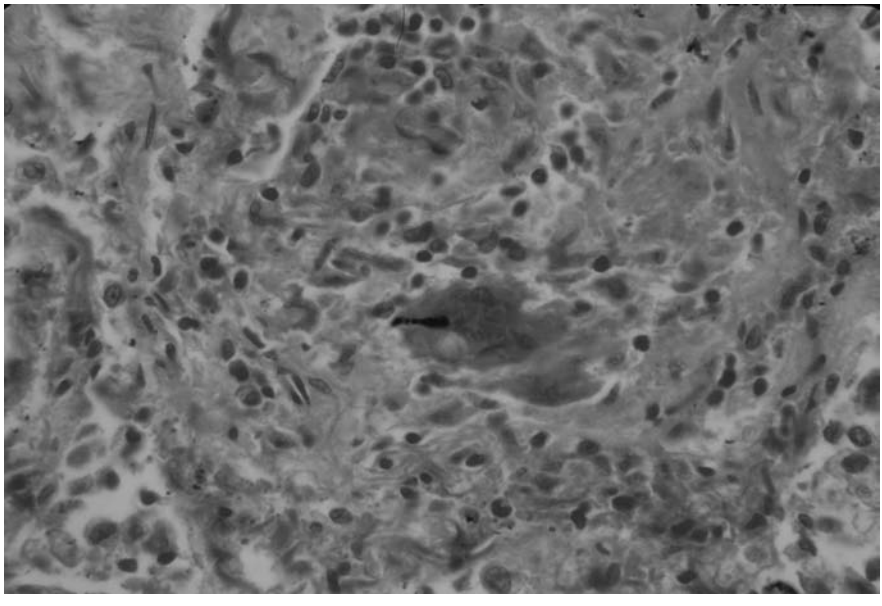

Figure 5.22 This lung tissue shows granulomatous inflammation in which asbestos bodies are identified in multinucleated macrophage giant cells (H&E 100×).

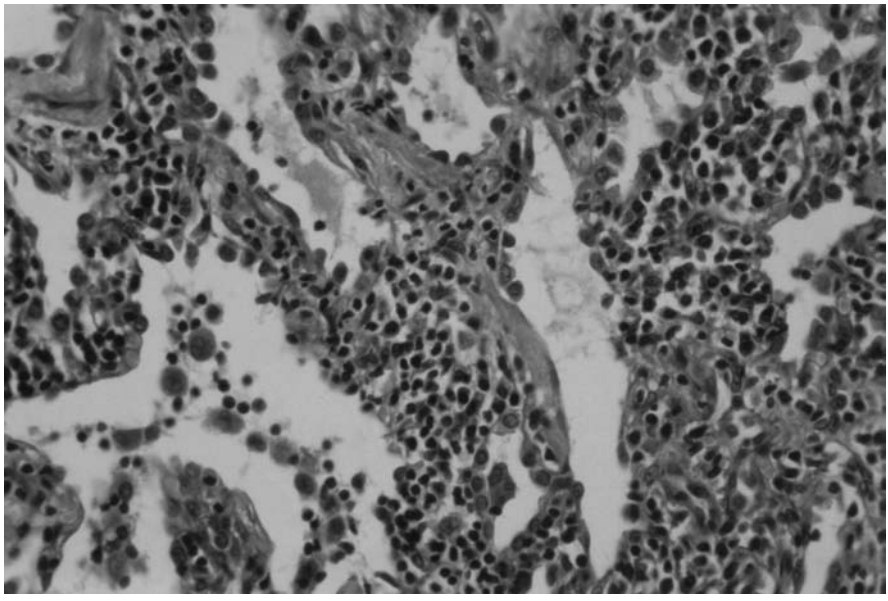

Figure 5.23 This lung tissue from a person occupationally exposed to asbestos with a high concentration of asbestos in his lungs shows a diffuse interstitial lymphocyte-plasma cell infiltrate admixed with multinucleated macrophage giant cells resembling the pathologic changes seen in hypersensitivity pneumonia (H&E 200×).

changes reported by Rom and Travis, in this author's opinion, were identical to those seen in hypersensitivity pneumonitis, although there is no proof that asbestos induces hypersensitivity pneumonia. Hammar and Hallman[96] described a patient who was occupationally exposed to asbestos, who had high concentrations of asbestos fibers in his lungs, who developed a diffuse lymphocytic–macrophage interstitial infiltrate that had the features of hypersensitivity pneumonitis (Figure 5.23), in which no other cause was identified.

The mechanism by which asbestos causes localized or unusual inflammatory reactions in the lung is unclear, although there is extensive information, as reported in other chapters of this book, that asbestos induces a fibroinflammatory-type process and granulomatous inflammation.

5.2 NEOPLASMS CAUSED BY ASBESTOS

In the neoplastic arena, asbestos most frequently causes primary lung cancer and mesothelioma. A variety of other neoplasms have been reported to show an increased incidence in persons who are occupationally exposed to moderate-to-high amounts of asbestos.[105]

5.2.1 Asbestos and Lung Cancer

The ability of asbestos to cause lung cancer can be traced to publications beginning in the mid-1930s. In 1934 Wood and Gloyne[106] reported two cases of lung cancer in 43 patients with asbestosis. In 1935 Gloyne[107] reported two women (one aged 35 years and another aged 71 years) with moderately severe asbestosis, who developed squamous cell carcinoma of the lung. Gloyne also identified a patient with small cell lung cancer in association with asbestosis. In 1936 Egbert and Geiger[108] reported a case of an acinar adenocarcinoma arising from the mainstem bronchus of the left-lower lobe in a 41-year-old Hungarian factory man, who at autopsy was found to have extensive pleural adhesions with obliteration of pleural cavities and diffuse pulmonary asbestosis. This tumor was extensively metastatic. Interestingly, Egbert and Geiger[108] cited a publication concerning asbestosis by Gloyne in which a case of asbestosis with "carcinoma of the pleura" was identified which this author would interpret to either be a pseudomesotheliomatous carcinoma (see subsequently) or mesothelioma. Egbert and Geiger[108] reported the relationship between exposure to irritating dusts like asbestos and malignancies of the lung that aroused a great deal of interest because various statistics showed there was an increased incidence of pulmonary cancer in patients who were exposed to various dusts. They cited the publication by Hruby and Sweany[109] who analyzed the incidence of lung cancer in persons exposed to dust and concluded there was an approximate tenfold increase in the number of cases coming to autopsy in the previous 40 years and a twofold increase that occurred in the previous 10 years. Klotz and Simpson[110] indicated that lung cancer was frequent in other forms of pneumoconiosis and Obendorfer[111] described an increased incidence of lung cancer in tin miners who came to autopsy. Egbert and Geiger[108] concluded the irritating effects of inhaled asbestos particles may be a significant factor in the development of primary lung cancer in the patients they described.

In the United States, the first report of lung cancer in association with asbestos was described by Lynch and Smith.[112] They referred to a report by Nordmann[113] who reported two cases of lung cancer in patients with asbestosis and suggested a cause–effect relationship. The association between lung cancer and asbestosis was rapidly accepted in Germany, in part on the basis of an experimental study in white mice that developed pulmonary cancers after inhalation of asbestos dust.[114] Wedler,[115] a German pathologist, studied the association of lung cancer and asbestosis by reviewing public records from several countries. He found 14 cases of malignant neoplasms of the lung, and pleura in 92 postmortem examinations (16%). This was in excess of the proportion of lung cancers that occurred in the general autopsy population, which was between 2 and 6%. Wedler[115] found carcinoma as a complication of asbestosis that was observed most frequently in males between ages 35 and 41 in the part of the lung that was affected with asbestosis. In Wedler's cases,[115] the latent period was between 12 and 42 years and there was often a long interval between cessation of exposure to asbestos and the development of cancer. Wedler[115] hypothesized that the increased frequency of lung cancer in persons with asbestosis resulted from mechanical and probable chemical

reactions to asbestos which caused proliferation of lung tissue, including epithelial desquamation and cell modification, macrophage response, giant foreign body cell formation, and epithelial metaplasia of the bronchial mucus membranes. Wedler[115] concluded the development of cancer was attributed to metaplasia of the bronchial mucus membrane and accompanying inflammatory reactions, and further concluded that cancer of the lung and asbestosis was a disease legally justified for insurance claims.

Of further interest was the report by Merewether,[116] who in 1947 suggested an association between asbestos exposure and lung cancer. In the Annual Report of the Chief Inspector of Factories in England, 235 deaths were reported between 1924 and 1946 that were either caused by asbestosis or occurred in persons in whom asbestosis was proven at autopsy. In these 235 cases, there were 31 (13.2%) recorded cases of carcinoma of the lungs or pleura. Of this group of 235, 22 out of 128 male deaths (17.2%) were caused by carcinoma of the lung and pleura and 9 out of 107 female deaths (8.4%) were caused by cancer of the lung and pleura. The cases of asbestosis developing carcinoma of the lung or pleura had a mean exposure to asbestos of 16.5 years compared to 13.4 years for those dying only of asbestosis without cancer. Merewether's report[116] was significant because lung cancer among the adults examined at necropsy in England at that time who had no exposure to asbestos was 4% and the male:female sex ratio in the general population was 5:1, whereas the ratio in persons who were exposed to asbestos who developed lung cancer, the male:female ratio was 2.4:1. The Merewether data strongly suggested a causal relationship between asbestos, asbestosis, and lung cancer.

The first epidemiologic study evaluating the association of lung cancer in asbestos workers was published by Doll in 1955.[117] Doll studied 113 men who had worked for at least 20 years in places where there was likely exposure to asbestos and determined the mortality among them compared to that which would have been expected. Thirty-nine deaths occurred in the exposed group, whereas only 15.4 deaths were expected. The excess deaths were from lung cancer (11 occurring, 0.8 expected), and from other respiratory diseases and cardiovascular diseases (22 observed, 7.6 expected). Doll concluded lung cancer was a specific industrial hazard in asbestos workers and the average risk among men employed for 20 or more years was of the order of tenfold greater than in the general population.

In 1980 McDonald[118] published an epidemiologic study of 17 cohorts, one of which represented the Doll study. Many different occupations were represented in the various cohorts and all revealed an increased incidence of death from lung cancer. Acheson and Gardner[119] came to a similar conclusion in their report published in 1979. Finally, the information presented by Selikoff et al.[120] at a conference held in 1964 in New York City left little doubt that asbestos was causally related to an increased incidence of lung cancer.

Information on the incidence of asbestos-induced lung cancer is described by Hammar and Dodson.[121] The pathogenesis of asbestos-induced lung cancer is described in detail in this book by Atkinson (Chapter 4) and by Kamp and Weitzman.[78]

There have been primarily two issues concerning asbestos and lung cancer. The first has to do with the issue of the interaction between cigarette smoke carcinogens

and asbestos. This was reviewed by Saracci in 1987.[122] Saracci listed 13 studies evaluating the issue of cigarette smoke and asbestos in causing lung cancer and concluded that in ten studies there was an evidence of multiplicative synergism between cigarette smoke carcinogens and asbestos in causing lung cancer (Table 5.3). The exact mechanism by which cigarette smoke interacts with asbestos to produce an increased incidence of lung cancer is not entirely understood, but it is known that asbestos and cigarette smoke carcinogens can cause the same mutations in proto-oncogenes and tumor suppressor genes. It has been hypothesized that because of differences in surface charge, asbestos fibers can directly carry cigarette smoke carcinogens into the nucleus of cells.

The other issue concerns whether asbestosis is necessary to attribute lung cancer causation to asbestos. There is no doubt that there is a significant increased incidence of lung cancer in persons who have clinical and pathological asbestosis. The question arises as to whether or not asbestosis is a necessary prerequisite for associating asbestos and lung cancer or if it is an issue of concentration of exposure to asbestos that is most important. This issue has been extensively reviewed by Henderson et al.[123,124] While there is no doubt that there appears to be an increased incidence of lung cancer in cases of usual interstitial pneumonia (idiopathic pulmonary fibrosis) and in collagen vascular disease associated interstitial fibrosis, the majority of evidence suggests it is the concentration of asbestos that is most important in causing lung cancer and not presence of the disease asbestosis.

The issue of parietal pleural plaques and their association with lung cancer has been extensively discussed.[121] A study by Hillerdal[125] in 1994 found a slight increase in the incidence of lung cancer in persons who had pleural plaques. However, other studies have shown no increased incidence of lung cancer in persons with pleural plaques. Of interest, the most recent document published by the American Thoracic Society[126] suggests plaques are associated with an increased incidence of lung cancer.

The type and morphology of lung cancer associated with asbestos exposure is relatively straightforward. Although several reports have suggested that adenocarcinoma is the most common type of lung cancer in persons occupationally exposed to asbestos,[121] the majority of opinion at this time is that all four major types of lung cancer (adenocarcinoma, squamous cell carcinoma, small cell lung cancer, and large cell undifferentiated carcinoma) occur in persons occupationally exposed to asbestos, at about the same rate as that seen in the general population not exposed to asbestos.

Adenocarcinoma is currently the most common primary lung cancer seen in the United States and in many other parts of the world (Figure 5.24). The primary criterion for diagnosing adenocarcinoma is the presence of glandular differentiation or mucus production by tumor cells. Most primary pulmonary adenocarcinomas occur in a subpleural location and often show a variety of differentiation.[127,128]

Squamous cell carcinoma usually occurs in the central region of the lung arising from the distal trachea, mainstem bronchi, or lobar bronchi (Figure 5.25). Histologically, squamous carcinomas show a gamut of differentiation from well differentiated, in which the cells resemble normal squamous cells, to poorly differentiated, in which the cells show areas suggestive of squamous differentiation.

Table 5.3 Interaction of Asbestos and Cigarette Smoke in Causing Lung Cancer

Author(s), Reference No., Design, Years of Observation, Exposure Investigated	Exposure Assessment to		No. of Lung Cancer Cases	Controls or Expected Cases	Relative Risk for Asbestos[c]		Interaction Magnitude	
	Smoking	Asbestos			Smokers	Nonsmokers	Absolute	Relative (PERDI)[a]
Liddell et al., case control within cohort, 1950–1975, chrysotile mining and milling	O, P	D	223	715	1.67	2.97	~ A	<25
Baker, historical cohort, 1944–1981, crocidolite mining and milling	D, O	D	62	29[b]	4.98	0.71	>M	≥75
Selikoff et al., historical cohort, 1961–1977, amosite factory	P	D	50	9.8	4.69	25	I	25–49
Acheson et al., historical cohort, 1947–1980, amosite factory	D	D	23	14.5	1.57[c]	2.00	~M	25–49
Berry et al., historical cohort, 1960–1970, mixed asbestos factory	D, O	D	27 Males	12.0	2.25[c]		>M	50–74
			15 Females	2.1	7.36[c]	5.00	>M	≥75
Berry et al., cohort, 1971–1980, mixed asbestos factory	P	D	53 Males	26.0	2.01[c]	6.25	A	0
			13 Females	2.58	4.27[c]	12.50	I	<25
Selikoff and Hammond, cohort, 1963–1974, chrysotile and amosite in insulation (New Jersey)	P	D	45	7.62	6.0	0.0	>M	≥75
Hammond et al., cohort, 1967–1976, chrysotile and amosite in insulation (Unites States and Canada)	P	D	272	51.7	5.25	5.71	M	50–75
Blot et al., case control, 1970–1976, shipyard exposures	R, O	R,O	458	553	1.61	1.28	~M	<25
Blot et al., case control, 1972–1976, shipyard exposures	O	O	319	341	1.57	1.88	~M	25–49

(*Table continued*)

Table 5.3 *Continued*

Author(s), Reference No., Design, Years of Observation, Exposure Investigated	Exposure Assessment to		No. of Lung Cancer Cases	Controls or Expected Cases	Relative Risk for Asbestos[c]		Interaction Magnitude	
	Smoking	Asbestos			Smokers	Nonsmokers	Absolute	Relative (PERDI)[a]
Martischnig et al., case control, 1973–1974, any asbestos exposure	R	R	201	201	3.19	1.08	>M	≥75
Pastorino et al., population case control, 1976–1979, any asbestos exposure	R	R	204	211	1.80	2.80	I	25–49
Kjuus et al., case control, 1979–1983, any asbestos exposure	R	R	176	176	2.05	2.40	~M	25–49

O, exposure information collected prospectively or retrospectively from informants other than the study subjects, for example, relatives; P, exposure information collected prospectively (i.e., before cancer occurrence) from study subjects; D, exposure information extracted from existing documents, for example, medical records, company rolls, etc.; R, exposure information collected retrospectively from study subjects; A, additive; M, multiplicative; I, intermediate.

[a]PERDI, percent of excess risk due to interaction.

[b]Lung cancers in control cohort.

[c]Excluding ex-smokers from both the category of smokers and that of nonsmokers.

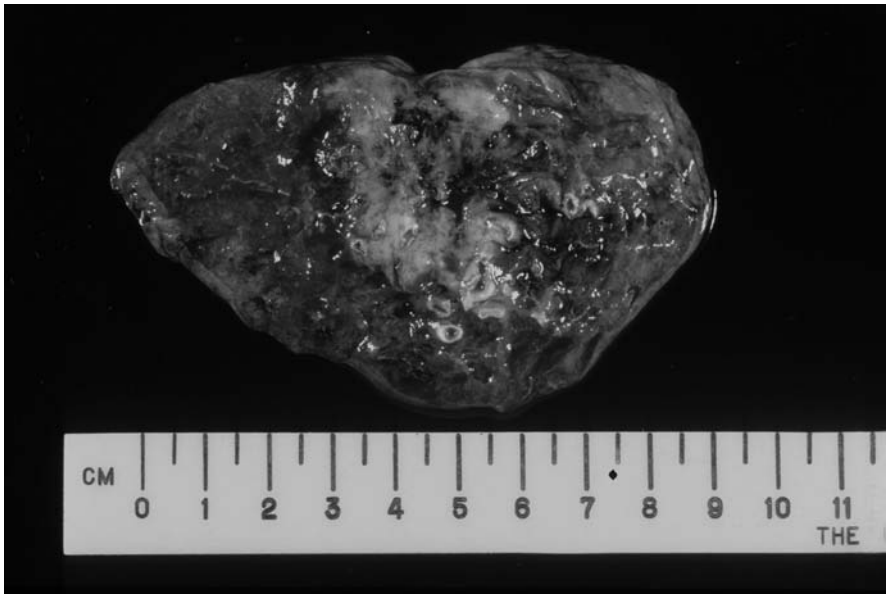

Figure 5.24 This subpleural lung neoplasm had the histologic features of an adenocarcinoma. Adenocarcinoma is the most common lung neoplasm in the United States and in many other countries.

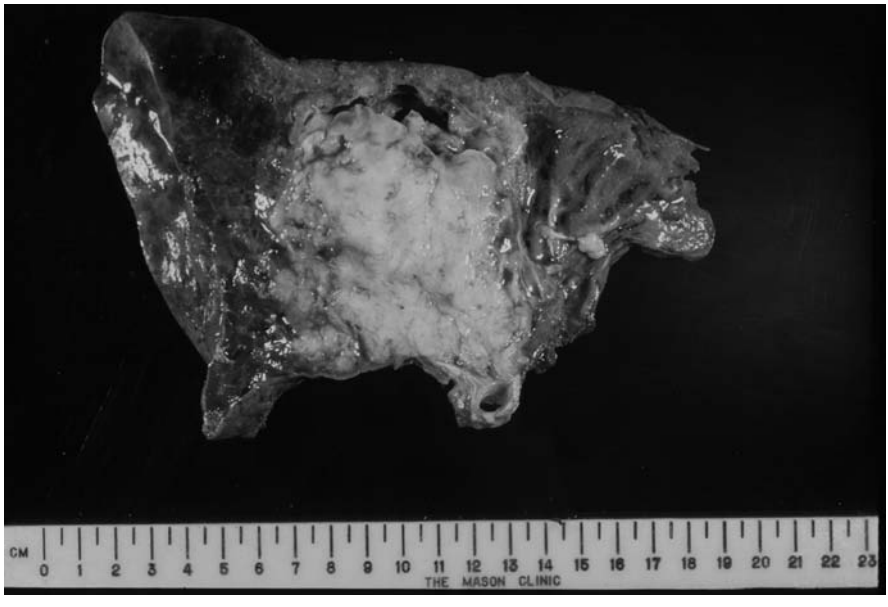

Figure 5.25 This squamous cell carcinoma arose from a centrally located bronchus and occluded the bronchus.

The primary pathologic features of squamous differentiation are circumferential intercellular junctions (desmosomes) and keratin formation.

Small cell lung cancer makes up about 20–25% of primary lung cancers and is usually found in a central location of the lung. Approximately 10% of small cell lung cancers occur as isolated nodules. In contrast to squamous cell carcinomas that frequently invade bronchi, small cell lung cancer frequently invades the adjacent lymph nodes and metastasizes to mediastinal lymph nodes (Figure 5.26). Histologically, small cell lung cancers are composed of relatively small cells that have high nuclear:cytoplasmic ratios with relatively little cytoplasm. The nucleus frequently has a ground glass appearance or a speckled chromatin pattern with inconspicuous nucleoli. These cells show features of neuroendocrine differentiation in which the cancer cells express substances such as synaptophysin, neuron specific enolase, chromogranin-A, and thyroid transcription factor-1.

Large cell undifferentiated carcinomas are the least common of the four major types of lung cancer and, when studied by other methods such as immunohistochemistry or electron microscopy, can frequently be subclassified into either a squamous cell carcinoma or an adenocarcinoma. Large cell carcinomas are composed of large cells that histologically show no squamous or glandular differentiation.

For treatment purposes, lung cancers are frequently classified as small cell or nonsmall cell primarily because small cell lung cancers are treated in a very specific way, which is different than the treatment used for adenocarcinomas, squamous carcinomas, and large cell undifferentiated carcinomas (nonsmall cell lung cancers).

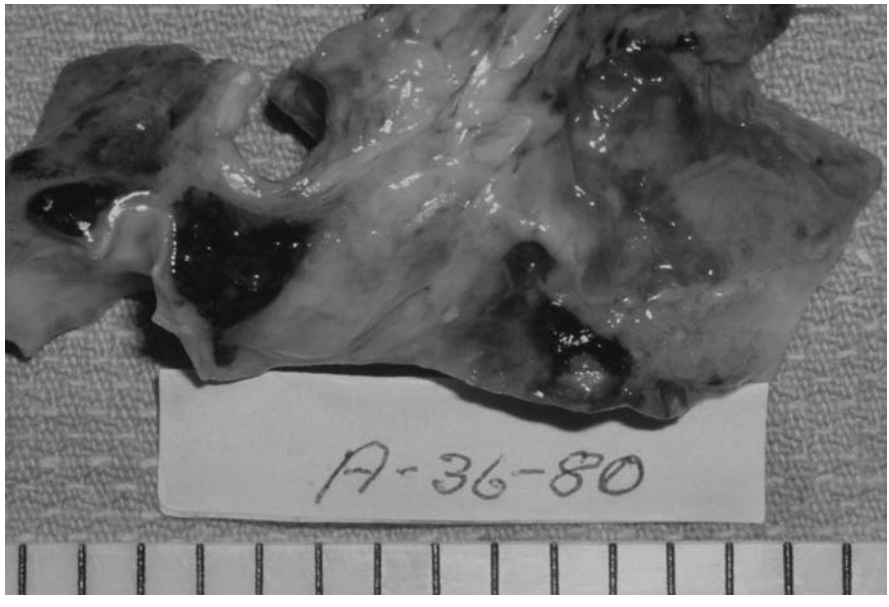

Figure 5.26 Small cell lung cancer arises from neuroendocrine cells and produces a tumor that has a propensity to invade lymph nodes and adjacent tissue.

Sometimes it can be difficult to determine whether a tumor in the lung is a primary tumor or a metastatic tumor. It can be determined by using a battery of immunohistochemical tests.

Primary lung cancers are anatomically staged according to the TNM system as shown below (Figure 5.27). This information is vital for treatment purposes and has significant prognostic information. Small cell lung cancer is staged differently than nonsmall cell lung cancer. Small cell lung cancers are staged according to whether the disease is limited, in which the neoplasm is confined to the chest cavity, or extensive, in which there is spread of the tumor outside of the chest cavity.

There is a rare type of primary lung cancer that can be confused with mesothelioma (see subsequently). This neoplasm is referred to as pseudomesotheliomatous carcinoma or adenocarcinoma. It was first described in 1956 by Babolini and Blasi.[129] They described eight cases and cited reports of similar tumors observed in Italy. In 1976 in the United States, Harwood et al.[130] described six cases of a tumor that was in a diffuse pleural distribution that macroscopically resembled mesothelioma that histologically had the features of an adenocarcinoma. Harwood et al.[130] coined the term "pseudomesothelioma" to describe this tumor. In 1992 Koss et al.[131] published a series of 30 cases of pseudomesotheliomatous carcinoma (15 from their own files and 15 from the published literature) and reported that 17 were associated with possible or definite asbestos exposure. In 1993 we[132] reported on 27 cases of pseudomesotheliomatous lung carcinoma describing it as a rare asbestos-related malignancy that could be separated from pleural mesothelioma.

Hartmann and Schütze[133] described 72 cases of mesothelioma-like tumors of the pleura found among 35,000 autopsy cases in Germany, of which 65 were primary lung cancers and seven were metastatic tumors. Two cases described were squamous cell carcinomas that occurred in patients with asbestosis.

In 1998 Koss et al.[134] described 29 cases of pseudomesotheliomatous adenocarcinoma. Once again, Koss et al.[134] found an association between pseudomesotheliomatous adenocarcinomas of the lung and asbestos exposure.

In 1999 three cases of pseudomesotheliomatous lung cancer were described, one of which occurred in a person exposed to asbestos.[135] Most recently, Attanoos and Gibbs[136] reported on 53 cases of pseudomesotheliomatous lung cancers most representing adenocarcinomas; and finding a potential association with asbestos in that 40 persons were stated to have had a history of occupational exposure to asbestos. Hammar et al.[137] recently submitted a paper concerning over 150 cases of pseudomesotheliomatous lung cancer, most of which were primary lung cancers that appeared to be associated with asbestos exposure. Rare types included metastatic melanoma, metastatic sarcomatoid renal cell carcinoma, and pseudomesotheliomatous epithelioid hemangioendothelioma. It should be pointed out that sarcomatoid carcinomas of the kidney can metastasize to the lung in a pleural distribution and resemble a sarcomatoid mesothelioma.

Pseudomesotheliomatous lung cancers are dramatic in that they closely resemble mesothelioma (Figure 5.28). Histologically, most are adenocarcinomas that have the immunohistochemical features of a primary lung adenocarcinoma.

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus* (i.e., not in the main bronchus)
T2	Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; involves main bronchus, 2 cm or more distal to the carina; invades the visceral pleura; associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T3	Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or tumor with a malignant pleural effusion**
	*Note: the uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.
	**Note: Most pleural effusions associated with lung cancer are due to tumor. However, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is non-bloody and is not an exudate. When these elements and clinical judgement dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2 or T3

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, including direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

MX	Presence of distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
	T2	N0	M0
Stage II	T1	N1	M0
	T2	N1	M0
Stage IIIA	T1	N2	M0
	T2	N2	M0
	T3	N0, N1, N2	M0
Stage IIIB	Any T	N3	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

Figure 5.27 Primary lung tumors are staged according to the tumor size (T), lymph node status (N), and whether there are metastases (M).

Figure 5.28 This tumor has the macroscopic features of a pleural mesothelioma being encased by a rind of tumor that when examined microscopically has features of a primary lung cancer and not a mesothelioma.

5.2.2 Mesothelioma

The celomic cavity develops early in embryogenesis and is divided by partitioning membranes into the pleural, pericardial, and peritoneal cavities. These body cavities are lined by tissue referred to as serosa that has a visceral and parietal layer. The serosal tissue is composed of a layer of epithelial mesothelial cells separated from the underlying connective tissue component by a basement membrane. Mesotheliomas arise from cells forming this serosal membrane. The majority of mesotheliomas (90–95%) arise in the pleural cavity whereas about 5–10% arise in the peritoneal cavity. Primary pericardial mesotheliomas are extremely uncommon. Mesotheliomas can arise in the tunica vaginalis, which is an invagination of the peritoneum.

A detailed discussion of the pathologic and clinical features of mesothelioma is given in Refs.[138–144].

5.2.3 Macroscopic Features of Mesothelioma

At the time most pleural mesotheliomas are diagnosed, they are composed of multiple small nodules studding the visceral and parietal pleural surface (Figure 5.29). These nodules range from 1 to occasionally 1 cm. In the majority of cases, this proliferation is associated with a pleural effusion, the pleural fluid usually having the features of an exudate.

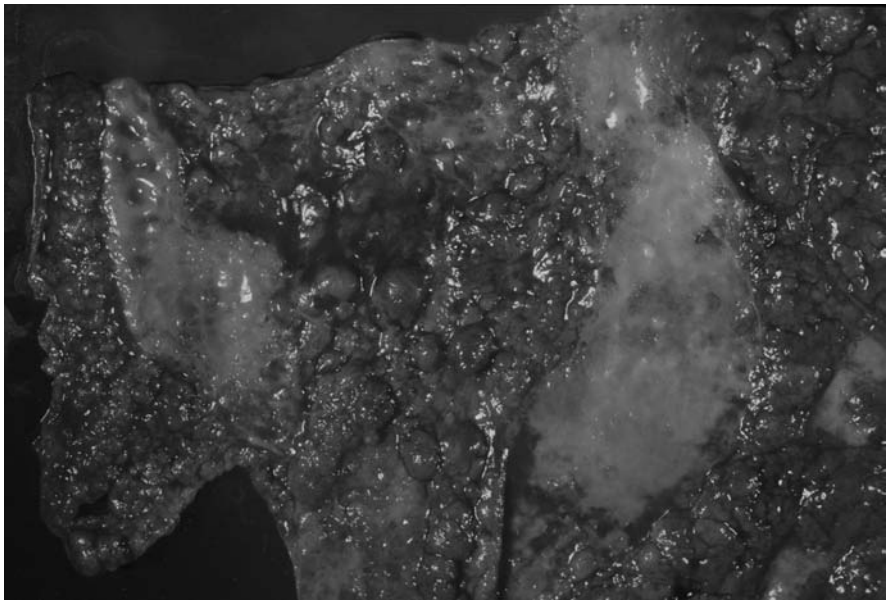

Figure 5.29 Most pleural mesotheliomas present with pleural effusions. When patients are evaluated thoracoscopically, they usually have small nodules of grayish-white tumor studding the visceral and parietal pleural surfaces as shown in this photograph.

As time progresses, the nodules coalesce to form solid tumors that in the case of pleural mesotheliomas encase the lung and obliterate the pleural cavity (Figure 5.30). Mesotheliomas frequently invade chest wall skeletal muscle and sometimes directly invade skin and subcutaneous tissue. They likewise invade lung parenchyma. It is common for mesotheliomas to show variability in the thickness of the rind of tumor that encases the lung (Figure 5.31). In general, the tumor is usually much thicker at the base of the pleural cavity than at the apex. Frequently, mesotheliomas have a nodular morphology and if the rind of tumor is relatively thin, these nodules can be confused with primary lung cancers (Figure 5.32). Occasionally, mesotheliomas metastasize to hilar lymph nodes and produce a hilar mass (Figure 5.33) that is significantly more recognizable radiographically than the thin rind of tumor that encases the lung. Frequently, mesotheliomas directly invade pericardium and sometimes myocardium (Figure 5.34). It is common for pleural mesotheliomas to invade through the hemidiaphragms and extend into the abdominal cavity.

Some epithelioid mesotheliomas produce excess amounts of hyaluronic acid and proteoglycans. Tumors that produce these substances are "slick" and "slimy." They often have large cystic areas filled with a tannish gelatinous material (Figure 5.35).

Peritoneal mesotheliomas are similar to pleural mesotheliomas in that they also begin as multiple small nodules that over a period of time coalesce to form a rind of

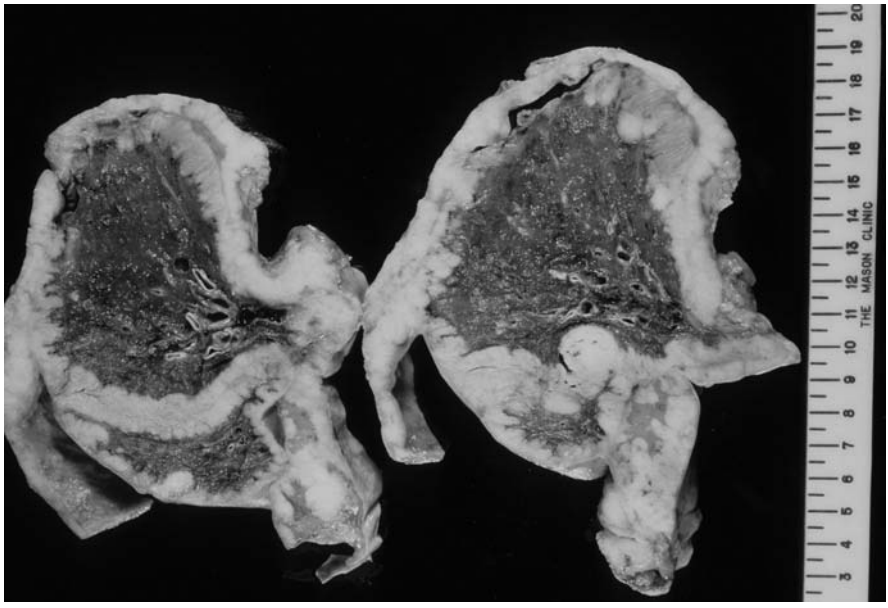

Figure 5.30 With progression, the small nodules of tumor coalesce to form a mass that encases the lung.

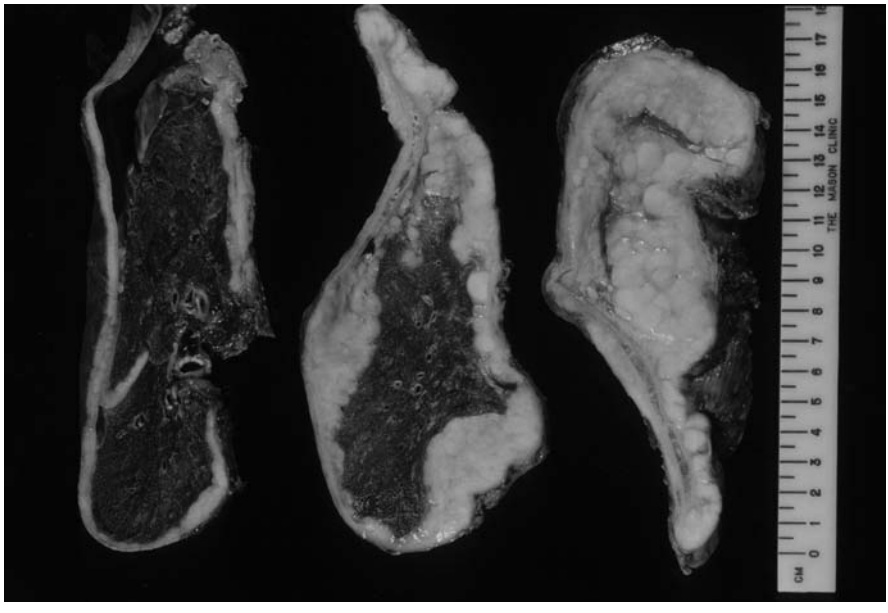

Figure 5.31 Most pleural mesotheliomas are thicker at the base than at the apex of the chest cavity.

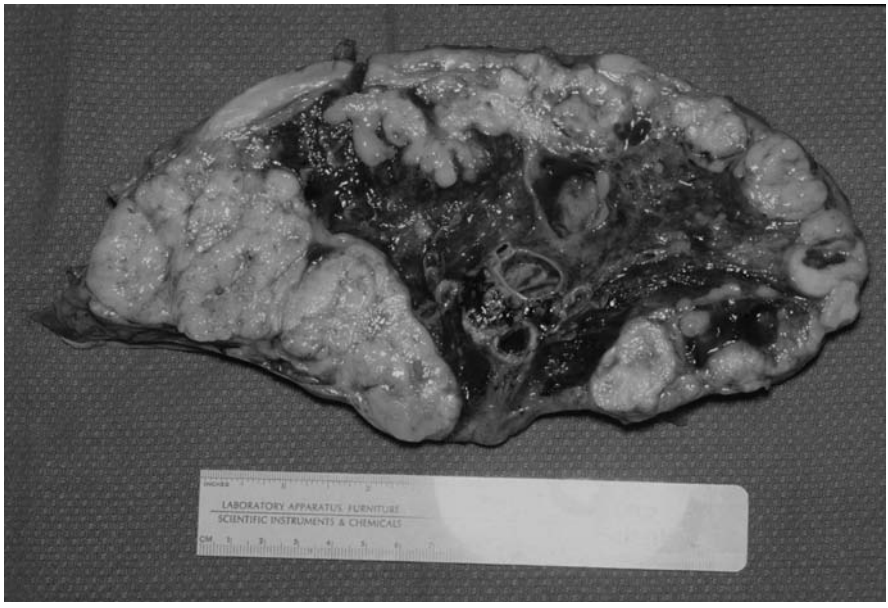

Figure 5.32 Not infrequently, pleural mesotheliomas are nodular and invade lung parenchyma.

Figure 5.33 Some mesotheliomas present as hilar masses due to large deposits of metastatic tumor in hilar lymph nodes.

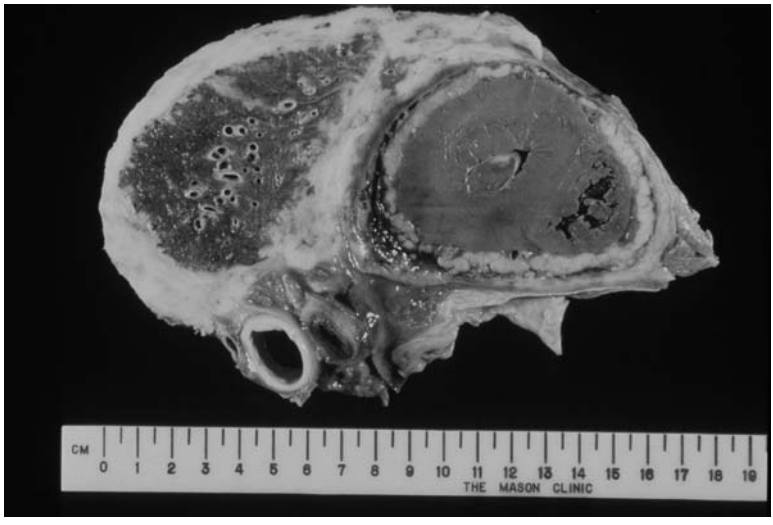

Figure 5.34 Not uncommonly, mesotheliomas directly invade the pericardium and occasionally the myocardium.

tumor tissue that encase various organs within the abdominal cavity. Sometimes this can be so extensive that the bowel and other organs are compressed to the point of being nonexistent (Figure 5.36). As with pleural mesotheliomas, most peritoneal mesotheliomas initially are associated with an effusion.

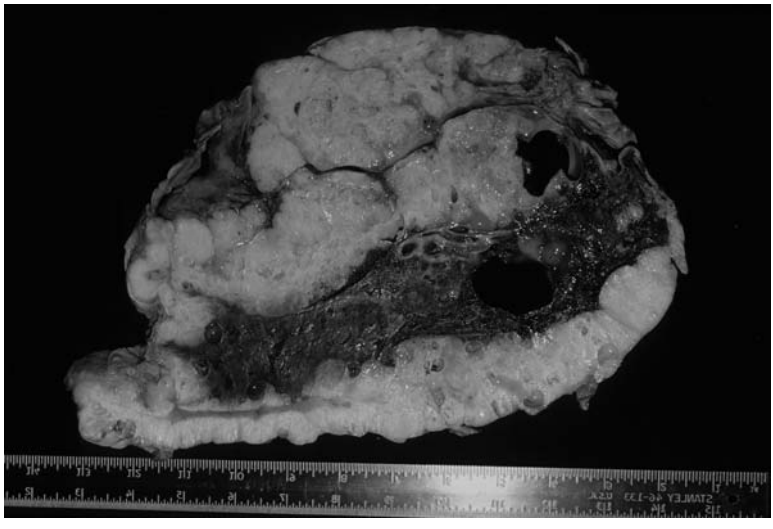

Figure 5.35 Some epithelial pleural mesotheliomas produce excess amounts of what normal mesothelial cells produce (hyaluronic acid and proteoglycans) forming cystic spaces filled with these substances.

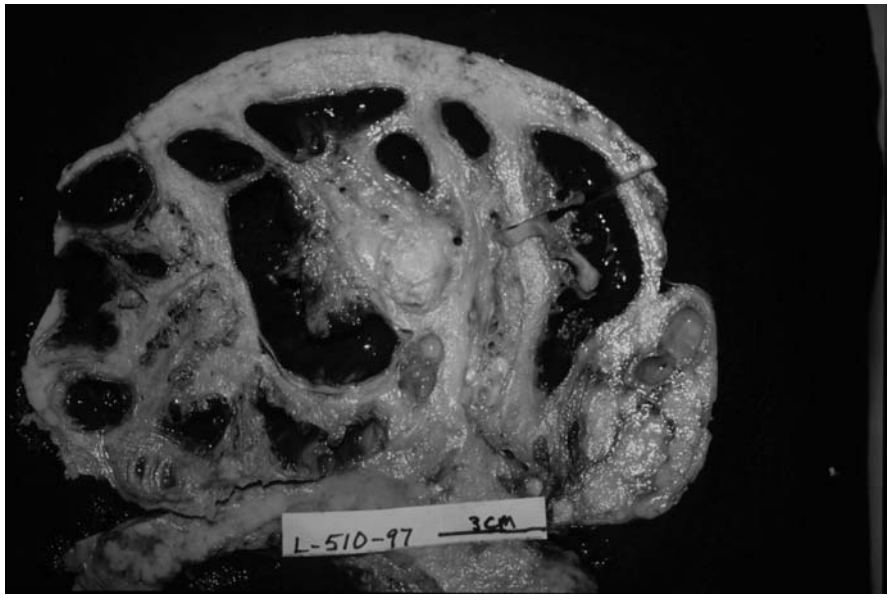

Figure 5.36 Peritoneal mesotheliomas comprise approximately 5–10% of mesothelioma and form tumors that encase the abdominal organs.

Primary mesotheliomas that arise in the tunica vaginalis often present as a mass in that location. They sometimes remain localized, although frequently invade the peritoneal cavity and extensively involve it.

Primary pericardial mesotheliomas are rare. To diagnose a primary pericardial mesothelioma, one has to be certain that the tumor involving the pericardium does not represent an extension of a pleural mesothelioma. Pericardial mesotheliomas are like other mesotheliomas in that they start out as small nodules that coalesce to form a rind of tumor around the heart with obliteration of the pericardial cavity (Figure 5.37).

Rarely, mesotheliomas occur as localized masses rather than diffusely involving a body cavity. These occur most frequently in the pleural cavity and are called localized malignant mesotheliomas.

Symptoms referable to the site where mesotheliomas begin are often so dominating that metastases are not searched for in mesothelioma. However, metastases are relatively common in mesothelioma, although not as common as one sees in primary lung cancers. The most common sites mesotheliomas metastasize into are bronchopulmonary and hilar lymph nodes. The next most common site is the pleural surface of the lung not involved by tumor (Figure 5.38). Mesothelioma metastases can involve almost any organ, including adrenal glands, liver, kidneys, etc. There have been about 20 or 25 reported cases of mesotheliomas metastasizing to brain.

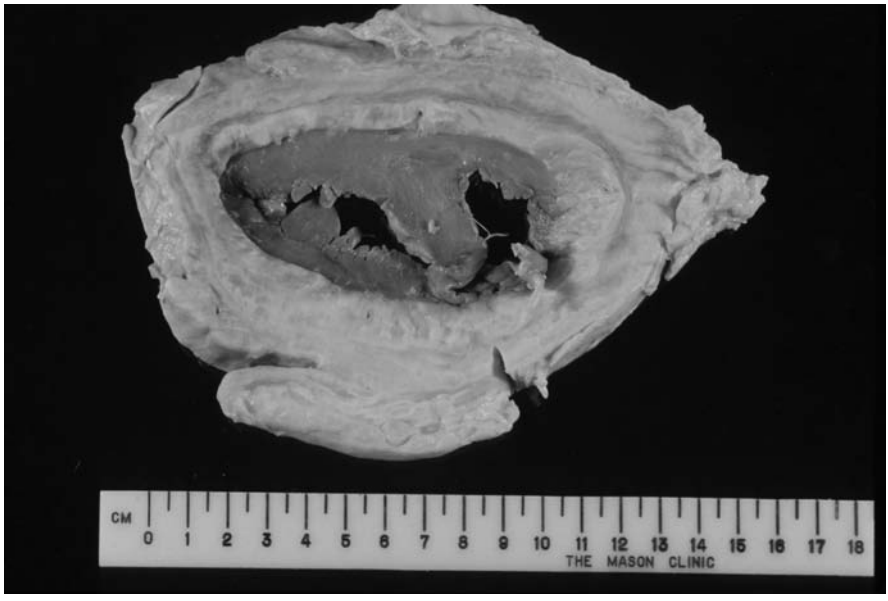

Figure 5.37 Pericardial mesotheliomas are exceedingly rare and form a mass that encases the heart.

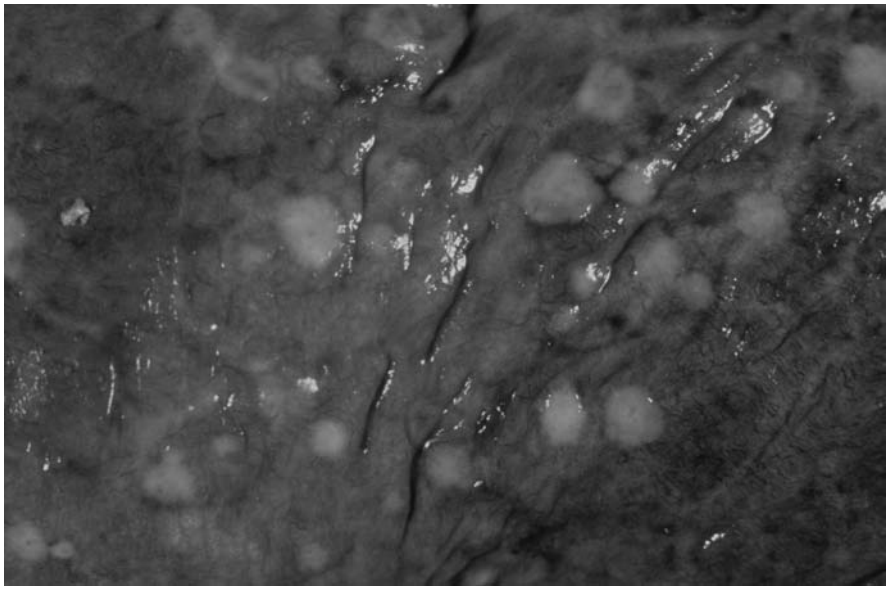

Figure 5.38 Mesotheliomas occasionally metastasize. One of the most frequent sites of pleural mesothelioma metastases is the pleural surface of the opposite lung.

Desmoplastic mesotheliomas have a propensity to metastasize to bone and can be a diagnostic dilemma because they resemble benign fibrous tissue.

5.2.4 Histologic Types of Mesothelioma

Mesotheliomas are subtyped into four major categories based on the appearance of the cells and tissues as viewed through a light microscope.

1. Epithelial.
2. Sarcomatoid — fibrous.
3. Biphasic — mixed.
4. Desmoplastic (this is considered a variant of a sarcomatoid mesothelioma).

This classification scheme is extremely simple compared to what actually exists. There are numerous subtypes of epithelial mesothelioma (Table 5.4) and there are numerous patterns that one sees with sarcomatoid mesotheliomas and biphasic mesotheliomas. When large tissue samples are available such as a pleural pneumonectomy specimen or an autopsy specimen, it is common to see variable differentiation (Figure 5.39). One can often see five or six histologic types of differentiation by the tumor and the more sections one take, the more likely the tumor is found to be biphasic. Sarcomatoid mesotheliomas can show homologous or heterologous differentiation including osteocartilaginous and lipomatous differentiation. It is debatable whether they show vascular differentiation.

Desmoplastic mesotheliomas are probably the most difficult of all mesotheliomas to diagnose. They should not be diagnosed from a needle core biopsy.

Table 5.4 Epithelial Mesothelial Subtypes

Tubulopapillary
Glandular
Histiocytoid
Adenoid cystic
Microcystic
Macrocystic
Signet ring
Single file
Diffuse — NOS
Glomeruloid
In association with excessive amounts of hyaluronic acid or proteoglycan
Small cell
Poorly differentiated (large cell) or pleomorphic
Deciduoid
Mucin positive
Gaucher cell-like
In situ
Well-differentiated papillary

The primary differential diagnosis is fibrosing pleuritis. The criteria for diagnosing desmoplastic mesothelioma include:

1. Over 50% of the tumor has to be composed of relatively dense hypocellular fibrous tissue that frequently forms vague nodules.
2. Areas of increased cellularity that have the features of a sarcomatoid mesothelioma.
3. Focal areas of stellate necrosis.

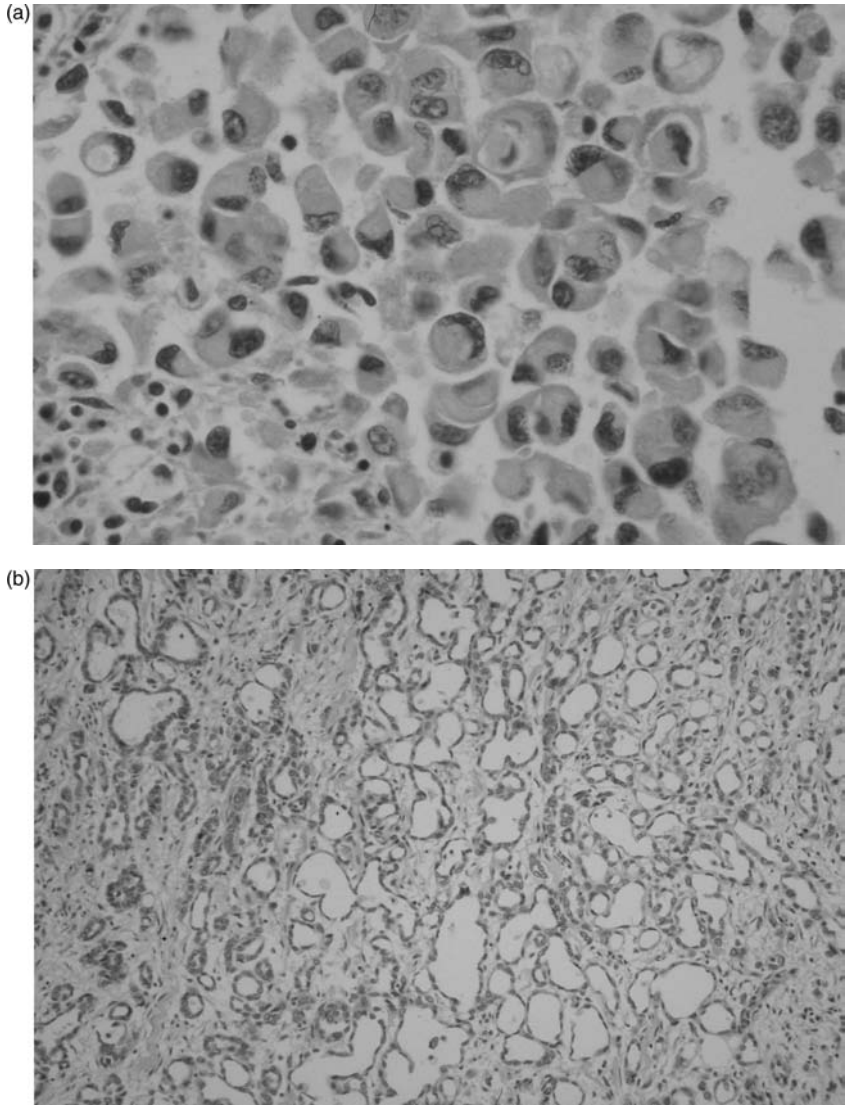

Figure 5.39 When a large tissue sample of mesothelioma is available for microscopic examination, it is not uncommon to see several different histologic patterns of tumor. (a–e) Each photo magn. 400×.

4. Invasion of subparietal pleural fat or chest wall or invasion of the lung (most important).
5. Absence of fibrin deposition, inflammation, and vascular proliferation.

In fibrosing pleuritis, there are more reactive tissue changes with capillary proliferation, inflammation, and fibrin deposition. The capillaries that proliferate

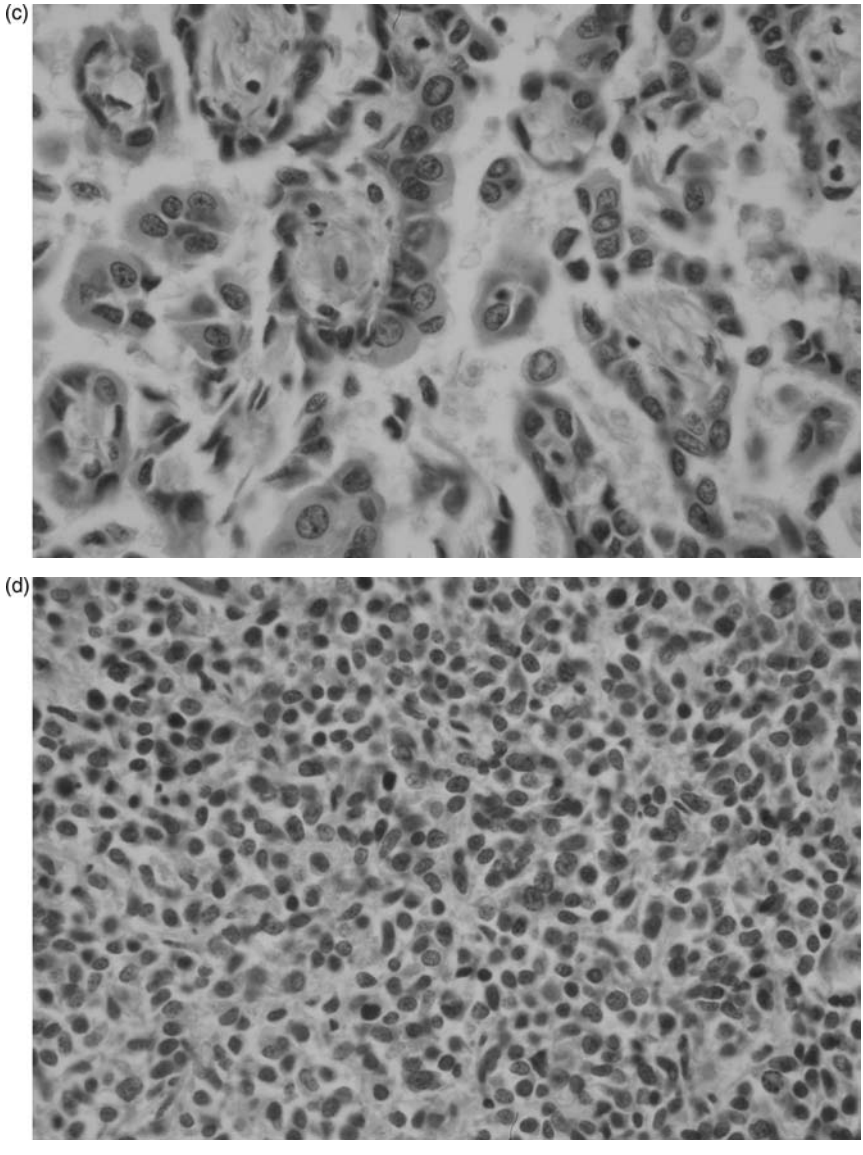

Figure 5.39 *Continued.*

(e)

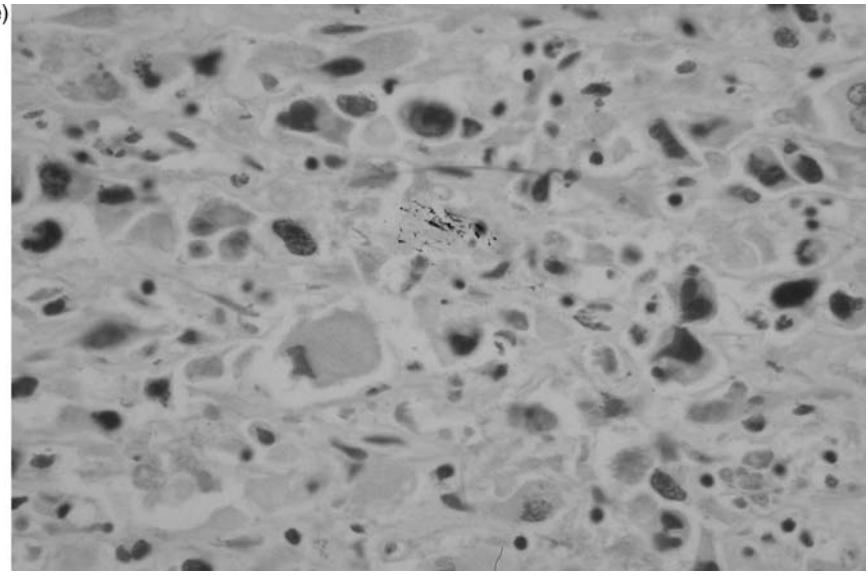

Figure 5.39 *Continued.*

in the pleura are usually perpendicular to the surface of the pleura, which is not seen in desmoplastic mesothelioma.

One has to remember that when desmoplastic mesotheliomas invade or metastasize, they can look extremely bland and can be misdiagnosed as benign fibrous tissue.

5.2.5 Histochemical Features of Mesothelioma

Histochemistry is infrequently used now in diagnosing mesotheliomas, although occasionally it can be helpful. Histochemistry is used primarily to differentiate epithelial mesotheliomas from mucin producing adenocarcinoma like primary pulmonary mucin producing adenocarcinoma. The general rule of thumb is that most epithelial mesotheliomas do not produce mucin and therefore are PAS diastase, mucicarmine and Alcian blue or colloidal iron negative. Epithelial mesotheliomas frequently contain glycogen and are PAS positive; this reaction is eradicated by pretreatment with diastase. Likewise, the epithelial mesotheliomas that produce abundant hyaluronic acid or proteoglycans frequently stain strongly positive with Alcian blue or colloidal iron with this reaction often being eradicated by pretreatment of the tissue with hyaluronidase. Approximately 2–5% of all epithelial mesotheliomas stain positive with a mucin stain such as mucicarmine, PAS diastase, and Alcian blue or colloidal iron even after pretreatment with hyaluronidase. These mesotheliomas are referred to as mucin positive epithelial mesotheliomas. When evaluated ultrastructurally, they frequently show crystalloid material, which is discussed in Section 5.2.7. The mucin positive epithelial mesotheliomas are ones that often

show focal positive staining for immunohistochemical markers that are often associated with primary pulmonary adenocarcinoma such as CEA, LeuM1, and B72.3.

5.2.6 Immunohistochemical Markers of Mesothelioma

There is extensive literature on the immunohistochemistry of mesothelioma. Immunohistochemistry is most useful in differentiating epithelial mesothelioma from other types of an epithelial neoplasm. Epithelial mesotheliomas characteristically express broad spectrum cytokeratin, cytokeratin 5/6, cytokeratin 7 and about 5–10% show staining for cytokeratin 20. Epithelial mesotheliomas likewise express calretinin in both nuclear and cytoplasmic distribution (Figure 5.40), and show cell membrane staining for HBME-1 and epithelial membrane antigen. About 20% of epithelial mesotheliomas show cell membrane staining for BerEP4 and thus finding a BerEP4 positive tumor does not rule out mesothelioma. Occasional epithelial mesotheliomas show diffuse cell membrane staining for BerEP4. Other antibodies that are used to diagnose epithelial mesothelioma include thrombomodulin, WT-1, mesothelin, and cadherin. The antibodies we use in differentiating mesothelioma from primary lung cancer are shown in Table 5.5 and Table 5.6.

Immunohistochemistry is much less useful in sarcomatoid mesotheliomas, although in the majority of cases, the neoplastic spindle cells co-express broad spectrum keratin (Figure 5.41) and vimentin. In approximately 30% of the cases,

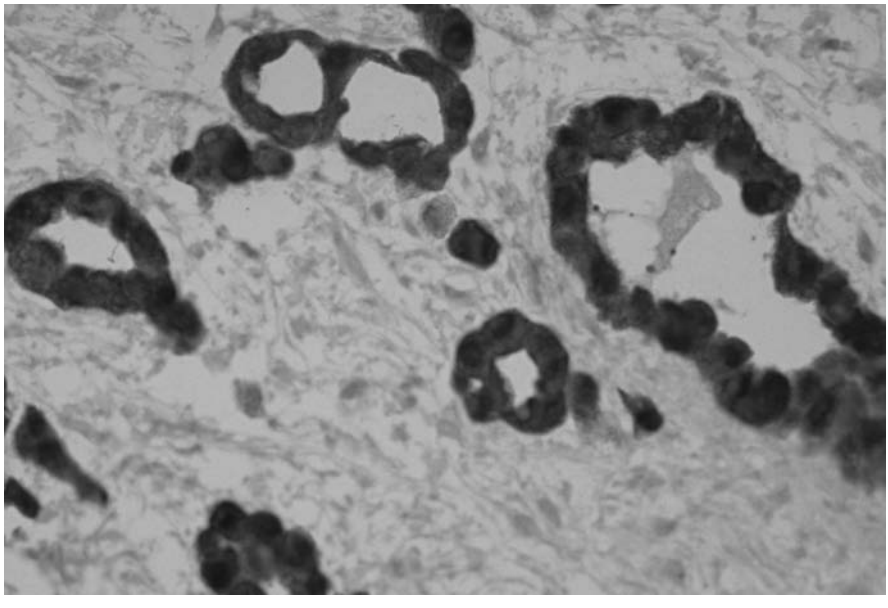

Figure 5.40 The majority (90–95%) of epithelial mesotheliomas show cytoplasmic and nuclear immunostaining for calretinin, which is one of the most sensitive and specific immunohistochemical markers of epithelial mesothelioma.

Table 5.5 Immunohistochemical Features of Epithelial Mesothelioma and Pulmonary Adenocarcinoma

	Antibody Directed Against													
Type of Neplasm	**AE1/ AE3 Ker**	**LMWK**	**HMWK**	**Ker 7**	**Ker 5/6**	**CEA**	**CD15/ LeuM1**	**B72.3**	**BerEP4**	**TTF-1**	**Calretinin**	**HBME-1**	**EMA**	**HMFG-2**
Well-moderately, well differentiated epithelial mesothelioma	+	+	+	+	+/−	R	R	R	−/+	N	+/−	+/−[a]	+/−[a]	+/−[a]
Well-moderately, well differentiated pulmonary adenocarcinoma	+	+	+/−	+	R	+	+/−	+/−	+/−	+/−	R	R	+/−[b]	+/−[b]

LMWK, low molecular weight keratin; HMWK, high molecular weight keratin; CEA, carcinoembryonic antigen; TTF-1, thyroid transcription factor-1; EMA, epithelial membrane antigen; HMFG-2, human milk fat globule protein-2; +, almost always diffuse strong positivity; +/−, variable staining, mostly positive; −/+, variable staining, mostly negative; R, rare cells positive; N, almost always negative.

[a]Cell membrane distribution.

[b]Cytoplasmic distribution.

Table 5.6 Keratin Patterns in Epithelial Mesothelioma, Pulmonary Adenocarcinoma, and Squamous Cell Carcinoma

	Cytokeratin MoII Number, Molecular Weight (kDa), and Isoelectric pH																			
Type of Neplasm	**1, 68, 7.8**	**2, 65.5, 7.8**	**3, 63, 7.5**	**4, 59, 7.3**	**5, 58, 7.4**	**6, 56, 7.8**	**7, 54, 6.0**	**8, 52.5, 6.1**	**9, 64, 5.4**	**10, 56.5, 5.3**	**11, 56, 5.3**	**12, 55, 4.9**	**13, 54, 5.1**	**14, 50, 5.3**	**15, 50, 4.9**	**16, 48, 5.1**	**17, 46, 5.1**	**18, 45, 5.1**	**19, 40, 5.2**	**20, 46**
Primary pulmonary adenocarcinoma	N	N	N	N	N	N	+/−	+/−	N	N	N	N	N	N	N	N	N	+/−	+/−	R
Epithelial mesothelioma	N	N	N	N	+/−	+/−	+/−	+/−	N	N	N	N	N	+/−	N	N	+/−	+/−	+/−	R
Primary pulmonary squamous cell carcinoma	N	N	N	+/−	+/−	+/−	R	−/+	N	N	N	N	N	+/−	−/+	−/+	+/−	−/+	+/−	R

+, almost always diffuse strong positivity; +/−, variable staining, mostly positive; −/+, variable staining, mostly negative; R, rare cells positive; N, almost always negative.

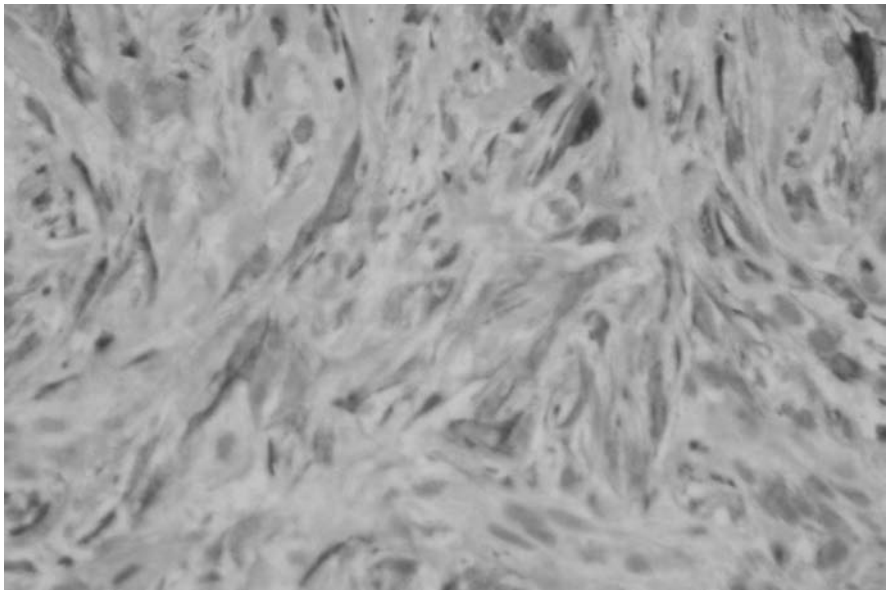

Figure 5.41 Most sarcomatoid mesotheliomas express broad spectrum cytokeratin such as AE1/AE3 keratin that includes ten different molecular species of keratin.

the spindle cells express cytokeratin 7 and only rarely express cytokeratin 5/6. Vimentin staining is seen in essentially 100% of sarcomatoid mesotheliomas. About 30–40% of sarcomatoid mesotheliomas express alpha actin. The intensity of the staining can vary from being low intensity to high intensity. Rare sarcomatoid mesotheliomas do not express keratin.

As time has progressed, epithelial and sarcomatoid mesotheliomas have been identified to express other substances including a number of "cluster designation" antigens. Also, epithelial mesotheliomas express neuroendocrine markers. Small cell mesotheliomas are characteristically stated not to express neuroendocrine markers, although this author has seen at least one case where the small cell mesothelioma expressed neuroendocrine markers and typical epithelial markers of mesothelioma, specifically calretinin and CK5/6. Caution is urged in interpreting immunohistochemical markers and it is always better to do a fairly large battery of tests in trying to determine if a neoplasm is a mesothelioma or some other type of neoplasm.

5.2.7 Ultrastructural Features of Mesothelioma

Electron microscopy is extremely useful in diagnosing mesothelioma, primarily well to moderately well-differentiated epithelial mesotheliomas. Epithelial mesotheliomas characteristically have fairly long sinuous microvilli that are not covered by a glycocalyx (Figure 5.42). They are not associated with rootlets in the underlying tumor cells and characteristically do not contain mucus granules.

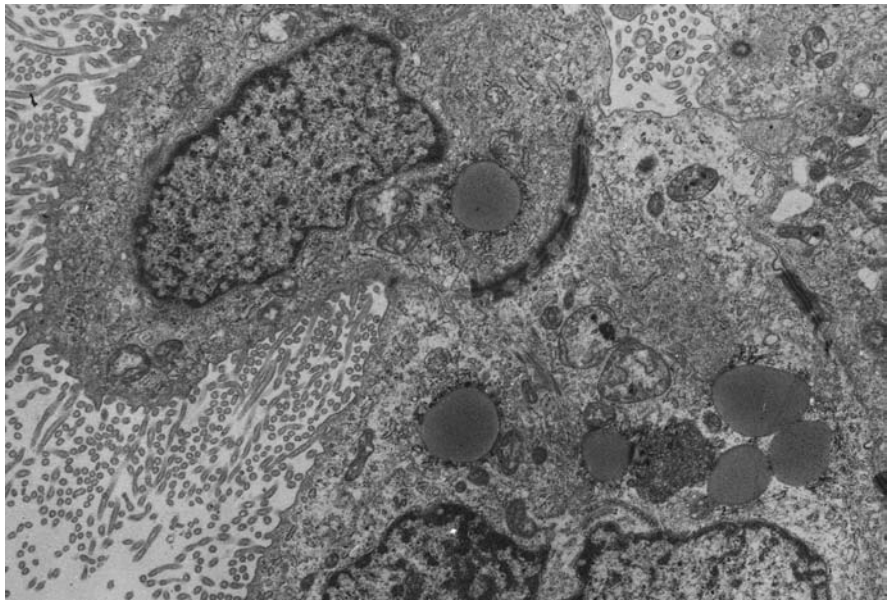

Figure 5.42 When studied ultrastructurally (with an electron microscope), most epithelial mesotheliomas have long, thin, sinuous microvilli that are not covered by a glycocalyx.

Epithelial mesotheliomas frequently show large desmosomes and prominent junctional complexes. They frequently show what is referred to as microvillous matrix interaction (Figure 5.43) in which microvilli directly "penetrate" adjacent collagen fibers. The tonofilaments that are identified in neoplastic epithelial mesothelial cells frequently are in a perinuclear distribution, although sometimes they are distributed throughout the cytoplasm. Some primary pulmonary adenocarcinomas have long microvilli, but these microvilli are invariably covered by a glycocalyx. Epithelial mesotheliomas frequently form intracellular canaliculi that are not a specific finding, but may be more common in epithelial mesothelioma than pulmonary adenocarcinoma. Epithelial mesotheliomas may produce excess amounts of hyaluronic acid that appears as a medium electron dense material that covers the microvilli. Proteoglycan granules are not specific for mesothelioma, but are frequently seen in glandular lumens of mesothelioma and ultrastructurally have a somewhat stellate appearance and are electron dense.

Mucin positive epithelial mesotheliomas are frequently associated with extracellular and sometimes intraluminal crystalloid structures (Figure 5.44) that in my experience are 100% unique for mucin positive epithelial mesotheliomas. These crystalloid structures occasionally can be seen in the cytoplasm of the neoplastic mesothelial cells. In cross-section, they somewhat resemble chrysotile asbestos fibers in that have a scroll-like appearance.

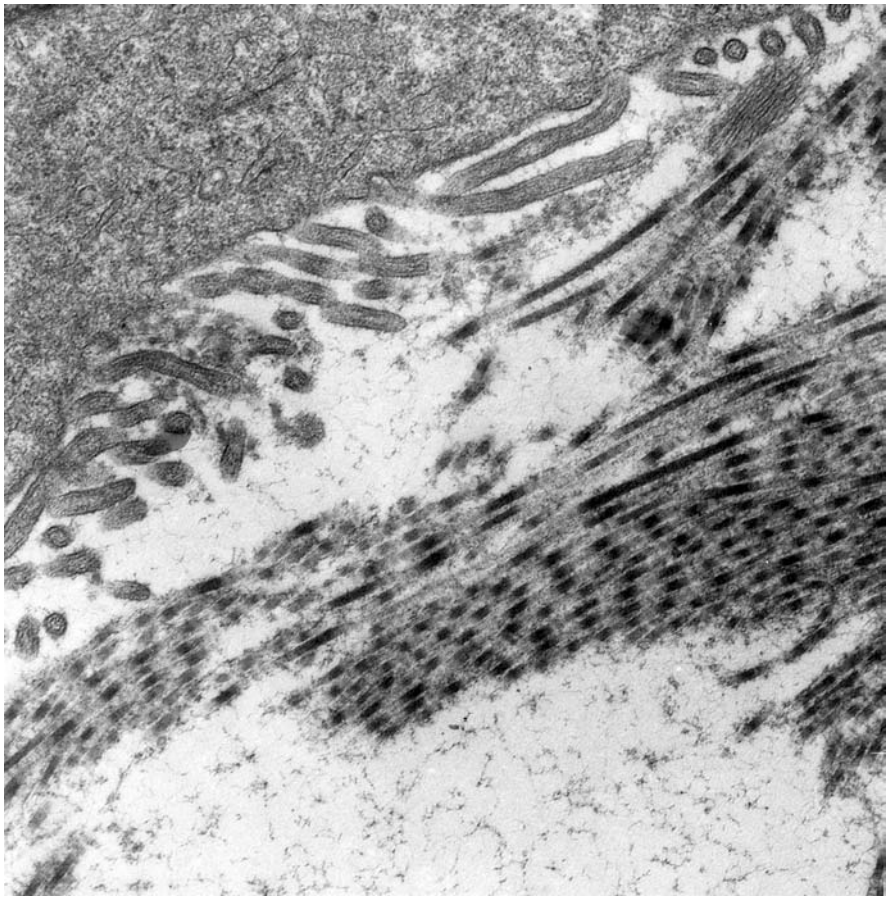

Figure 5.43 The microvilli of epithelial mesotheliomas occasionally project into adjacent collagen fibers. This is referred to as "microvillous matrix interaction" and is a relatively specific ultrastructural feature of epithelial mesothelioma (magn. 42,000×).

Rare mesotheliomas have a Gaucher-like appearance (Figure 5.45) that ultrastructurally is associated with a unique crystalloid material within the cisternae of the rough endoplasmic reticulum of the neoplastic cells. These often form large scroll-like structures that in my experience are unique for mesotheliomas.

5.2.8 Differential Diagnosis

Epithelial mesotheliomas have to be differentiated from adenocarcinomas and other epithelial neoplasms. Small cell mesotheliomas have to be differentiated from neuroendocrine neoplasms. As discussed previously pseudomesothelioma looks identical to mesothelioma macroscopically, but is formed by tumor cells

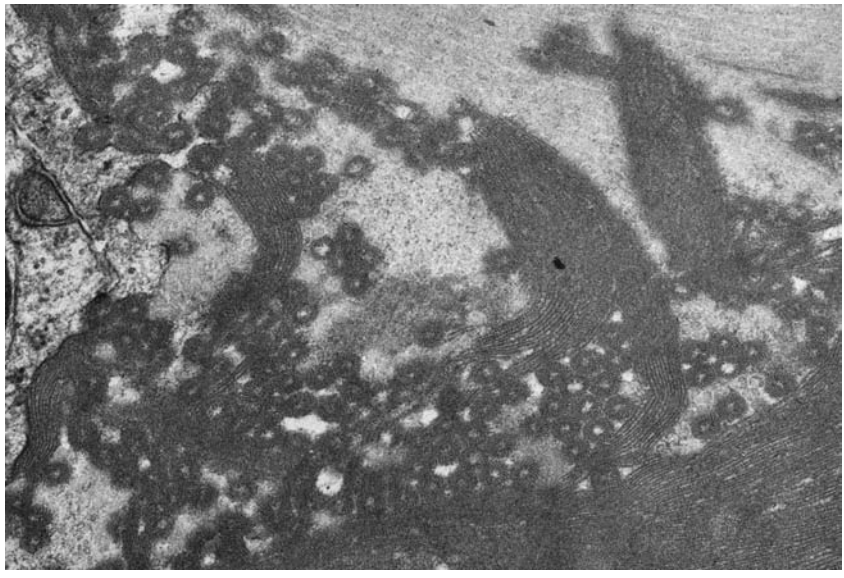

Figure 5.44 Some epithelial mesotheliomas are mucin positive using histochemical stains (mucicarmine, PAS-diastase, and Alcian blue/colloidal iron-hyaluronidase) and can be confused with mucin-producing pulmonary adenocarcinomas. The mucin positivity is usually associated with finding crystalloid material ultrastructurally as shown in this photograph.

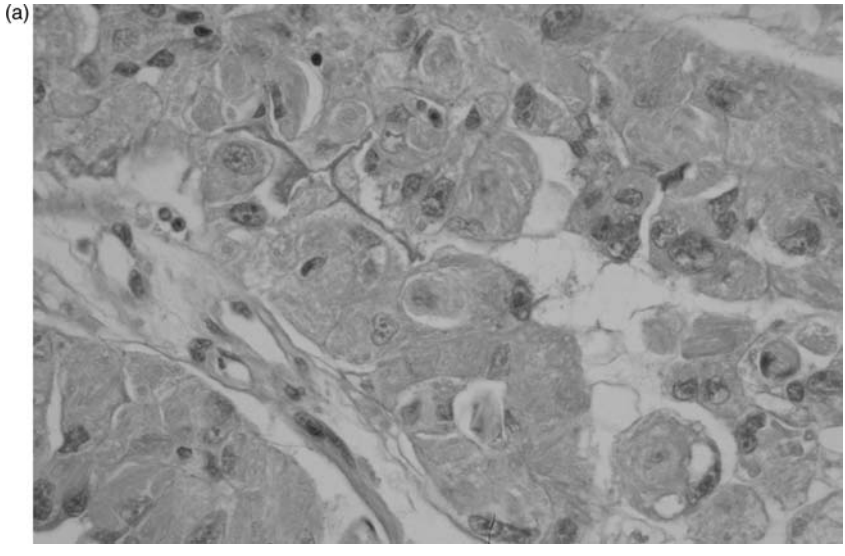

Figure 5.45 (a) Rarely, epithelial mesotheliomas are composed of cells that contain intracellular inclusions and resemble cells seen in lysosomal storage diseases such as Gaucher's disease. (b) These inclusions correspond to crystalloid structures within the cisternae of the rough endoplasmic reticulum.

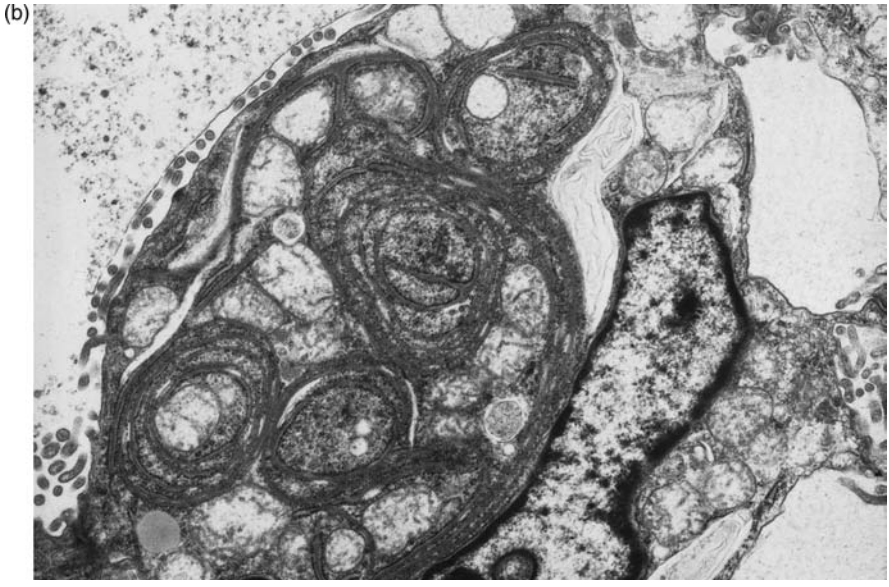

Figure 5.45 *Continued.*

that usually show glandular differentiation and have the characteristic features of an adenocarcinoma. Sometimes, these tumors can be metastatic from sites outside of the chest cavity and can be a difficult diagnostic dilemma. With respect to sarcomatoid mesotheliomas, one has to be aware that sarcomatoid carcinomas of the kidney and pancreas can metastasize to the lung and can display a macroscopic pattern characteristic of a mesothelioma (pseudomesotheliomatous metastatic sarcomatoid carcinoma).

Rarely, epithelioid hemangioendotheliomas can grow in a diffuse pleural distribution and microscopically mimics epithelial mesothelioma. These neoplasms can occasionally show immunostaining for keratin and if not considered can frequently be misdiagnosed as epithelial mesotheliomas. The neoplastic cells forming these tumors characteristically express endothelial markers such as CD31 and factor 8 antigen. Ultrastructurally, they contain Weibel–Palade bodies in their cytoplasm.

Some synovial sarcomas fairly extensively involve the pleura and can be extremely difficult to differentiate from a sarcomatoid mesothelioma or a biphasic mesothelioma. With respect to biphasic mesothelioma, the epithelial component of a synovial sarcoma can have many of the same immunostaining patterns as an epithelial component of a mesothelioma. In cases where this is a question of synovial sarcoma, molecular studies are the only certain way to determine whether a tumor is a synovial sarcoma or not.

A number of other rare sarcomatoid tumors occur in the pleura, including primary desmoid tumors of the pleura, calcifying fibrous pseudotumor of the pleura, primary pleural thymomas, and pleural pulmonary blastomas.

Tumor

T1	T1a - Tumor limited to the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; no involvement of the visceral pleura; T1b – Tumor involving the ipsilateral parietal pleura, including mediastinal and diaphragmatic pleura; scattered foci of tumor also involving the visceral pleura
T2	Tumor involving each of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: - involvement of diaphragmatic muscle - confluent visceral pleural tumor (including the fissures) or extension of tumor from visceral pleura into the underlying pulmonary parenchyma
T3	Describes locally advanced but potentially resectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: - involvement of the endothoracic area - extension into mediastinal fat - solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall - non-transmural involvement of the pericardium
T4	Describes locally advanced, technically unresectable tumor. Tumor involving all of the ipsilateral pleural surfaces (parietal, mediastinal, diaphragmatic and visceral pleura) with at least one of the following features: - diffuse extension or multifocal masses of tumor in the chest wall, with or without associated rib destruction - direct transdiaphragmatic extension of tumor to the peritoneum - direct extension of tumor to the contralateral pleura - direct extension of tumor to one or more mediastinal organs - direct extension of tumor into the spine - tumor extending through to the internal surface of the pericardium, with or without a pericardial effusion; or tumor involving the myocardium

Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastases in the ipsilateral bronchopulmonary or hilar lymph nodes
N2	Metastases in the subcarinal or the ipsilateral mediastinal lymph nodes, including the ipsilateral internal mammary nodes
N3	Metastases in the contralateral mediastinal, contralateral internal mammary, ipsilateral or contralateral supraclavicular lymph nodes

Metastases (M)

MX	Presence of distant metastases cannot be assessed
M0	No distant metastasis
M1	Distant metastasis present

Staging

Stage Ia	$T1_a$	N0	M0
Stage Ib	$T1_b$	N0	M0
Stage II	T2	N0	M0
Stage III	Any T3	Any N1 Any N2	M0
Stage IV	Any T4	Any N3	Any M1

Figure 5.46 The TNM staging system for mesothelioma.

Lymphomas rarely involve the lung and pleural surface. When they do, they can occasionally be mistaken for a mesothelioma, although with immunohistochemistry and EM, this usually is not a problem.

Like lung cancers, mesotheliomas are staged according to the TNM classification (Figure 5.46).[145] This is important because, like lung cancers, mesothelioma prognosis is related to stage, as is potential therapy like radical extrapleural pneumonectomy.

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CHAPTER 6

Epidemiology of Asbestos-Related Diseases and the Knowledge that Led to What is Known Today

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CONTENTS

6.1 INTRODUCTION

"Asbestos is one of the most marvelous productions of inorganic nature. It is a physical paradox, a mineralogical vegetable, both fibrous and crystalline, elastic and brittle; a floating stone, as capable of being carded, spun, and woven, as wool, flax, or silk." "Occupying the apparent position of a connecting link between the mineral and vegetable kingdom, it would appear to possess some of the characteristics of both, while being altogether different from either."[1]

6.1.1 Usage of Asbestos

The use of asbestos dates back to thousands of years when asbestos fibers were being incorporated into pottery.[2,3] In 1924, asbestos was discovered in the United States near Lowell Vermont, but not much interest was shown until the 1890s.[4] In 1879, a Canadian chrysotile mine opens in the Province of Quebec.[1] The modern industry dates from 1880, when asbestos was used to make heat- and acid-resistant fabrics.[5–7] In Osaka, the first Japanese asbestos factory opens in 1886 making packing and other insulation products.[8] In the early 1880s crocidolite, meaning "woolly stone," asbestos was first found northwest of the Cape Province of South Africa, but was not actively mined until the demands for asbestos during World War II.[9–12] A patent was awarded, in England in 1895, for railroad brake linings containing asbestos and by 1903 friction brake products were sold in the United States.[13] During 1904, a second deposit of asbestos was found in South Africa, in northeast Transvall, and in 1918 it was named amosite, from the village Amosa, which was the acronym for the term Asbestos Mines of South Africa. Production began in the mid-1920s, by Cape Asbestos Company, the same company already mining and producing crocidolite.[12,14] The commercial importance of asbestos was well recognized when on January 13, 1906, Johns-Manville ran full page advertisements in The Saturday Evening Post© saying [asbestos] "serves more people in more ways than any institution of its kind in the World." Products for the home-builder, the industrial and commercial builder, and the automobilists were included in this ad. Asbestos was also being used by American steel companies for insulation of large furnaces.[15]

"On its [asbestos] introduction it was looked upon with some degree of suspicion and only 300 tons were mined during the first year, which realized no more than $19,500. But in proportion as it became better known the rapidity of its progress was prodigious. By 1890, the output had grown to 9860 tons, and its saleable value hand reached $1,260,240. This was a grand time for mine owners, when even by straining every nerve, under the stimulus of daily advancing prices, they were unable to supply the demands of the manufactures; while these last daily found increasing difficulty in their endeavors to obtain adequate supplies of the raw material to meet their requirements. No forward contracts could be made, and it was impossible to foretell to how high a figure prices would eventually reach."[1] Often asbestos is referred to as the "magic mineral" having 3000 or more uses,

including uses such as being woven into cloth, with vegetable fibers, to still the sound of falling trees during construction projects, within the Roman empire; for wrapping the corpuses, referred to by Pliny as the funeral dress of kings, prior to cremation in order to help collect the ashes; in making clay pots some 4000 yr ago; and was even mentioned by Marco Polo, during his travels to the far east, where he find it called "salamander" which was mined from the mountains, extracted then crushed, by subjects of the Great Khan, into a fibrous-like wool that was then spun and made into cloth of which some were used for table cloths, that when soiled, were thrown into the fire and came out "white as snow" for use again; one was sent to the Pope, in Rome, "in which cloth he keeps the Sudarium of our Lord."[1] Also, Pope Clement the Eleventh ordered an intact shroud of considerable length, in good condition and as pliant as silk, found in a sarcophagus by the Via Praenestina in 1702, a road to the very ancient city of Latium, lying 23 miles east of Rome, placed in the Vatican library where it can still be seen.[1] Both Strabo and Plutarch have mentioned the use of asbestos for wicks used in the lamps of the Vestal Virgins as well as being used for sacred fires in the temples, being referred to as perpetual since the flames do not consume the wicks or the asbestos placed in the fires.[1] Charlemagne used the "amianthine" (asbestos) table cloths to astonish his rude warrior guests, throwing them into the fire then withdrawing it cleansed and unconsumed.[1] At the Royal College of Surgeons in England, the oldest mummy in the world, upwards of 6000 yr old, was unwrapped by Prof. Stewart who found the body wrapped in gauze-like material and the cavities of the body stuffed with the same type of material, which later was identified as a linen-like material thought to be made of asbestos fibers.[1] Tribes of Indians were known to have made dresses of asbestos, "which they cleanse by throwing them into fire."[1] Benjamin Franklin even bought a purse from the "northern part of America" made from woven tremolite asbestos, a picture of which is found in the book by Selikoff and Lee.[16–18] Giuseppe della Corona, a Florentine priest, is credited with the introduction of asbestos millboard in the mid-1800s.[1] A unique use can be found in John Baxter's book *A Pound of Paper* ©, in which he discussed the use of Johns-Manville Quintera, a form of asbestos, to cover a limited edition of author Ray Bradbury's book *Fahrenheit 451*, published in 1953.[19] The manufacture of asbestos-paper dates back to around 1700, when it was made in Norway and for printing banknotes and other securities in Italy, in the mid-1800s.[1] More in-depth descriptions of the ancient uses of asbestos can be found in the first chapter of the book written by Robert H. Jones, a mineralogist, published in 1897 and also in discussions of the *Magic Mineral* by Paul Brodeur.[1,20,21]

Some of the highlights of the modern uses of asbestos included asbestos used as a heat insulation, beginning in 1866[22] and then mixed with cement as a boiler covering in 1870.[23] The first asbestos factory was opened, in 1871, in Great Britain.[24] The commercial production of asbestos insulation materials began in 1874[23] and in 1890 the first processing of Canadian asbestos into textile began in the United States.[25] By the turn of the 20th century, the asbestos cement pipe industry had its origins in Italy[26] and by 1903 asbestos cement production started in the United States but the pipe-making machines were not imported into the United States until 1928.[25]

Cement-based flat asbestos cement board, now a major building product of the third world, was first produced in the United States in 1904.[27] Brake linings containing asbestos was first used in 1906.[24] Asbestos spraying of deck heads and bulkheads began in 1944 for British navy ships and was discontinued in 1963.[28,29]

6.1.1.1 Asbestosis

The evolution of epidemiologic knowledge of exposure to asbestos spans the millennium of human history. While the first writings of human history lead to clues of worker diseases and work with asbestos, they did not illuminate the nature of or the degree of the epidemic as experience beginning with the modern advent of asbestos usage during the 20th century. In her historical sketch, Anderson, tells of such early millennial knowledge "In the great civilizations of antiquity, whether in the East, West, or in Europe generally, there was sufficient concentration of the forces of labour to produce the intensest forms of the maladies classed by Pliny as the "diseases of slaves." Some of the most injurious processes known to us now are extremely ancient. To mention but a few: . . . weaving asbestos and flax."[30]

Dean, predecessor to Anderson as Women Inspector of Factories writes in the 1899 Annual Report on the Health of Workers for 1898, that "[T]he evil effects of asbestos dust have instigated a microscopic examination of the mineral dust [asbestos] by HM Medical Inspector . . . , the effects have been found to be injurious as might have been expected." She continues "the worker can continue for a very long time apparently unaffected, before the symptoms of the evil become marked."[31] Three years later, Anderson, Lady Inspector of Factories, included asbestos among the dusts known to cause injury to man in a publication on dangerous industries in England.[30] The first recorded case of "asbestosis" was reported, in London, in a 33-yr-old man who worked in an asbestos textile plant for 14 years, by a Charing Cross Hospital physician Dr. Murray in 1906.[32] Numerous deaths (at 50) were also reported in a French asbestos textile factory.[33] Italian physicians reviewed the cases of 30 asbestos workers seen in a Turin clinic, between 1894 and 1906 as having a serious pulmonary disease thought to be tuberculosis; however, it was extremely progressive and unlike the typical tuberculosis case. This was the first indication of the progressive nature to the asbestos-induced lung disease, a finding later confirmed through epidemiological studies of asbestos workers conducted during the 1930s.[34]

Animal studies had also begun around the turn of the 20th century and it was reported in the Annual Report of HM Chief Inspector of Factories for 1910 that Prof. J.M. Beattie, of Sheffield University in the U.K., had shown mild degree of fibrosis in experimental animals after inhalation of asbestos-containing dust and that five deaths of persons with phthisis occurred among a workforce of less than 40 in the production of woven asbestos. This lead to the industrial practiced, later emphasized by Merewether and Price[35] for dust suppression as prevention tool that could be obtained though ventilation to protect workers from asbestos-induced lung disease.[36]

Around the same time, The American Association for Labor Legislation mentioned asbestos-related disease in their industrial diseases[37] and the government of Canada's Department of Labour included asbestos-related diseases as an industrial disease.[27]

Just a couple of year's later in Germany, the report of a woman having worked in a German asbestos factory and dying of an acute lung illness resembling pleural pneumonia, on autopsy there were "... large number of crystals of a peculiar nature" was presented to the medical society of Hamburg and later was recognized as a case of asbestosis.[38] In 1918, it was reported in the *Bulletin of US Labor Statistics* that American and Canadian insurance companies would not insure asbestos workers due to the unhealthy conditions in the industry.[39]

With the advent of the discovery, by Wilhelm C. Roentgen, of the x-ray on November 8, 1895, the imaging of the respiratory system developed quite rapidly (*Nobel Lectures*, Physics 1901–1921, Elsevier Publishing Company, Amsterdam, 1967) with the first descriptions, in the medical literature, on x-ray changes in 15 individuals exposed to asbestos reported in 1918.[40] Pancoast and Pendergrass[41] published a review of the present knowledge on the pneumoconiosis,* including asbestosis, in 1925 in *The American Journal of Roentgenology and Radium Therapy*, a journal read by mainstream general medicine radiologists.

Clinical descriptions of the disease asbestosis were now becoming more common in the medical literature. The case of Nellie Kershaw, a 33-yr-old asbestos factory worker who had worked since the age 13 in the textile factories, was the sentinel case accounting for both the naming of asbestosis, as a distinct pneumoconiosis and gave the first discussions on asbestos bodies. Five years prior to her final illness and due to failing health she had only worked intermittently. She died on March 15, 1924. Cooke's presentation of this case give the best and most complete description of the effects of asbestos on the lungs in which he also notes Prof. J.M. Beattie had earlier shown in guinea pigs having developed similar chronic bronchitis and fibrosis after exposed to asbestos-containing dust. This case presented with pleural thickening over the entire surface of the lung and dense adhesions on the chest wall and the pericardium. The right lung showed the most extensive fibrosis, caseous foci, with cavities having thick fibrous walls. Giant cells were found to be numerous around the caseous areas and there was also tuberculosis lesions present.[42] In 1927, Cooke and Hill[43] reported that while the asbestos industry goes back some 2000 years, the industry was to "... have been devoid of appliances for the prevention and extraction of dust." The fibers found in the lung tissue of Mrs. Kershaw, varied from 3 to 360 μm in length and appeared to be "... the heavy, brittle, iron-containing fragments of the asbestos fibre." In comparing the two sources of asbestos used in the textile factories where Mrs. Kershaw worked, Cooke reported the only significant difference between the Italian fiber and the Canadian Chrysotile was that the Italian fiber had less iron in the form of ferrous oxide 0.87% versus 2.81% in the Canadian Chrysotile and the Italian fiber had more Alumina 2.27% versus 0.90% than in the Canadian Chrysotile. Because the

*A term meaning dust affecting the lung, taken from Zenker's original term pneumonokoniosis.[331]

ferrous oxide fibers are heavy, Cooke felt this explained the greater amount of fibrosis in the right lung, due to the ease of the particles to pass ". . . more easily down the more vertical right bronchus than the horizontal left bronchus." During the carding process, the collected dust, as analyzed by Byrom, contained 18.4% ferrous oxide compared with the 2.8% found in the raw material thus indicating the removal of much of the iron content during this process. The finished product contained only 0.1% iron. Dr. Cooke also gives the first detailed description of "curious bodies" having "discoid arrangement and globular ends." within a phagocytic cell. Dr. Cooke refers to the case described by Murray,[32] who died of pulmonary fibrosis as having "spicules of asbestos" as the first and only recorded case of death due to asbestos before his report of 1924, that of Nellie Kershaw.

McDonald,[44] Cooke and Hill,[43] and Cooke[45] continued to describe the curious bodies in the lungs now known as asbestos bodies. Now it has been shown that asbestos bodies can form in extra-pulmonary sites such as the liver and spleen.[46] McDonald confined his comments to the histological appearances of the bodies which are found both in the alveoli and interstitial substance of the lungs. In addition to the case described by Cooke,[47] he also examined a second case obtained from a physician in Leeds, U.K. Some of the bodies were free while others were phagocytized by the large mononuclear cells found in the alveoli. Some were small and easily phagocytized but the majority was of between 20 and 70 μm or more. All had a distinct yellowish-brown color, which he suggested as a blood pigment and some had club-like extremities either at one or both ends. Those bodies too large for the phagocytes were then surrounded by plasmodial masses. McDonald had the bodies examined by both experts in zoology and botany, both of whom said they were neither of animal nor vegetable nature. He further explained that the fiber type of the second patient was to Canadian serpentine (chrysotile) which had about equal parts silica and magnesium salt (40%), 3% ferrous oxide, 1% alumina and water. While tuberculosis was present in both cases, it was Dr. McDonald's opinion that it was a superadded infection since there was a considerable degree of fibrosis without the tuberculosis infection in the second case he examined. Cooke[45] felt that when curious bodies were found "in any numbers" they would be "pathognomonic of pulmonary asbestosis." Today they are thought to be the histologic hallmark of exposure to asbestos and their presence not necessarily a marker of disease.[48–50] Some studies have shown a correlation with the number of asbestos bodies (ferruginous bodies)[†] in the sputa and radiographic finding of interstitial pulmonary disease and pleural thickening as well as with spirometric findings of a restrictive lung disease.[51] Sporn and Roggli[52] refer to ". . . the identification of asbestos bodies within tissue sections remains the diagnostic *sine qua non* in view of the nonspecificity of interstitial fibrosis as a response to diffuse lung injury, and the large number of disorder that may cause scarring in the lung."

In May 1928, four cases of asbestosis were reported, one case having only 2 yr of exposure to asbestos and having no histological evidence of tuberculosis.

[†]Ferruginous bodies is another name given for asbestos bodies (see Ref. 48 for a complete description of the etymology of the term).

The study report stated that it had been known for sometime that workers exposed to asbestos materials suffer from pulmonary disabilities.[53] One case, a South African asbestos mill worker, was only exposed 12 months died of rapid TB and on autopsy was found to have moderate fibrosis. Simson also reported that asbestos dust was much more rapid than the fibrosis produced by silica. In examination of the lungs of a guinea pig, supplied by Dr. Mavrogordato of the same Institute as Simson, found the presence of golden yellow bodies similar to those found in human lungs with asbestosis. The lungs of the guinea pig came from an experiment which was exposed to Southern Rhodesian Chrysotile for 2 h per day for 50 days. As more case reports of asbestosis appeared in the literature, the *Journal of the American Medical Association* ran an editorial on pulmonary asbestosis in January because of asbestosis' continuing presence in the medical literature and because of the dangers of asbestosis' and its unique pathologic features deserved more attention than had been given to the disease.[54] In December 1928, a case report of fibrosis in a 40-yr-old man, who had worked in the asbestos industry for 22 yr, was published in which all other potential causes were excluded including tuberculosis.[55] Cooke and Gloyne further describe the presence curious bodies found in pulmonary asbestosis and Gloyne suggest that these curious bodies be called asbestos bodies as this more adequately describes their origin.[45,56] Stewart and Haddow[57] demonstrate asbestos bodies could be found in the lung, in the lung juices, and in the sputum of asbestos workers. Reports of curious bodies, asbestos bodies, and ferruginous bodies would continue to be discussed in the literature and their relationship to the etiology of asbestos-related disease would continue.

Wood[58] provides a good description of 16 cases of the radiological appearances of the chests of asbestos workers as seen in skiagrams. He concludes that with reference to the radiograms that ". . . in general the density and extent of the lung shadows is proportional to the duration of the exposure to the dust." An article in the *British Medical Journal* reviewed occupational induced dust diseases, including asbestos-related disease stated that "Prevention does not, in the case of disease produced by occupational dusts, rest with the medical profession, although we may be able to assist. The sure and only certain way of preventing dust affecting the worker is to prevent its formation, or, if this is impossible, to secure its removal before reaching the workers."[59] Klokov[60] finds it is necessary to do pulmonary function testing, for early diagnosis, such as changes appear before the appearance of radiological changes.

Five additional studies led many investigators to conclude that people exposed to asbestos dust, including during manufacturing, developed the disease "asbestosis."[35,61–64] Merewether and Price,[35] performing the first epidemiology investigation of a cohort of asbestos workers (textile mill), found 28.1% of the 374 asbestos textile workers examined with pulmonary fibrosis and for those with greater than 20 yr exposure, 80% had x-ray abnormalities. Even after excluding any of those with other known or suspected dust exposure history, there remained 26.2% with pulmonary fibrosis that could only be explained as a result of their asbestos exposure. Suppression of dust was recommended to control the lung fibrosis caused by asbestos and a specific set of recommendations were given in order to

achieve this. Merewether[61] described the pulmonary fibrosis, from asbestos, as affecting the basal region of both lungs and discusses other differences between silicosis and asbestosis. He also discusses the dose–response relationship between exposure and the risk of disease, which is independent of age. Wood and Page[63] evaluated the case of a 21-yr-old female with a rapid evolution of tuberculosis exposed to asbestos with asbestosis bodies developing within 2 yr from first exposure and asbestos fibers found in the lungs on post mortem. Soper's case report was of a 30-yr-old man who began work in an asbestos plant at the age of 17. Soper[64] reports that the most common symptom in pulmonary asbestosis is dyspnea and that the lung fibrosis is a *progressive disease* with fibrosis of both lungs and basal pleurisy.

The first reported *case* of asbestosis in the United States was reported in Minnesota of a man who had worked previously in a South American asbestos mine starting in 1911.[65] The first official *claim* for asbestosis reported in the United States was filled in Massachusetts in a foreman in the weaving department of an asbestos plant and a fatal case of uncomplicated asbestosis was reported to the Medical Society of South Carolina.[66]

The Journal of the American Medical Association published statistical highlights of asbestosis as reported by Merewether and others and of the other knowledge of asbestosis as well as the introduction of a bill by Lord Russell into the parliament to amend the workmen's compensation act to processes involving exposure to asbestos.[67] The *JAMA* was mailed, by 1920, to 48% of U.S. doctors but estimated to be read by 80% of U.S. physicians.[68] The *Lancet*, the joint American and British medical journal, published an editorial on pulmonary asbestosis discussing the Merewether Price report and others highlighting the need for prevention and recommended prohibiting young persons from working in especially dusty work.[69] *The Asbestos Worker*, the trade union journal for the asbestos worker, made reference to asbestosis.[70] Pedley[71] who predicted that the literature on asbestos would "grow very much larger as time goes on" did not see asbestosis of much public health importance either from the standpoint of morbidity or mortality. However, as Greenberg[72] points out the actuaries knew better.[39,73] Pedley[71] further stated that while most of the cases of asbestosis were reported in the manufacture of asbestos that other cases have probably gone unrecognized because they were not in large cities, where the factories were located, but in the mines, located in rural areas, and that autopsies were more likely in the larger cities. LeDoux[74] also concluded that much of the disease found in miners at Thetford Mines attributed to tuberculosis were inaccurately diagnosed and were in reality asbestosis. LeDoux further suggested that both North American mining and medical circles knew of the hazards of asbestos dust.[72]

Asbestos exposure studies continued to be reported showing the development of asbestosis,[75,76] indicating that asbestosis was not just a disease found in the human work force. Schuster[77] discussed the case of asbestosis in a 10-yr-old wired-haired terrier used as a ratter in an asbestos factory.

By 1932, the disease asbestosis was causally liked with end-product usage of asbestos-containing materials when a maintenance employee, working with

asbestos-containing insulation products, developed the disease. A workers' compensation claim was even awarded, in this case, without any medical challenge.[78]

Asbestosis is described in seven cases. While Ellman[79] states that most develop the disease after 5–15 yr and some after they leave the industry, his experience has been that in some cases the symptoms may occur after exposures as short as 1–3 yr. Sometimes symptoms may be absent even in the presence of clinical and radiological findings. The paper reported the asbestosis cases occurring among production workers, describing the slow development of the disease, patients often free of symptoms for several years, and that latency plays a major role in the etiology of asbestosis. Finger clubbing and asbestos corns were also described as resulting from exposure to asbestos. Case 1 was a 22-yr-old female with only 4 years as a mattress maker. Case 2 was a 35-yr-old female asbestos factory worker with 5 years exposure. Case 3 was a 26-yr-old card room worker for 6 yr with progressive spread of her fibrosis in both lungs in less than 9 months. Case 4 was a 31-yr-old female asbestos factory worker making mattresses for 3 years. Case 5 was a 34-yr-old female asbestos factory worker for 6 years and seen 13 years later with a progressive cough and dyspnea and with asbestos corns on the hand and elbow. Case 6 was a 43-yr-old man who was a superintendent of the card room for 9 years who first started developing dyspnea after 4 years to the extent he was forced to quit 5 yr later. He had marked clubbing of the fingers. Case 7 was the case of asbestosis in a 10-year-old rough-haired terrier dog used as a ratter in an asbestos factory that had been reported previously in 1931 by Schuster. Ellman discussed another case of asbestosis in a person exposed to asbestos dust for 10 yr, which did not entail exposure to high dust concentrations, in coating lead pipes. The role of tuberculosis in asbestosis cases was uncertain and in a series of 17 cases examined by Ellman only six had tuberculosis and only four of the cases were active. Ellman concludes that *pulmonary asbestosis is a progressive disease* with a bad prognosis and its treatment can only be symptomatic. Unlike silica, which damages pulmonary macrophages, asbestos does not appear to do the same and thus tuberculosis does not appear to be increased in connection with asbestosis as it is with silicosis.[80,81]

In a study of 1561 employees of an asbestos company to examine nonoccupational respiratory disease, 45% of the claims occurred among those working in dusty conditions. This cross-sectional study in a subset of 708 employees found seven cases of asbestosis and the author accepts that the fibrosis is due to the mechanical action of the fibers and not their chemical composition.[82] The radiological findings of asbestosis, unlike silicosis, are related to the severity of symptoms with the greater the severity, the greater the expected findings on the x-ray. The most common symptoms are again affirmed; shortness of breath (dyspnea).[83]

6.1.2 Latency, Progression, and Asbestosis

Merewether[84] concludes that exposure to asbestos for a period of less than 5 yr can cause asbestosis which can result in death. He emphasizes that the prevention of

asbestosis is to reduce the concentration of dust. The "dusty trades" have been considered "inimical" [hostile] to the health of employees for a long time and that asbestosis once acquired is definite and a serious industrial hazard which is permanent and more or less rapidly progressive.[85] Wood and Gloyne[86] concluded that whether or not tuberculosis is associated with asbestosis, it is certainly less than that found with silicosis.

The Department of Labor and Industry, in Pennsylvania starting in 1933, concerned with a lack of information in their state asked the asbestos industry in the state to help survey the hazard as pertains to dustiness and physical condition of their workers. They found that in counting all particles those particles less than 10 μm in diameter averaged 95% of the total and that the length of the crude fiber were less than 5 μm in >95% of the total samples. Crude fibers were used in the cheaper grades of textile and in asbestos shingles, paper, plaster, and cement. The milled fibers were less than 5 μm in length in 97% of those counted. The best grades of crude asbestos fiber are used in manufacturing asbestos textiles. Preparation of the asbestos had the highest concentrations which were up to over 100 mppcf averaging 44.26 in preparation and carding, 16.37 mppcf in weaving and mule spinning, and 4.61 in other operations such as gasket making, etc. Milled asbestos fiber gave rise to the higher concentrations of crude fiber. Wet methods significantly reduced the counts. Of the 64 workers examined, 57 with exposures to asbestos 14 had asbestosis (25%). The most common symptoms were cough and dyspnea; and pleural thickening were found in some.[87] In the study by Lanza et al.,[88] of asbestos textile workers, they found overall 43% had fibrosis (lung scaring), 58% of workers with 10–15 yr exposure, and 87% of workers with over 15 yr exposure. Cases of cardiac enlargement were frequently found (later described as Corpulmonale); no predisposition to tuberculosis due to asbestos exposure was found; and the authors suggested physical examination at least every 2 yr including x-ray examination of the chest. The authors found the dustiness was greatest in the preparation areas of the five plants studied and that engineering controls reduced the dust by 50% and with further alterations could be reduced by 75% but that it was cost prohibitive to install equipment that would make the environment dust-free.

McPheeters[89] described continued exposure to asbestos could increase the fibrosis in existing asbestotics, and reported some evidence that asbestosis develops more rapidly in younger persons, no connection to tuberculosis found, and reduction of the asbestos dust should significantly reduce the incidence of asbestosis.

Shull[90] discusses his examination of 71 workers dismissed from local asbestos plants in North Carolina beginning in 1934. He concludes that asbestosis is a definite disease entity; that one case had only 16 months of exposure; that asbestosis differs for silicosis clinically, pathologically, and roentgen-logically; that asbestosis does not predispose to tuberculosis; though he did not observe asbestosis as primarily a progressive disease. The United States Public Service Health study of 541 men and women in three asbestos textile factories found asbestosis dose–response-related and thus used this finding for setting guidance limits for occupational

exposure to asbestos at 5 mppcf.[91‡] Asbestosis is described as a latent disease with x-ray changes occurring early to the lower lobes of the lung and that improved dust controls will reduce the disease and that asbestosis is a preventable disease.[92]

6.1.3 Pleural Plaques and Asbestosis

Asbestos-induced discrete pleural thickening (pleural plaques) were first reported by Sparks.[76] He also described small irregular calcareous deposits in the lower parts of the lung. He also concluded that because all his patients came for examination voluntarily, once symptoms appeared, thus an examination of a group of workers from an asbestos factory was unlikely to discover gross changes, therefore questioning the value of cross-sectional screening of the active workforce.

The first description of typical pleural plaques was by Porro et al.[93] from a survey of 15 cases in the talc industry. Other reports followed including Siegal et al.[94] also in talc workers exposed to talc dusts containing tremolite asbestos. Siegal et al. also noted that it was reported at the 57th Annual Medical Report of the Trudeau Sanatorium that experimental production of intrapleural adhesions were produced in exposed animals. In the 1950s, other reports of pleural calcification and pleural activity were reported in asbestos workers: Smith[95] tremolite talc; Jacob and Bohlig[96] pleural thickening among a cohort of 343 cases in Dresden Germany; Fehre[97] observed pleural calcifications thought to be due to inhalation of silica, however, the author concludes they are similar to those observed in persons exposed to asbestos dust; and Frost et al.[98] observed 22 cases of x-ray changes in 31 laggers surveyed from a trade union in Denmark, 19 having had pleural abnormalities including pleural thickening and calcifications. In a review, from China, of six studies on the complications of pleural plaques in asbestosis patients found a range for plaques from 34.2 to 100% and in another six studies of asbestos workers the prevalence of pleural plaques ranged from 1.3 to 29.8%.[99]

Calcifications resulting from fibrous dust generally are bilateral and situated on the parietal pleura and probably very small amounts of dust are capable of causing pleural calcifications which appear to be due to mechanical irritation.[100] The plaques are progressive and do cause adverse respiratory symptoms, such as dyspnea (breathlessness) and decrements in pulmonary function while it is more likely that diffuse pleural thickening will cause functional impairment.[101–104] Pleural thickening is considered a marker of past exposures.[105] There is evidence that persons with pleural plaques are more likely to develop asbestos-induced parenchymal fibrosis than those without such plaques.[106] Further, it has been found that, in occupationally exposed persons, appreciable amounts of fibers were found in their thoracic lymph nodes as well as in pleural plaques.[107,108] Asbestos-induced pleural plaques are the most common finding of the asbestos-related abnormalities.[109] Asbestos and erionite fibers appear to be the only causative agents for the typical pleural plaques with the latency normally several decades. Also, they can result from low exposures which

‡Mppcf = million particles per cubic foot.

are not an important risk factor for asbestos-induced lung cancer.[109] Others believe that there is evidence that individuals with asbestos-induced pleural plaques are at a marked increased risk of developing and dying of lung cancer or malignant mesothelioma.

Fletcher[110] reported asbestos-exposed shipyard workers diagnosed with pleural plaques were at a 137% greater risk from dying of cancer of the lung (16 obs. vs. 6.74 exp.; $p < 0.005$; calculated RR = 2.37; 95% CI: 1.36–3.86), none of which had radiological evidence of asbestosis; a 2900% increased risk of dying from mesothelioma (3 obs. vs. 0.10 exp.; $p < 0.001$; calculated RR = 30, 95% CI: 6.19–87.67) and a 55% increased risk of other cancers when compared with the general population of the same age but not occupational exposed to asbestos. The risks were not significant among those without pleural plaques. The workers included a variety of crafts workers. In another study of shipyard workers, Edge[111] reported that workers with mixed asbestos exposures and pleural plaques (without evidence of pulmonary fibrosis) had a 2.5 times greater risk of developing carcinoma of the bronchus, when compared with the matched controls who had a 1.2 times greater risk without plaques. Also, Edge observed three mesotheliomas in those with plaques while none occurred in those with no plaques. Edge[112] in a later study of shipyard workers found that out of 156 workers with asbestos-induced pleural plaques, but with no other radiographic evidence of pulmonary fibrosis, had eight deaths from lung cancer compared with three in those without pleural plaques, a two-fold increase and that smoking could not explain the increase in lung cancer in these workers; and 13 mesotheliomas among those with plaques with two in those without plaques, a six-fold increase. Edge also observed that if he removed the one mesothelioma occurring within the first 2 yr of observation that seven cases occurred in 2637 man-years of observation for an incidence of $1/377$ case per year.

Hillerdal gives several facts concerning pleural plaques: first, plaques are always more widespread on autopsy than x-ray; second, in populations without endemic plaques 80–90% of the strictly defined plaques are due to occupational exposures and they can also be found in persons with low-level exposures; third, asbestos bodies are more prevalent in person with pleural plaques; fourth, pleural plaques are related to time after exposure to asbestos rather than to dose; fifth, in industrially developed countries 2–4% of all males over the age of 40 usually have plaques; sixth, plaques themselves are usually harmless, but as an indicator of exposure they are indicators of sufficient latency for asbestos-induced cancers, for example, persons with pleural plaques are twice as likely to develop lung cancer as those without such plaques and those with plaques are more at risk of mesothelioma; seventh, those with pleural plaques, in general, have lower lung function; finally, persons having high rates of pleural plaques from living in areas of local deposits of asbestos such as tremolite, amosite, and crocidolite have a high risk of mesothelioma while those with high rates of living in areas of anthophyllite do not.[113] In residents of Da-yao, China, with environmental exposure to crocidolite, pleural plaques were prevalent in 11% of those over 20 yr of age and in 20% in those over 40 yr old.[114] Pleural effusions diffuse pleural thickening and rounded atelectasis are also caused by exposure to asbestos.[115]

6.1.4 Lung Cancer

In early studies, asbestosis was frequently found in conjunction with lung cancer among workers exposed to asbestos.[116–118] This lead some to speculate that asbestosis was necessary and somehow associated in the etiology of lung cancer among those exposed to asbestos, some attributing this association to the "scar" theory of carcinogenesis. This is not strongly supported for all asbestos-associated lung cancers according to Hillerdal,[119] as he observed that a majority of tumors were squamous cell cancers and not adenocarcinomas. Adenocarcinomas were found most commonly among patients with asbestosis and in the lower lobes of the lung, where asbestosis is most prevalent.[120] It is true, however, in some cases of advanced asbestosis, that scar carcinomas may develop as an outgrowth of uncontrolled fibrogenesis, just like they do with usual interstitial pneumonitis (UIP), the typical pathologic lesion in asbestosis.[121] Asbestos exposure appears to increase the risk for all histological types of lung cancer.[120] Both those with asbestos exposure and also those with asbestosis have risks of lung cancer higher than found in the general population not exposed to asbestos.[122] It is more likely that asbestosis is not a precursor to lung cancer, but that both are independent diseases related with a dose–response from exposure to asbestos, and that cancer of the lung can and does occur in the absence of asbestosis.[119,120,123–125] McDonald et al.[126] have presented epidemiological data showing increased risk of lung cancer in occupations with exposure to asbestos in the absence of radiological evidence of pulmonary fibrosis. Hillerdal,[119] in a well-designed study having sufficient statistical power, found lung cancer to occur in patients with bilateral pariental pleural plaques but without radiological evidence of asbestosis. Lung cancer continues to be statistically elevated among asbestos workers under surveillance [standard incidence ratio, SIR 1.14; 95% CI: 1.01–1.26].[127] In a Chinese study of eight asbestos factory cohorts and three mining cohorts, the complication rate of lung cancer among asbestotics ranged from 3.5 to 26.9%.[99] That exposure levels for carcinogens were safe (including asbestos) is brought into question by the findings that the lungs may accumulate massively more cancer-causing airborne particles than previously thought. The bifurcations within the lung may allow high concentrations of particles to build up as much as 100 times as in the other parts of the lung.[128]

6.1.5 Smoking and Risk

Increases of lung cancer in smokers are more than just additive but are multiplicative in nature. Both asbestos and smoking are independently capable of increasing the risk of lung cancer. One of the largest cohorts of asbestos workers to demonstrate this is that of the North American insulators studied by Dr. Selikoff. His co-investigator Cyler Hammond of the American Cancer Society (ACS) reported among 12,051 insulation workers with more than 20 years of work experience when compared with a control population from the ACS of 73,763 men, both of whose smoking history was known, that the RR went up to 53.24 for smoking

asbestos insulation workers compared with nonsmoking asbestos workers which was only 5.17 and smoking nonasbestos exposed workers, as controls, of 10.85.[129] A study of 912 smokers out of 1479 asbestos-exposed workers among the industries of Barcelona Spain found the incidence of asbestosis was significantly higher in the smokers 161 (17.65%) versus 44 (11.39%) in the nonsmokers; as were the clinical symptoms (cough, expectoration, and dyspnea) 72.58% versus 55.18%, respectively. Nonsmokers with asbestosis had more restrictive disease or mixed-type syndromes than did smokers with asbestosis. A linear relationship between asbestosis and duration of exposure was found in 1% of those having less than 5 yr exposure up to 65% among those with 30 or more years of exposure.[130] In addition, another summary of smoking and asbestos exposure combined reported the RR for three additional studies to be 8.2, 32.7, and 25.7.[131] Asbestosis patients had a standard mortality ratio (SMR) of 15.47 (95% CI: 11.2–20.8) for lung cancer.[132] An analysis of 23 studies on asbestos exposure and smoking shows that asbestos multiplies the risk of lung cancer in nonsmokers and smokers by a similar factor and that the combined relationship of exposure to asbestos and smoking can be best described by a multiplicative rather than an additive model.[133] Berry and Liddell estimate the relative risk (RR) to be about three times higher in non-smokers than smokers and that the RR is highest for the interaction of asbestos and smoking in the very light smoker and nonsmoker when compared with the light or heavy smokers. They concluded that if the populations studied include smokers and nonsmokers, then the calculated RR, from the epidemiology study, applies to that of the smokers.[134]

6.1.6 Relative Risk

The RR for lung cancer has varied from 1.0[135] to 17.6[136] with an average 9.8 RR. The prognosis and treatment of asbestos-induced lung cancer is no different than lung cancer having another etiology. It appears that all cell types of lung cancer occur in asbestos workers and that the presence or absence of one cell type cannot be used to prove or disprove and association of asbestos exposure with the lung cancer.[137] Since 1997, asbestos has been the leading cause of occupational lung cancer in Japan.[138] Most studies of asbestos workers have been among white males, however, when race is considered black men also are at a higher risk when exposed to asbestos. One study reports an OR of 1.8 (95% CI: 1.03–3.1) for lung cancer in black men, however, when using SEER data from 1988 to 1992 mesothelioma was higher in white men than black (1.7 vs. 0.9/100,000).[139] In a survey of Hungarian workers exposed to asbestos with lung tumors, 72 patients (24%) of 297 had cumulative occupational asbestos exposures assessed as below 25 fiber-years (between 0.01 and 23.9 fiber-years).[140] In West Germany, a case–control study reported by Pohlabeln et al.[141] supported a doubling of the lung cancer risk with 25 fiber-years of exposure and when using a two-phase logistic regression model showed odds ratio (OR) increases from 0 to $\leq$1 fiber-years (0.86; 95% CI: 0.55–1.33), 1 to $\leq$10 fiber-years (1.33; 95% CI: 0.80–2.33), and 10+ fiber-years

(1.94; 95% CI: 1.10–3.43) which are similar to those found by Stayner et al.[142] and Dement and Brown.[142] A case-referent study of Swedish lung cancer patients found clear evidence for the risk of lung cancer at low-dose levels and that linear extrapolation from high exposure levels may underestimate the risks for low doses. Never smokers exposed at 1–2.49 fiber-years had an RR of 2.7 (95% CI: 0.7–9.5) and for those smoking >20 cigarettes/day an RR of 80.6 (95% CI: 20.2–322.0).[143] There is also evidence of an increased number of multiple primary cancers at the same time among those exposed to asbestos compared with the general population.[144]

6.1.7 Mesothelioma

Mesothelioma is a cancer of the mesothelium, the thin lining that covers the major internal organs of the body. The rarity and the fact that this type of tumor is strongly associated with exposure to asbestos make it a "signal tumor." This means that it is considered an epidemiological marker for exposure to asbestos.[48,145] Wagner was the first to recognize and report primary pleural tumors in 1870.[146] Credit is given to Adami for the term mesothelioma in 1909.[147] The modern concepts concerning the pathology and diagnosis of mesothelioma were set forth in 1931 by Kemperer and Rabin.[148] Gloyne described the migration of fibers to the lymph stream and especially into the mediastinal glands in a person with asbestosis.[149] It is interesting to note that Hesychius the lexicographer defined asbestosis as stuccoing or plastering and Cooke gave the name asbestosis which now, in addition to asbestosis, "may indeed stucco the pleura or the peritoneum" as well as other organs having mesothelial linings.[150] The dose–response relationship for mesothelioma was first shown among textile workers exposed to asbestos and then among gas masks workers, miners and millers, and shipyard yard workers.[151–154]

This uncommon tumor, mesothelioma, is now today being reported in almost every major study of persons exposed to asbestos. Some have estimated that pleural mesothelioma occurs with an incidence of one for every two lung cancers; however, these estimates have generally be related to the overall mortality within specific cohorts of asbestos workers and in some based on cumulative asbestos exposure of 25 or more fiber-years and can be rather misleading either as overestimates or *vice versa*.[140] In one analysis, the authors have thrown out the three highest and the three lowest ratios and report then a range of ratios for mesothelioma to lung cancer from 1.0 to 5.2, however, they actually threw out the four lowest so the range is really 0.5–5.2 (median 2.4). If they had looked at the entire range it would have a range from 0.3 to 18.5 (median 3.67).[155] Thus, the actual ratio does vary between studies and any reflection on just the median ratio is misleading. Pleural mesothelioma incidence has been increasing in all asbestos using countries despite control measures put in place since the 1970s.[156] Jarbholm et al.[157] report the annual incidence of pleural mesothelioma attributable to occupational exposures in larger than all fatal occupational accidents in Sweden and that prevention measures have not been evident in decreasing the risk.

Using the Surveillance, Epidemiology, and End Results (SEER) data of the National Cancer Institute, which covers nine geographic areas and represents about 10% of the U.S. population, 542 incident cases of mesothelioma were reported between 1998 and 1999 and 447 between 1999 and 2000.[158] Pinherio et al. concluded that these nine areas were generally representative of the entire United States and that using the ICD 10 coding which went into effect in 1999 that the accuracy for reporting mesothelioma was now about 80% effective, thus this would mean that in the United States there are over 6000 cases of mesothelioma per year and the mortality and incidence ratios average about 80–85%. They note that prior to the implementation of the ICD 10 code that previous codes did not permit analyses of specific data for mesotheliomas and for example in Minnesota only one of eight cases of pleural mesothelioma were coded correctly using previous ICD codes. Because of this inaccuracy of reporting, due to the absence of an appropriate ICD code until the implementation of the new ICD 10 coding system, the projections of mesothelioma in the United States were based on insufficient data to obtain an accurate picture of the U.S. mesothelioma trends. Unfortunately, the new ICD 10 code has only been in existence for the past 5 years and any trends based on this data are unwarranted and it will be many years until an accurate picture can be seen as to the real mesothelioma trends within the United States. What is clear, however, is that the projections using SEER data prior to the implementation of the ICD 10 codes are most like inaccurate and most likely underestimate the true incidence of mesothelioma in the United States, as projected by such studies concluding the risk of mesothelioma in the United States is on the decline.[159,160] Trends in mesothelioma are on the rise in many countries and a large multicentric[161] study on malignant pleural mesothelioma and nonoccupational exposures to asbestos projects that low doses from the home and general environment may carry a measurable risk of mesothelioma over the next few decades.[127,162–166] The new ICD 10 codes for mesothelioma are C45.0 for pleural and C45.1 for peritoneal (ICD 10, 1994). As the incidence of mesothelioma in women is much less associated with asbestos exposure, Steenland et al.[167] suggest that if take-home asbestos exposure were considered the attributable risks may rise to around 90%. Price and Ware[160] suggest that because the female lifetime mesothelioma risk across birth cohorts has remained constant, this supports a threshold exposure for mesothelioma, which is yet to be shown and no epidemiological study to date has been able to demonstrate such a threshold. As the bans on asbestos take effect in many countries, the incidence of mesothelioma should begin to decrease several decades into the future.

Peritoneal mesothelioma is a much rarer tumor than pleural; for example, in Sweden, the male incidence is 10-fold less than for pleural tumors, but in females it is somewhat higher or about half that of the pleural tumor. Swedish males have shown no increase in peritoneal mesothelioma since 1985 but in females peritoneal mesothelioma has been steadily increasing and has surpassed the rate of pleural mesothelioma (0.16/100,000).[156] Neumann et al.[168] report from the German mesothelioma registry that peritoneal mesothelioma was associated with higher lung burden than were pleural mesothelioma. Suzuki[169] reported that peritoneal mesothelioma was more commonly found in his group of 1517 mesothelioma case

among asbestos insulation workers and that the ratio between pleural and peritoneal was approximately 3:1, but that this was reversed when only insulation workers were evaluated (1:2.6). Israeli researchers found the incidence by anatomical site to be 74.1% for pleural compared with 24.6 for peritoneal among 317 cases reported between 1960 and 1996.[170]

The National Institute for Occupational Safety and Health in conjunction with The National Center for Health Statistics reports between 1987 and 1996 that various work groups had extremely elevated proportional mortality ratios (PMRs) for pleural malignancies such as insulation workers at 23.08 (95% CI: 10.59–43.80), boilermakers at 15.37 (95% CI: 7.68–27.50), plasterers 11.61 (95% CI: 3.76–27.13), sheet metal workers 10.35 (95% CI: 6.55–15.54), plumbers, pipefitters, and steamfitters 7.02 (95% CI: 5.12–9.40), and 13 other specific occupations with PMRs of 2 or greater. They also report that these occupations taking place in several industries including ship and boat building and repairing with a PMR for pleural tumors of 12.60 (95% CI: 8.75–17.52) and petroleum refining with a PMR of 5.76 (95% CI: 3.29–9.35). Another 15 industries also had PMRs over 2 with all 95% confidence intervals that did not include one.[171] The finding of such a high PMR for ship and boat building and repair is consistent with the study of Tagnon et al.[172] of the shipbuilding in coastal Virginia which found 61 cases of mesothelioma among white males with an RR of 15.7 for the shipyard employees reporting exposure to asbestos compared with 4.9 for shipyard employees who did not report exposure to asbestos. Statistics from the latest SEER data also point out the highest incidence for mesothelioma occurring in a major shipbuilding areas: being Seattle (Puget Sound) Washington and San Francisco–Oakland California area.[158]

The ratio of occurrence for mesothelioma in the pleural area to the peritoneal area appears to be associated with the degree of exposure.[173] Among the large occupational exposed groups studied approximately 5–10% of the deaths have been due to mesothelioma.[174–176] In Scotland only 5% of the mesothelioma cases gave no history of asbestos exposure, while in Canada this lack of association was higher; the Canadian survey gave the annual incidence of about one per million.[177] Other studies have shown the ranges higher up to 23%.[178] Another estimate has projected that as many as 11% of all asbestos workers' deaths in England will be from mesotheliomas.[151] RRs ranged between 2.3 and 7.0 with a mean of 4.6 for studies published between 1965 and 1975.[179–187] Mesothelioma association with asbestos exposure has generally been very high, generally over 80% and in those that have not stated such exposures when followed up have actually shown such exposures.[188] Dodson et al.[189] have shown that 10–15% of the mesotheliomas arise in the peritoneal area and that fibers also reach the mesentery and omentum in the peritoneal region.

In a 1960 report of abdominal cancers, eight cases of peritoneal cancers were reported in women, four of which were suggested to be primary from the ovary and four only of the peritoneum and all of the cases were diagnosed with asbestosis. One case was reported in the same series in a male ventilator cleaner with asbestosis.[190] Previously a case of peritoneal cancer had been reported in a 53-yr-old asbestos

worker with asbestosis and asbestos fibers were found in the tumor tissue.[191] Three cases of peritoneal mesothelioma were reported among 36 asbestosis cases and another case of peritoneal mesothelioma was reported in an insulation worker.[192,193] In another series of 72 asbestosis cases, four peritoneal cancers were reported, one in a male and three in females, two of which were thought to be primary ovarian cancers.[194] Eleven cases of peritoneal mesothelioma were reported among eight men and three women between the ages of 38 and 78, with latency periods of 20–46 years and exposures between 10 months and 32 years. The authors reported that a "remarkable feature" of the cases was the minimal degree of fibrosis in the lungs.[195] Peritoneal mesotheliomas continued to be reported among various occupations with exposure to asbestos including: in a 47-year-old insulator and a 46-year-old insulator,[196,197] three cases among radiologically confirmed asbestotics,[198] four among asbestos textile workers,[199] 17 cases with known asbestos exposures,[200] a 60-year-old former shipyard insulator,[201] three cases among asbestos textile workers,[202] and four cases among asbestos textile workers.[203] Newhouse and Thompson[180] reported 27 peritoneal mesotheliomas in London with both occupational and some with domestic exposures.

Other sites of mesothelioma have been reported but not of the same incidence as for the pleural or the peritoneal and their relationship to asbestos exposure needs further analysis. Pericardial mesothelioma has also been reported but it has a very low incidence, as reported in one large autopsy study, of less than 0.0022% and by some estimates is related to about 6% of all mesotheliomas.[204] Dusting of the pericardium with mixed dusts, including asbestos, was reported in an individual when treated for angina pectoris 15 years earlier.[205] Also, congenital malignant peritoneal mesothelioma has been observed albeit very rarely, with only three cases documented and their association with asbestos is unclear.[206]

6.1.8 Other Malignant Diseases

Other malignant diseases the most common of which are gastrointestinal tract cancers with an RR range from 0.5[207] to 3.1.[208,209] By the 1960s, epidemiological studies suggested exposure to asbestos with the increase in gastrointestinal tract malignancies.[210–212] The Selikoff et al.[210] study found stomach, colon, and rectum cancer increase three times more than expected (29 vs. 9.4; RR = 3.09; CI: 2.07–4.43). Among 370 New York–New Jersey asbestos insulation workers, 12 stomach, colon, and rectal cancers were observed when 3.09 were expected (RR = 3.90; 95% CI; 2.01–6.81).[209] At the meeting of the New York Academy of Sciences, Mancuso[213] reported, during the discussion of these papers, that he had located 16 additional deaths since his original publication[213] and that five of them were due to cancer. They included one of the stomach, one of the colon, and two of the rectum, which increased their earlier observation up to 11 gastrointestinal cancers, whereas 4.55 had been expected in his earlier study. Mancuso and El-Attar[208] reported SMRs in the 25–44-year age group of 264 and 1235 after cumulative employment-years of 2.1–7.0 and 7.1–12.0, respectively. Selikoff[214] found

increased rates for cancer of the stomach and esophagus (20 obs. vs. 6.46 exp. [SMR 3.09; 95% CI: 1.89–4.78]) as he did also for cancer of the colon (23 obs. vs. 7.64 exp. [SMR 3.01; 95% CI: 1.91–4.52]) among the 632 asbestos workers, from New Jersey and New York. In his larger study of 17,800 asbestos insulation workers, from the United States and Canada, Selikoff et al.[215] reported similar observations for cancer of the esophagus (18 obs. vs. 7.1 exp. [SMR 2.54; 95% CI: 1.50–4.00]), stomach (18 obs. vs. 14.2 exp. [SMR 1.27; 95% CI: 0.75–2.00]), and colon and rectum (58 obs. vs. 38.1 exp. [SMR 1.52; CI: 1.16–1.97]).

Others have observed similar results for gastrointestinal cancers among workers exposed to asbestos in various countries.[216–218] Schneiderman,[219] then senior statistician for the National Cancer Institute, in his early version of his analysis of the existing literature, up to 1974, concluded that "increased exposure to inhaled asbestos particles leads to increased digestive system cancer." Newhouse and Berry[220] reported an RR, among male asbestos factory workers with exposure less than 2 yr of 2.11 (20 obs. vs. 9.5 exp.; cal. 95% CI: 1.29–3.25) and greater than 2 yr of 2.32 (19 obs. vs. 8.2 exp.; cal. 95% CI: 1.40–3.62). For females, the corresponding SMRs were 2.46 (obs. 14 vs. 5.7 exp.; cal. 95% CI: 1.34–4.12) and 3.46 (obs. 9 vs. 2.6 exp.; cal. 95% CI: 1.58–6.57), respectively. McDonald et al.[221] reported abdominal cancers in males with 20 years latency and with cumulative dust exposures of 10 to $<$20 mpcf years of 231.6, 20 to $<$40 mpcf years 247.0, and 40 to $<$80 mpcf years of 383.6, respectively. Nine of the 12 deaths reported were from colon and rectum cancers. Enterline et al.[222] reported on the mortality of cancer in a cohort of 1074 white male followed to death and found the expected number of deaths from cancers of the stomach, large intestine, and rectum of 30.99 when 43 were observed (SMR 1.43; 95% CI: 1.03–1.92) with the SMR for stomach cancer being 180.4 ($p < 0.05$). A dose–response relationship was reported, in a fiber year analysis, for gastrointestinal cancers and years since first exposure increased the SMR rate from less than 1 during the first 20 yr to 231, 273 and 500 after 20–24, 25–29; and 30–34 yr from first exposure.[223]

One of the most recent reviews on the epidemiology of gastric cancer and its risk factors[224] points out that many methodological problems have cast doubt on the causal association between asbestos exposure with gastrointestinal cancers. Even though such methodological errors were never discussed in the review, the authors point to only one study to dispute an association. This study had heavy exposures to crocidolite with no observed excess of gastrointestinal cancers, even though this study also suffered from a major methodological problem that being over 25% of the total cohort of 6506 were lost to follow-up.[225] Albin et al.[226] reported among asbestos cement workers an RR of 3.4 (95% CI: 1.2–9.5) in those workers with $\geq$40 f yr/ml for colon and rectum cancer. Among pipe fitters and boilermakers, a case–control study reported an OR for colon cancer of 10.7 (95% CI: 1.07–103).[227]

That it was biologically plausible for the fiber to pass through the human gastrointestinal mucosa, under conditions in the alimentary canal, was shown by Cook and Olson[228] when they were able to show that sediment in human urine contained amphibole fibers. Asbestos fibers and asbestos body formation have been shown

in tumor tissue taken in the colons of asbestos-exposed workers.[229] Reports of gastrointestinal tract cancers associated with asbestos exposure have been reviewed by the World Health Organization (WHO)[229] in which they have concluded that "overall, there seems that there is a correlation between lung cancer and gastrointestinal cancer rates in occupational cohorts [exposed to asbestos] which is not due to chance."[230] Both the Surgeon General of the United States and the Department of Health, Education, and Welfare have concluded that past asbestos exposure can result in an excess of gastrointestinal cancers.[231,232]

Frumkin and Berlin[233] did a meta-analysis[§] of cohort studies to estimate the risk of gastrointestinal cancer mortality. They divided their exposure categories for asbestos exposure into two groups: the first representing heavy asbestos exposure was defined by any cohort having an SMR of 200 or greater for lung cancer and the low-exposure category represented by any cohort with an SMR below 200. In the cohort with high exposures to asbestos all of the gastrointestinal cancers, except esophageal cancer, were significantly elevated with 95% confidence limits that excluded 100. For the low-exposure cohorts all of the SMRs were close to 100 for gastrointestinal cancers. Homa et al.[234] report, in their meta-analysis on 20 asbestos-exposed cohort, that the summarized SMR for colorectal cancer in those cohorts exposed only to amphibole asbestos to be 1.47 (95% CI: 1.09–2.00) as compared with those cohorts exposed to chrysotile which was 1.04 (95% CI: 0.81–1.33). In a recent study, death certificate data were analyzed from 4,943,566 decedents from 28 states in the United States from 1979 to 1990. In the analysis, the authors identified 15,524 cases of gastrointestinal cancer among 12 occupational groups having elevated PMR for mesothelioma, a sentinel tumor for exposure to asbestos, and found slightly elevated PMR for esophageal (108; 95% CI: 107–110), gastric cancers (110: 95% CI: 106–113), and colorectal cancer (109; 95% CI: 107–110). The authors, from the National Institute for Occupational Safety and Health, conclude that their large death certificate study support an association

[§]Meta-analyses of observational studies can present inherent biases such as selection bias and other confounding biases. Meta-analysis is a technique which was first envisioned for evaluating clinical studies where combining results, based on individual participation data, would be less likely to suffer from such biases and thus be homogeneous; however, its further application to the analysis of observational studies thus becomes problematic. If the data relied upon for meta-analysis have flaws, such as confounders, lack homogeneity, or other methodological issues, then the outcome of the meta-analysis will also suffer from the impact of such flaws as will their conclusions. IARC states that pooling of data, such as done in meta-analysis, from observational studies can provide useful answers to causation if: "In addition, all studies that are judged to be methodologically sound should be consistent with a relative risk of unity for any observed level of exposure to the agent and, when considered together, should provide a pooled estimate of relative risk which is at or near unity and has a narrow confidence interval, due to population size." Systematic reviews, examining the strengths and weaknesses of observational epidemiology studies, remain a far superior method in determining their meaning when the compared observational epidemiology studies lack homogeneity and thus cannot be used adequately for meta-analysis unless such heterogeneity can be controlled for. Frumkin and Berlin attempted to control this by used lung cancers, having significant elevations in the cohorts of asbestos workers to compare with those studies not having such significance. NIOSH used a similar method for addressing the lack of homogeneity for their meta-analysis where they only looked at cohorts with significantly elevated PMRs for mesothelioma, a sentinel tumor for asbestos exposures.

between asbestos exposure and some gastrointestinal cancers.[235] Results of a mortality study of textile and cement pipe manufactures between 1933 and 1980 found colon cancers statistically significant (27 obs. vs. 14.78 exp.; SMR 1.83; 95% CI: 1.20–2.66).[236]

Stomach cancer was increased among rubber workers who worked in the early production stages of mixing and weighing which the authors concluded may point to the role of either asbestos-contaminated talc or carbon black, but their results do not support the causal role of nitrosamines.[237] The role of carbon black in the etiology of stomach cancer is also not supported.[238] A risk of stomach cancer was evaluated for 12 workplace hazards, including asbestos, but did not find any significant relationship. The study was a death certificate analysis from 24 states in the United States using exposure data from a variety of sources including two textbooks, computerized databases from OSHA and NIOSH, unpublished industrial hygiene reports and personal experiences. The exposure surveys based on the computerized databases, while containing some quantifiable data, are mainly based on subjective interpretation by the surveyors. Any use of the two textbooks for exposure classification is very questionable because the very limited exposure data reported conversion from mppcf to fibers/ml and one of the authors[239] warns using such conversions is done "... with considerable risk to the validity of the results." Readers of the paper cannot judge the author's conclusions adequately when based on unpublished industrial hygiene data or personal experiences. Given these factors, limited validity to the author's conclusions must be questioned.[240]

Limited evidence has also shown an association between gastric cancer and asbestos exposure. In a plant manufacturing fireproof textiles and friction materials, a digestive cancer registry since 1978 was analyzed. The authors did not find any significant excess of digestive cancers, except for the peritoneum, however, more than expected deaths occurred for other digestive cancers which led the authors to conclude that their study provides initial evidence suggesting a relationship between occupational exposure to asbestos and risk of digestive cancer and that evidence of a dose–effect relationship is seen among the whole population at risk. An important finding of this study is that the authors feel that intensity of exposure is more important than the duration of the exposure.[241] In a multicenter case–control study in Italy involving interviews with 640 histologically confirmed male cases and 959 controls, randomly selected from the resident populations of the study areas found workers with 21+ yr of potential exposure had nonsignificantly increased risks related to asbestos exposure.[242] In a study of 1756 male workers at a nitrate fertilizer plant employed for 1 yr or more between 1947 and 1980 and using asbestos and nitrogen derivatives for surrogates of individual exposure found a slight increase for stomach cancer (28 obs. vs. 19.9 exp.; RR = 1.41; 95% CI: 0.93–2.03).[243] Norwegian lighthouse keepers exposed to asbestos in their drinking water, collected in cisterns collecting the water off roofs made of asbestos cement tile, had fiber counts ranging from 1,760 to 71,350 million fibers per liter, which were higher that measured in the general Norwegian water supplies. Measurements were taken 20 yr after the roof tiles were installed and those keepers with 20 yr latency or more experienced a stomach cancer incidence of

11 observed when only 4.57 were expected (RR = 2.41; 95% CI: 1.20–4.31).[244] These increases for stomach cancer were occurring during a period of time that the overall rate of stomach cancer was going down, for males and females in all age groups, in Norway.[245]

Case reports have also identified associations between exposure to asbestos and gastrointestinal cancer. Case reports taken alone and without connection with the numerous epidemiological studies, as discussed previously, would be mostly of clinical interest or suggestive of hypothesis generation, however, when connected with the well controlled and conducted epidemiological studies are of much greater importance. In a series of five cases of double cancers involving the lung and the stomach and after determining if the subjects had exposure to asbestos, three had such occupational histories and many crocidolite fibers were found in their autopsied lungs. The authors suggest there could be an association between these three cancers and their exposures to asbestos.[246] One case report, of an 84-yr-old man with pleural plaques with calcification and a history of working in shipyard having known asbestos exposure, presented with a double cancer of the stomach and colon. Asbestos bodies were also found in his autopsied lung tissue. Given the epidemiological literature, the authors suggest there might be an association with exposure to asbestos.[247] In a series of 35 primary multiple cancers, confirmed by autopsy, 25 (71%) were proven to have exposure to asbestos. In these, lung and stomach cancers were the main components of the multiple cancers, and in addition 13 of these cases had asbestos bodies in 5 g of autopsied wet lung tissue which amounted to more than 1000. The authors, given the epidemiological literature, suggest that asbestos exposure might possibly have induced a high incidence of multiple cancers. Kishimoto and Shimamoto[248] continued their evaluation of case reports and now report ten cases of double cancers of the lung and stomach. Five of the cases had developed their cancers simultaneously while the other five had developed their lung cancer after stomach cancer surgery. Eight of the cases had histories of asbestos exposure, and almost all cases had significantly high numbers of asbestos bodies in autopsied lung tissue. The fiber type found in the lungs was all chrysotile. The final case report, by Kishimoto and Yamaguchi,[249] describes a 76-yr-old male with simultaneous double cancer of the lung and stomach. Histologically the two tumors were different (stomach: well-differentiated tubular adenocarcinoma and lung: moderately differentiated papillary adenocarcinoma), while the stomach cancer was in an early stage and the lung cancer was stage IIIa. The case had a definite exposure to asbestos in a Japanese naval shipyard. On x-ray, pleural plaques with calcification were found as were numerous asbestos bodies in resected lung tissue which were chrysotile and tremolite. Even though he was a heavy smoker, the authors suggest that asbestos exposure and smoking are considered as etiological factors independently and together act synergistically for cancer development in the lung.[249]

6.1.9 Laryngeal Cancers

Doll and Peto[250] have suggested exposure to asbestos as a risk factor for cancer of the larynx. The International Agency for Research on Cancer (IARC), of the World

Health Organization, reported in 1977 and again in 1987 about an excess of cancers of the larynx observed in workers exposed to asbestos. In a review of 12 cohort studies, half did not show any significant excess in laryngeal cancer and the other studies had SMRs that ranged from 1.91 to 5.41, however, the authors contend that none had adjusted for confounders such as alcohol and smoking.[251] Looking at six cohorts with lung cancer RR of 2 or more found two with the highest RR estimates for lung cancer of 4.06 and 3.28 which gave strong findings for a causal relationship between asbestos exposure and laryngeal cancer with RRs of 1.91 (90% CI: 1.00–3.34) and 3.75 (90% CI: 1.01–9.68). Confounders of smoking and alcohol consumption did not explain the excess.[252] Edelman[253] reviewing 13 cohort studies found two studies out of 13 with SMRs that were statistically increased for laryngeal cancer from asbestos exposure. While no causal association was found among 322 workers examined at a friction products manufacturing plant, 20% with asbestos exposure had laryngitis when compared with only 11% in the lower risk group and they concluded that asbestos may act as an irritant to the larynx.[254] Maier and Tisch[255] found that the majority of laryngeal cancers were identified in blue-collar workers exposed to a variety of hazards including asbestos, but do not make any conclusions concerning a causal association. A case–control analysis of 112 patients in Uruguay found an OR of 2.4 (95% CI: 1.2–4.8) for those exposed to asbestos for over 21 yr.[256]

A meta-analysis of 69 asbestos-exposed occupational cohorts found a meta-SMR of 157 (95% CI: 95–245) with latency of at least 10 yr and a meta-SMR of 133 (95% CI: 114–155) without any latency association but when analyzed by work group found meta-SMRs for latency among asbestos miners and millers (135, 95% CI: 124–146), asbestos products manufacture (192, 95% CI: 176–209), and friction materials workers (112, 95% CI: 101–124). Without latency asbestos miners and millers had a meta-SMR of 153 (95% CI: 144–163, $p = 0.002$) and asbestos products manufactures of 188 (95% CI: 173–203, $p = 0.0001$). Based on these results, the authors concluded there was a suggestion of an association between asbestos and laryngeal carcinoma.[257] Asbestos exposure had an RR of 1.8 (95% CI: 1.1–3.0) in the highest exposure group, in a case–control study of 545 cases of squamous cell cancer of the upper gastrointestinal tract compared with 641 referents, among Swedish men age 40–79 living in two regions, between 1988 and 1990.[258] In a French study asbestos exposures, controlled for both smoking and alcohol, found and excess in hypopharynx (OR = 1.8, 95% CI: 1.1–2.7), which was consistent with an IARC case–control study that found an OR of 2.1 (95% CI: 1.2–3.8) associated with cancers of the hypopharynx and epilarynx, both of which are contiguous with similar clinical characteristics, thus making an etiology of common cause plausible. The highest risk was for the epilarynx at the highest asbestos exposure (OR 2.22, 95% CI: 1.05–4.70). The authors found a nonstatistical excess for laryngeal cancer, which they concluded points into the same direction as those significant for the subsites. The authors did not find any significant interaction between smoking and asbestos for laryngeal cancer.[259] In a Japanese study of 525 autopsy cases of asbestosis between 1958 and 1996 compared with 1,055,734 nonasbestosis cases, laryngeal cancers were

significantly higher (6 obs. vs. 3 exp. or 1.1% compared with 0.3%, $\chi^2 = 12.0$, $p < 0.001$).[260] In a study by Browne and Gee[261] of mortality and morbidity prospective studies, the authors found only one of the mortality studies had clear evidence of an excess for laryngeal cancer (8 obs. vs. 3 exp.; SMR 2.7; 95% CI: 1.15–5.25) and of two morbidity studies one study had a significant excess for those hired between 1928 and 1940 (5 obs. vs. 0.9 exp.; SMR 5.5; 95% CI: 1.8–12.9) while those hired after 1940 did not (9 obs. vs. 7.5 exp.; SMR 1.2; 95% CI: 55 –2.28). The later finding might reflect an inadequate latency factor for those hired after 1940. It appears that the authors grouped their analysis together for the 22 mortality studies and then summed the observed and the expected values, for all studies, and then calculated an SMR for the total in order to come to the conclusion that there was no causal association between asbestos and laryngeal cancer, a technique not epidemiologically valid for such analysis without weighing the studies for comparison to account for their heterogeneity. In reviewing case–control studies, the authors throw out three studies because of reported methodological errors and include 17 other studies, on which the authors make no comment as to their methodological accuracy. As a result, the authors conclude that the 17 studies show no causal relationship based on the nonsignificance of 15 of the studies, when comparing them to two studies having statistical significance. Such analysis equating studies based on only numerical analysis and not considering the various weights of the individual studies is not only misleading but in the worst tradition of epidemiology and represents a misapplication of the methods used for meta-analysis. A NIOSH study of the proportionate mortality among unionized roofer and water-proofers found a statistically significant increase in cancer of the larynx with a PMR of 145 (95% CI: 106–193).[262]

In conclusion, while there is equivocal evidence for a causal association between asbestos exposure and laryngeal cancer as compared with asbestosis, lung cancer, mesothelioma, and gastrointestinal cancers, the evidence that does exist, from some very well-controlled epidemiology analyses, do point to such a casual association. Biologically plausible is also a factor to consider when evaluating the ability of the asbestos fibers to reach the larynx, as is the case for inhaled dusts, including those containing asbestos, to cause repeated irritation that may well act as a cofactor in the etiology of laryngeal cancer.[263]

6.1.10 Kidney Cancers

Asbestos bodies have been found in the kidney which the authors feel either could have formed in the lung and then migrated to the kidney or that the asbestos fibers themselves may have migrated and then formed the asbestos bodies in the kidney, which is the theory that the authors favor.[264] Higher risks of kidney cancer were reported among males in asbestos mining areas of Quebec.[265] Selikoff et al.[215] reported an RR of 2.3 for renal cancer among the 17,800 asbestos insulators under study. In a discussion paper, published in *Dust and Disease*, Cook[266] reported finding fibers in the urine of person's drinking water containing amphibole

asbestos which were in the same size range, leading him to the conclusion that the kidney is also a target organ for such fibers. A study of 1500 asbestos-exposed workers found malignancies of the kidney that the authors considered related to asbestos exposure.[267] A case–control study of renal adenocarcinoma in 518 cases, identified between 1981 and 1984, from 37 Massachusetts area hospitals found the incidence of asbestos-induced renal adenocarcinoma to be 1.6, with a one-sided 95% confidence limit of 1.0, leading the authors to conclude asbestos was a cause of the renal adenocarcinoma in their study.[268] An analysis of three cohorts, having a RR in excess of 2 for lung cancer, identified all three cohorts with an excess of kidney cancers. Kidney cancers in the three cohorts had SMRs of 2.22 (95% CI: 1.44–3.30),[215] 2.76 (95% CI: 1.29–5.18),[222] and 1.63 (95% CI: 1.31–2.00).[269] The authors concluded that because of the results in their analysis, good evidence existed that asbestos can reach the target site for the kidney cancers and because animal evidence also supports a causal association with kidney cancer that it is probable that asbestos exposure can also cause human kidney cancer.[270] A more recent interpretation of the Smith et al.[270] study by Pesch et al.[271] concludes that the Smith et al. analysis disputes the role of asbestos in the etiology of kidney cancer, which is quite the opposite of the conclusions of the Smith et al. analysis. In a letter to the editor commenting on the Smith et al.[269] analysis, Enterline and Henderson[272] conclude that they feel the available data point to asbestos as a cause of human kidney cancer. In a continuing evaluation, through 1986, of the large North American insulators Seidman and Selikoff[273] reaffirmed that the original findings for the major causes of mortality continued, with about the same distributions, including those for kidney cancers. In New South Wales, asbestos was found to significantly increase the risk of kidney cancer (RR = 1.62, 95% CI: 1.04–2.53).[274] McDonald et al.[275] found elevated kidney cancers in workers having accumulated exposures of 300 mpcf years, but with no dose–response tendency. In looking at risk factors for renal cancer, in Denmark, a high number of cases were found related to asbestos exposure.[276] An international renal-cell cancer study found, when looking at occupation, that asbestos exposure resulted in an RR of 1.4.[277] A review of the case–control studies of asbestos exposure and renal cancers was negative, however, the authors concluded that the power of the studies were too limited, because of the low number of workers exposed and did report two of the case–control studies with elevated risks from Denmark and Australia.[278] Kidney cancers were increase, after 3 yr employment, among deck officers of merchant seamen potentially exposed to asbestos (OR 2.15, 95% CI: 1.14–4.08.[279]

6.1.11 Lymphomas

Multiple studies have reported lymphomas in persons exposed to asbestos. Lymphoma encompasses more than 40 related diseases that develop from lymphocytes.[280] The American Cancer Society projects that lymphomas account for about 5% of all cancers in the United States, the majority being non-Hodgkins lymphoma.

One study published in 2001, reviewing the epidemiological literature from 6 cohort studies and 16 case–control studies published through 1999 concluded that their combined analysis indicated a weakly increased risk from exposure to asbestos and that future epidemiology studies should concentrate on defining such risks.[281] Schwartz et al.[282] observed an association between chronic lymphocytic leukemia and asbestos exposure and concluded that because of the pattern of immunologic abnormalities occurring in asbestos-exposed persons that their observation deserves further study.

6.1.12 Systemic Carcinogen

Because of the multiple sites of cancer seen in various epidemiology studies of asbestos-exposed persons and in some incidences occurring with a lack of statistical significance have suggested the possibility of asbestos acting as a systemic carcinogen in the etiology of these cancers. In other words, the asbestos itself may have other biological mechanism not directly affecting the site of the asbestos fibers final disposition possibly involving the immune system and overriding existing defense mechanisms. This has been suggested because of the observance of leucopenia in the peripheral blood of asbestos miners[283] as well as effects on the immune system of asbestos workers observed by both Turner-Warwick and Parkes,[284] Lange and Skibinski,[285] Lange et al.,[286] Lange,[287,288] and Lange et al.[289] Goldsmith[290] presents evidence to support such a theory as he analyzed evidence from 11 different cohorts of asbestos-exposed persons. Reviews of effects on the immune system also support such a theory.[291–293] Systemic immunity appears to be most in effect immediately after asbestos exposures and then tends to lag behind those of the local immunity during the later depressive effects of the asbestos fibers and also tend to exhibit a dose-dependent initial enhancement.[294] Such findings may have even further importance as they may help determine the identity of biomarkers. One such finding to support this concept is the systemic changes in the levels of CC16, a pneumoprotein, found in both smoking and nonsmoking asbestos-exposed persons.[295]

6.2 PRODUCT USAGE AND DISEASE

Products containing asbestos have been found in the shipyard industry, the construction industry, the brake repair and transportation industry, the electronic and electrical industries, the paint industry, the optical goods industry, the plumbing industry, and other general industry manufacturing sectors.[296–298] Hundreds of buildings were reported to contain "asbestic" (asbestos) in New York as early as 1897.[1] Exposures in the construction industry, in New York, varied as shown in the study by Reitze et al.,[299] when they measured fiber counts from spraying asbestos onto buildings. They found 70 fibers/ml 10 ft. from the nozzle of the spray gun and at 25 ft. from the nozzle, 3 fibers/ml. This indicates that not only were the spray operators at risk of exposure, but also the auxiliary workers such as carpenters, pipefitters, welders, electricians, plumbers, etc.[299]

Diseases occur in nonoccupational exposed persons living near industrial sources of asbestos, familial exposures to asbestos when the worker brought home asbestos-containing material from the worksite, or when the worker did not shower or wore the same clothes home that had been worn during the work process.[180,300–304] Also domestic exposures have been associated with household repairs, and do-it-yourself construction, using products containing asbestos or when disturbing products containing asbestos.[305] Pets, of owners, with asbestos-related occupations or hobbies that expose them to asbestos-containing materials have lead to their pets developing mesothelioma.[306]

In the first radiological description of asbestos-induced fibrosis, one of the cases reported was in a marine fireman.[307] The disease asbestosis was causally linked with end-product usage, by the United States Public Health Service, as early as 1932, when a maintenance employee, cleaning and restoring asbestos insulation on pipes, in a government run hospital, developed the disease. A workers' compensation claim was even awarded, in this case, without any medical challenge.[78] Concerns were raised by the British Government of the health risks from the sawing, grinding, and turning in the dry state of materials partly or wholly composed of asbestos. Examples included such products as motor car brakes and clutches, electric conductors, and packing and jointing materials thus demonstrating the ability of asbestos exposures from doing jobs outside the manufacturing sector.[308] Asbestos use and disease in the railroad industry was reported by the American Railway Association's Medical and Surgical Section and the term asbestosis was specifically referred to in 1935.[309,310] Ellman[311] discussed the same case as reported by Russell[78] and other cases from asbestos insulation used on lead pipes. Specific examples of other asbestos end-product uses, by worker category, can be found within the sections on worker exposures by trade. As a result of these reports, the American Medical Association (AMA) Council on Occupational Health published in *the Archives of Environmental Health*, in August 1963, a whole thesis titled "The Pneumoconioses," in which asbestosis was discussed. The intent of this document was to alert physicians throughout the country to the hazards of dust exposures and disease and how to recognize and treat them. The report was reprinted by the AMA and circulated widely.[312] By 1964 close to 50 medical articles were published, the majority in English, describing some 150+ cases of noncancerous lung disease (asbestosis) among end-product users of asbestos-containing products. Many of these products were used in construction of buildings and, as with any building, through periodic maintenance the asbestos was disturbed and released.

Cancer was first reported in end-product when lung cancer was reported in insulators by Holleb and Angrist.[313] Then mesothelioma was reported in a 37-yr-old Swedish insulator by Mallory et al.[314] Reports continued and further examples can be found in the specific section on worker exposures by trade. Mesotheliomas have also been observed in pets. In one study of 18 dogs diagnosed with mesothelioma, the owners for 16 were identified and 12 were able to identify possible sources of asbestos exposure. Nine of the dog's owners had asbestos-related occupations or hobbies, five had remodeled their homes, five had residential proximity

to an industrial source of asbestos, and five used flea powders known to contain asbestos-contaminated talc.[306]

Other cancers were also appearing in the scientific literature when Selikoff et al.[210] reported stomach cancer, colon cancer, rectal cancers, as well as lung cancers, pleural and peritoneal mesotheliomas in insulators. In October 1964, a watershed event occurred that brought broader international attention to the hazards of work with asbestos and to products containing asbestos, when the New York Academy of Sciences held a conference on the "Biological Effects of Asbestos" with presentations by over 80 of the World's leading researchers on asbestos. This conference was widely covered by the news media and the proceedings were published in 1965 in a 766-page annals.[315] While this conference reported on the known health effects exposure to asbestos (asbestosis and cancers), a major theme was the emphasis placed on the areas of prevention, including dust control techniques, community and other indirect exposures, and the significance of air pollution control.

6.2.1 Other Diseases Reported in Asbestos-Exposed Workers

Other diseases have been reported among persons exposed to asbestos include: oropharyngeal cancer,[316] multiple primary cancer,[317] suicides,[318,319] ovarian cancer,[320–322] renal cancer,[268,323] penile cancer,[324] bladder cancer,[325] breast cancer,[326] and leukemia, multiple myeloma, and Waldenstrom's Macroglobulinemia,[320,327–329] prostate cancer.[127] Whether these diseases are causally associated with exposures to asbestos have not necessarily been established using epidemiology or causal criteria established to determine causation. At the time of the writing of this chapter these are clearly associations only and should not be deemed as established, however, as research on asbestos continues these diseases may or may not be determined as causally associated with asbestos exposures.

6.3 OCCUPATIONAL REGULATIONS FOR ASBESTOS

6.3.1 Dust and Dust Control

The term dust, as described by Cox in 1857 is, "solid mechanical impurities floating in a minute sate of division" . . . "impalpable power." An International Conference of Experts, when defining pneumoconiosis, defined "The term 'dust' as particulate matter in the solid phase but excluding living organisms."[330] The measurement of dust is usually expressed in microns (μm). For example, one inch is about 25,000 μm, the human hair about 100 μm, cement dust 2–100 μm, bacteria 0.2–15 μm, and tobacco smoke 0.01–0.5 μm.[331] Dusts are found in every part of the world, most not being noxious while a few are toxic. The body defenses protect us from most of these and the body may inhale more of these dust particles in just a few seconds or minutes, like those of asbestos, even when the dust cannot

be seen. In other words, asbestos-containing dusts can be an invisible hazard, and hazardous levels may be present even in the absence of visible dust. Support for this opinion dates back to many years. Dr. M. E. A. Merewether in his scientific publication "Dusts and the Lungs with Particular Reference to Silicosis and Asbestosis" in *Industrial Medicine*, Symposium No. 3, in 1938 states: "The majority of the particles, however, which get into and stay in the lungs are much smaller in each case — up to 5 microns in the case of silica dust and up to about 50 microns in the case of asbestos. That is to say that, the dust particles which are invisible to the naked eye are the important ones: this leads us to the practical point that if silica or an asbestos process produces visible dust in the air, then the invisible dust is certainly in dangerous concentrations." — An industrial hygienist, Cook,[332] Director, Division of Industrial Hygiene and Engineering Research Zurick General Accident and Liability Insurance Company, Ltd., Chicago, stated that: "In the case of the asbestos dust condition, our evaluation of the exposure should be based on the knowledge that the present toxic limit for asbestos is five million particles of dust per cubic foot of air. This is a very small concentration, so small in fact that the condition may look good even to a critical eye and still present an exposure greater than this low limit." While these statements are based upon the judgment of both Dr. Merewether and Mr. Cook, the visibility of dust has been quantified by Hemeon,[333] Engineering Director, Industrial Hygiene Foundation of America, Inc., of the Mellon Institute of Pittsburgh, PA, where he finds that in "Bright daylight 'north' illumination (i.e., interior but no direct sun) that the visible concentrations range from 10 to 20 million particles per cubic feet; at distances of less than 10 to 15 feet and in 'low-intensity daylight' 20–40 million particles per cubic feet."

It has long been known that suppression of dust was the best method to control diseases associated with exposures to dusts and was described by Ramazzini[334] and by Oliver.[335] In the United Kingdom, the Chief Inspector of Factories, in London, recommended to one factory, after having experienced five deaths due to phthisis (asthma-like disease), exhaust ventilation and annual medical examinations.[336] Merewether and Price[35] were among the very firsts to set forth very specific recommendations for dust suppression in the asbestos industry that included: (1) application of efficient localized exhaust ventilation at dust producing points; (2) substitution of enclosed mechanical methods for hand conveyance, and for dusty hand work generally; (3) effective enclosure of dust-producing machines; (4) substitution of wet methods instead of dry material handling; (5) elimination of certain dust-producing appliances; (6) abandonment of settling chambers in manufacturing processes, to the utmost extent; (7) effectual separation of processes to prevent unnecessary exposure to dust; (8) wide spacing of dust-producing machines in new factories and, as far as practicable, in existing works; (9) use of sacks of close texture material for internal work; (10) efficient cleaning systems with wide use of vacuum methods; (11) storage of asbestos and other goods outside workrooms; and (12) exclusion of young persons from specially dusty work.

Safety Engineering magazine ran an article in 1931 on "The Very Least an Employer Should Know about Dust and Fume Diseases" warning that dust including asbestos could be seriously harmful and that controlling the dust was necessary.[337]

McPheeters[89] suggested engineering dust controls methods for the prevention of asbestosis. Many others have also given methods for preventive actions from hazardous dusts, including the classic work of the United States Public Health Service.[91,338] For asbestos disease control Lanza et al.[88] also described the serious hazard faced by the industry with dust and recommended studies on its control as related to disease prevention. However, not much attention was given to hygiene, in the early history of exposure to asbestos.[339]

The National Cancer Institute's pioneer cancer researcher Hueper, as early as 1942, in his historic book *Occupational Tumors and Allied Diseases* recommended controlling asbestos by methods of wetting, closed production, ventilation, or other engineering controls, as well as personnel protective devices.[6] Fleischer et al.[340] expanded this advise and gave even more extensive guidance for dust control to end-product users of asbestos-containing materials, when in their study of the construction of naval vessels, recommended wetting the material; exhausting the dust where possible; employing respirator usage by the workers; isolating dusty operations in order to protect other workers not directly working with asbestos; and providing room ventilation. Fleischer et al.[340] concluded that "There are no established figures for permissible or safe dustiness in pipe covering operations." They also describe that "During the handling, unwrapping and unrolling of the asbestos [material], considerable dust arises, but appears to settle readily. A very fine water spray should be used for wetting down the material as a high velocity spray stirs up dust." Pertaining to the use of saws, used to cut the end-product, Flesher et al. recommend that "... the band saw should be enclosed in a room by itself and should be equipped with adequate local exhaust ventilation both above and below the saw table." Further, Flesher et al. point out those end-product users such as "... asbestos pipe covering differs markedly from the asbestos textile industry where dust concentrations for an operation do not fluctuate widely and where a worker will usually remain at a specific job for some years." Finally, the Fleischer et al. recommendations were some of the most extensive ever made and were published in a prominent professional journal of that time.

6.3.2 Asbestosis and Cancers below Guidance Limits

Since 1935, several studies have shown asbestosis occurring in workers at concentrations below 5 mppcf.[87,91,340–344] Today the quest for a safe exposure concentrations is still ongoing and with unsettled answers. The only tools with which to make such assessments are confined to either exposure concentration analysis or tissue burden analysis. First, asbestos measurement techniques have evolved with time and make it difficult to compare one another. Second, because of the differences in biopersistence of fibers and their clearance from the lung such analysis also presents problems. Third, the presence of asbestos bodies is sometimes used as a surrogate for exposure analysis. When exposure data have existed and have been used to determine the risk of disease such determinations have been based on a calculation of fiber-years of exposure (fibers/cm^3 $\times$ years of exposure). Such

calculations have led to few conclusions as have lung-burden studies and analysis of asbestos-body counts. Pleural plaques have also been used as an indicator of exposure (see Section 6.1.3).

Fiber-year analysis has resulted in the estimation that, for lung cancer, the RR is increased from 0.5 to 4% for each fiber-year, indicating at 25 fiber-years a twofold risk for lung cancer exists.[105] Epidemiology findings have observed cumulative exposure in fiber-years below 25 fiber-years that support even lower cumulative exposures resulting in elevated SMRs for lung cancer: at 2.7–6.8 fiber-years the SMR = 2.1 (95% CI: 1.1–3.8); at 6.8–27.4 fiber-years the SMR = 1.8 (95% CI: 1.0–3.35).[345] A study of 297 Hungarian lung cancer patients reported 63% with no exposure to asbestos and 30% with <25 f-years but only 5.5% with >25 f-years.[140] For lung fibrosis the ORs at <0.1 fiber-years was 1.0 while between 0.1 and 5.0 it increased to 2.5 and at 5.1–25.0 fiber-years to 3.8 and over 25 fiber-years to 24.9. Analysis of fiber concentrations measured at the Uralasbesto Company Mine in Russian find background levels in the quarries around 0.08 fibers/cm^3 (range 0.01–0.27) which is similar to that found in both Zimbabwe and Indian chrysotile mining and also that because chrysotile ore is not very dusty it takes much effort to create fiber levels above 1 fibers/cm^3.[346] These findings bring into question the fiber concentrations stated for the Canadian cohort studies of Canadian miners and millers which may well be overestimated. This may also explain the differences between the Canadian studies and those of the textile mill studied by Dement. When lung burden data were included in the analysis, the ORs increase to 2.5 for 0.1–5.0 cumulative fiber-years exposure; 13.3 at 5.1–25.0 fiber-years and 46.2 at greater than 25.0 fiber-years.[345] Since chrysotile fibers clear from the lung rapidly compared with the amphibole forms of asbestos lung-burden studies, for the determination of causation, may not be reliable.[347–349] Asbestos-bodies can be misleading as chrysotile exposure tends to result in low or no asbestos-body production compared with the amphiboles.[346] Rodelsperger et al.[350] reports mesothelioma as having a distinct dose–response relationship at levels of exposure below 1 fiber-year. As a result of both animal and human studies, the identification of a safe concentration below which disease will not occur, especially for mesothelioma, has eluded researchers.[346,351–353] While there is no doubt, according to Valic,[354] that all forms of asbestos can cause lung cancer and mesothelioma, he suggests that "The practical application of unit risks of such uncertainty lead to unachievable exposure limits." In addition, Valic projects that "It cannot be predicted with any degree of certainty what will the consequences of the current, incomparably lower exposure levels be in the future. Yet, there is no doubt that it is advisable to replace any potential carcinogenic material whenever possible."

6.3.3 Effectiveness of Guidance Concentrations in Preventing Disease

Commenting on the effectiveness of such a guidance concentrations S.A. Roach of the University of London stated that "... 5 million particles per cu. ft., are simply

standards, although I hope I did not use the word 'safe.' These are standards which are actually used, although they are not ever expressed as being safe standards." Roach further went on to state that even if this was dropped to 2 million particles per cu. ft. this would not necessarily be a "perfectly safe level of dust."[355] It is interesting to note that a worker would not be able to see this concentration of dust in the ambient air and would not see any dust until a concentration of between 20 and 40 mppcf was reached.[333] Warren Cook in 1942 said "This [5 mppcf] is a very small concentration, so small in fact that the condition may look good even to a critical eye and still present an exposure greater than this low limit."[352] The 5 mppcf guidance concentration remained in effect until the 1960s.[356] Cooper[357] states the 5 mppcf recommendation for protection, from asbestos exposure, proposed by the ACGIH since 1946, rests on shakier evidence compared with other such recommendations.

6.3.4 Asbestos Counting and Fiber Size Implications

The British adopted a new counting method for fibers and instead of a concentration based on total dust particles actual fibers were counted if they met the criteria of greater than 5 μm in length and had an aspect ratio of 3:1 or greater.[358] Because this method became the choice for regulatory purposes using the phase-contrast microscopic (PCM) method, which counted only fibers greater than 5 μm in length, epidemiology studies that had compared dose within their cohorts and had relied on the total dust count before the PCM method came along now had to develop a way to compare the earlier doses of total dust to the new fiber counting method. One such comparison was developed by Ayer et al.[359] in which they estimated that 1 mppcf was roughly equal to 6 fibers/cm^3. Because only fibers longer than 5 μm in length are counted and only those impacted on a membrane filter other variables needed to be evaluated that might affect the airborne fiber counts. Peck and Serocki,[360] at the OSHA laboratory in Salt Lake City, Utah, reported a source of random error[‖] in the P&CAM-239 method, due to the presence of electrostatic charges generated within the plastic filter cassettes used. This OSHA laboratory finding indicated that their finding could result in sampling errors from nondetectable up to seven times those actually reported and thus result in airborne asbestos measurements that could underestimate of fiber count. The authors suggest that if antistatic spray is used on the cassette surface, this effect may be neutralized. However, the implications of this could indicate any samples taken prior to 1985, using this membrane method and without correcting for the static effect, may well have underestimated the actual exposures to fibers.

[‖]Random samples are difficult to control while systematic errors, that is, pump flow rate fluctuations, nonrandom fiber distribution on the filter membrane, counter proficiency, microscope differences, air leakage between filter membrane and cassette, fiber loss during fiber concentration, or collection of samples using high flow or volume pumps, can be controlled for through established standard procedures.

6.3.5 Short Fiber Toxicity

To assume that shorter fibers do not cause disease is not scientifically justified from the epidemiology or the toxicology studies. Unfortunately, the role of short asbestos fibers has been mostly ignored. What studies that have been done such as Stanton and Wrench[361] and Stanton et al.[362] found that the longer, thinner fibers were more carcinogenic, but could not identify a precise fiber length that did not demonstrate biological activity. In fact, Dr. Stanton has never said long fibers are bad and short fibers are good and appreciated that a large number of short fibers, individually of low tumorogenic probability might be more hazardous than fewer long fibers, individually of high probability.[363] It has been shown that it is not just the size and shape of the various asbestos fibers that are important, in the fiber's ability to produce disease, but other factors may also play a role in the carcinogenicity of the mineral fiber.[364,365]

Dement and Wallingford[366] found that in typical occupational environments fibers shorter than 5 μm outnumber the longer fibers by a factor of 10 or more. Studies looking at human tissues have also found that the majority of asbestos fibers in mesothelial tissues were shorter than 5 μm in length, thus indicating the ability of the shorter fibers to reach the tumor site, remain there, and therefore their role in the etiology of disease is implicated.[189,348] Shorter fibers must be studied in more depth and short fibers should not be disregarded especially when clearance is retarded.[367] That chrysotile fibers tend to spit longitudinally and partially dissolve, resulting in shorter fibers within the lung, was reported in a review of several articles.[368] Additionally, Fubini[369] (2001) argues that, because all asbestos appear nearly equally potent, length and fiber form do not appear influential on the outcome of disease. Fubini makes this conclusion based on the work of Boffetta[370] which concludes that the specific type of asbestos is not correlated with lung cancer risk but that industry-specific exposure appears to fit the linear slope best, a finding also supported by Dement and Brown.[368] For mesothelioma, induction was related to the time since first exposure and potency with both industry type and asbestos type.[370] Though longer fibers tend to be retained in the human lung parenchyma, those found in the pleural tissues show a predominance of shorter fibers, mostly chrysotile, with only 2% of the fibers in the pleural, longer than 8 μm in length compared with 15% in the lung parenchyma and mostly amphiboles.[371] These findings found no relationship between the fiber counts from the parenchyma of the lung with the parietal pleura. Fibers found from bronchoalveolar lavage (BAL) were shorter than those found from digestion studies of the lung parenchyma indicating the ability of the longer fibers to penetrate and stay within the alveolar tissue. The fibers found in the parietal pleura did not show uniform distribution though studies using radioactive particles have shown uniform distribution within the lung parenchyma appear more conducive in the development of lung cancers,[372] however, such a pattern within the parietal pleura has not been shown.

The fact that short fibers (<5 μm) have been shown to produce toxic effects in macrophages *in vitro* and to be fibrogenic and tumorigenic in animals *in vivo*,[373] and that they reach the site of mesothelioma development[189,348,374]

support the inappropriateness of discounting their role in asbestos-related diseases as has been done by the EPA contractors Berman and Crump in their risk assessment index.[375] The data, to date, strengthen the role of short fibers in the etiology of asbestos-related diseases. There remains a need to change the analytical methodology to include short fibers and a reevaluation of the current OSHA standard to include short fibers in addition to those greater than 5 μm in length.

6.3.6 Guidance Limits and Regulations for Worker Exposures to Asbestos in the United States

"No industry can proceed at full speed unless its individual human units have a fair degree of the personal (physical and mental) health so vital to the quantity, quality, and continuity of production. One skilled worker absent because of preventable illness can greatly disturb the smooth functioning of the production line and cause losses out of all proportion to expectation, because of the disruption of teamwork."[376] The first regulations were jointly prepared by the British government and the industry being regulated.[377] "The idea of adopting standards of permissible dustiness for each harmful dust has a mediolegal appeal that is not at all justified by the data available today."[378] The United States Public Health Service introduced guidance limit of 5 mppcf, as a guide for the control of asbestos dust even though they found three cases of asbestosis below this recommended guidance.[91] Fulton et al.[87] reported 2 of 20 workers exposed to an average asbestos dust concentration of 4.64 mppcf for greater than 5 yr to have both clinical and radiographic evidence of asbestosis. This recommended guidance concentration for exposure to asbestos of 5 mppcf was later adopted by the newly organized American Conference of Governmental Industrial Hygienists (ACGIH) in the United States.[379] In 1952, the U.S. Government set standards for workers including a specific asbestos standard for contractors performing Federal Supply Contracts under the Walsh-Healey Public Contracts Act of 5 mppcf.[380] Also, in 1960 the U.S. DOL set standards for employers under the Longshoremen's Act for asbestos of 5 mppcf.[356]

In 1968, the ACGIH proposed a new guidance limit of 12 fibers/ml or 2 mppcf.[381] Then the U.S. DOL adopted a new standard for asbestos of 12 fibers/ml or 2 mppcf under the Walsh-Healey Act.[382] The ACGIH recommended a change in their guidance limit of 5 fibers/ml for asbestos in April 1971.[383]

A major event occurred on April 28 when the Occupational Safety and Health Act of 1970 became effective.[384] The very next month the OSHA adopted the ACGIH recommendation of 12 fibers/ml or 2 mppcf as a legal standard under the provisions of the new OSHAct for adopting existing consensus recommendations, on a one-time basis, as initial start-up standards, after which they would develop their own official standards using the OSHAct promulgation procedures.[385] Then on November 17, the newly created National Institute for Occupational Safety and Health (NIOSH) Director Dr. Marcus Key sent a letter to OSHA recommended a reduction of the current OSHA asbestos standard from 12 to 5 fibers/cm^3.[386] In response to this, on December 7, OSHA set an emergency legal standard

of 5 fibers/ml[385] and following this, on January 12, OSHA issued an additional emergency standard covering the ship repairing, shipbuilding, shipbreaking, and longshoring industries. This emergency standard held the same requirements as the December 7, 1971 emergency legal standard.[387] At the same time OSHA proposed to modify their existing 12 fiber/cm^3 or 2 mppcf standard to 5 fibers/cm^3.[387]

On February 25, NIOSH sent OSHA its first criteria document on asbestos recommending that OSHA promulgate a standard for asbestos of 2 fibers/cm^3 based on a count of fibers greater than 5 μm in length and an aspect ratio (length to width) of 3:1.[386] Following this, on June 7, OSHA promulgated a new standard (permissible exposure limit — PEL) for asbestos of 5 fibers/cm^3,[¶] intended to prevent asbestosis and that would provide some degree of protection against asbestos-induced cancers and that in July 1976 this standard would be lowered to 2 fibers/cm^3.[387]

In October 1975, OSHA proposed to revise its asbestos standard to 0.5 fibers/cm^3 and to designate asbestos as a carcinogen.[388] In December, NIOSH sent to OSHA a revised recommended asbestos standard recommended OSHA promulgate a new standard for asbestos of 0.1 fibers/cm^3 based on its carcinogenicity and the available technology of the phase-contrast microscope to only measure fibers accurately down to this concentration. NIOSH stated that this recommendation was intended to (1) protect against the noncarcinogenic effects of asbestos and to (2) materially reduce the risk of asbestos-induced cancer and that only a ban on asbestos could assure protection against the carcinogenic effects of asbestos.[389]

In April 1980, the NIOSH/OSHA Working Group on Asbestos recommended that there is no safe level of exposure to asbestos and discussed the inadequacy or the current OSHA standard of 2 fibers/cm^3 thus recommending an immediate reduction to 0.1 fibers/cm^3.[390] On November 4, 1983, OSHA publishes Emergency Temporary Standard (ETS) for Asbestos of 0.05 fibers/cm^3 [Sic].[391] The following year on March 7, the OSHA ETS for asbestos was invalidated by the U.S. Circuit Court of Appeals for the Fifth Circuit.

Following this invalidation on June 20, 1986, OSHA issued two revised standards for asbestos, one for general industry and a second for the construction industry,[#] at 0.2 fibers/cm^3.[@392] Two years later, on September 14, 1992, OSHA adds a

[‖]The standard also included a 10 fibers/cm^3 15-min ceiling; required engineering controls to meet the standard along with specific work practices; established a respirator program when engineering controls did not work; required a protective clothing requirement when exposures were above the PEL; required notification of employees if their exposures exceeded the PEL; warning signs required to be displayed in areas when the PEL might be exceeded; and caution labels must be affixed to materials containing asbestos.

[#]Construction standard requires a competent person to oversee compliance; all onsite employers must be informed of asbestos work and all employees with over 30 days must be included in a medical surveillance program.

[@]The standard also included an action level of 0.1 fibers/cm^3; the implementation of compliance programs must be established; engineering controls required to meet a level of 0.5 fibers/cm^3; spraying of asbestos banned; monitoring required every 6 months; respirator program requires fit-testing and employees allowed to choose powered, air-purifying respirators; HEPA filters required for vacuuming along with wet methods to reduce dust; wastes required to be put in impermeable containers; and employee training program required.

30-min excursion limit of 1 fibers/cm^3.[393] In 1992, OSHA again revises this standard by deleting nonasbestiform, tremolite, anthophyllite, and actinolite.[394] This action was in direct contrast to the recommendations of NIOSH who indicated all fibrous asbestos material should be regulated whether or not they occurred just in the asbestiform asbestos minerals.[395] The current standard of asbestos was promulgated on August 10 setting the PEL at 0.1 fibers/cm^3,** the number recommended by NIOSH in 1976.[396]

6.3.7 Risk of Asbestos-Related Diseases from Exposure at the Current OSHA Standard

Asbestos-containing materials are regulated if they contain more than 1% asbestos.[397] Higher exposures to asbestos result in higher risks and lower exposures to asbestos result in lower risks of developing asbestos-related diseases. Humans breathe 12 cm^3 of air per day and at the current OSHA standard of 0.1 fibers/cm^3, this would equate to the inhalation of 1,200,000 fibers per day. The exposure–response relationship for lung cancer is linear.[398] At the current OSHA standard, the risk of death is 3.4 per 1000 at 0.1 fibers/cm^3.[392] A more recent study, discussed under the risk section for lung cancer, suggested the use of linear extrapolation from high-exposure levels may underestimate the risks at low doses.[399] Even at the current OSHA limit, it can be clearly seen that the risk for dying from cancer is not zero nor does it even approach it. Dement and Brown[368] reported statistically significant excess for lung cancer at exposures as low as less than 3 fiber/years. The WHO[230] stated that "[T]he human evidence has not demonstrated that there is a threshold exposure level for lung cancer or mesothelioma, below which exposure to asbestos dust would not be free of hazard to health." The International Programme for Chemical Safety (IPCS) has reiterated this position[351].

These conclusions continue to support what the industry representatives said in 1965 that the only safe level to prevent disease is zero and it also supports the finding that nonmalignant respiratory diseases need not be present before cancer of the lung or mesothelioma can develop. Addingley of the British Belting and Asbestos Ltd. industry stated, in 1965, that "We do not believe there is any safe limit. . . . Therefore, I would like it to be clearly understood that we do not accept four fibers per cc as a safe maximum limit in the asbestos industry."[400] At the same conference Wells of the American Asbestos industry, U.S. Rubber Co., said "Our own conclusion, as we began seeing what was happening in our own process, was that the only safe amount of asbestos dust exposure was zero and that the efforts in terms of achieving that lay basically in engineering, and, secondly, in education."[401] NIOSH, created with the passage of the Occupational Safety and Health Act of 1970, also concluded, in its early existence that for the complete elimination of the carcinogenic and preventable asbestos-related diseases that: ". . . (only a ban can assure protection

**Multiemployer work site requirements are specified.

against carcinogenic effects of asbestos) . . . .”[353] For the first time, the U.S. Government now concluded, as did industry representatives by 1965, that the elimination of all asbestos from the workplace was the only solution to the eradication of asbestos-induced cancer from the workplace.

Multiple studies and scientists have concluded that both asbestosis and lung cancer are independent diseases related with a dose–response from exposure to asbestos, and that cancer of the lung can and does occur in the absence of asbestosis.[119,120,123–125] Thus these conclusions support that any standard aimed at the prevention of asbestosis will not necessarily protect against the more longer term effects of asbestos exposure that result in cancers.

As discussed in the section on smoking and lung cancer there is a marked enhancement of the risk of lung cancer in workers exposed to asbestos who also smoke cigarettes.[129,174,402,403] Data from Hammond et al.[129] and Weiss[404] suggest cigarette smoking may also contribute to the risk of asbestosis. Smoking, however, has not been found to be associated with an increased risk of pleural or peritoneal mesothelioma, or cancers of the stomach, colon, and rectum, which occur with equal frequency among smoking and nonsmoking asbestos workers. OSHA attributes asbestos exposure with 79.4% of the lung cancer deaths among asbestos-exposed workers who smoke and 77.2% of lung cancer deaths among nonsmokers.[392] Most recently, Berry and Liddell[134] estimated the RR to be about three times higher, for lung cancer, in nonsmokers than smokers. This supports that nonsmoking asbestos workers face elevated risks of lung cancer.

6.4 FINDINGS SPECIFIC TO OCCUPATIONS

Specific occupations have been identified and some studied to better define their risk of asbestos-related diseases. Specific occupations do not need to be studied nor do epidemiological studies need to be preformed to show risk of disease before prevention actions are taken or causal connections concluded. To wait for epidemiology studies of each occupational group is not warranted but has been taken by many in the medico-legal profession as the only way to prove causation by occupation. Such misconceived thinking has been very harmful to the future prevention of asbestos-related diseases. This section will show what has been shown, what is known, and what job categories have been studied or in which asbestos-related diseases have been reported; it is not intended to stifle prevention of asbestos-related diseases which must proceed even in the absence of such studies or reports. Asbestos-related diseases do not occur to just those occupations that have been studied and to conclude such, until studies of each and every occupation or job categories are conducted or from which cases are reported, is to ignore the established fact that it is exposure to asbestos, not the occupation or the specific job that is responsible for asbestos-related diseases. Physicians, however, can further help clarify specific occupations and jobs where disease occurs by what Ramazzini suggested some 300 years ago in his classic works on *Diseases of Workers* “[T]here are many things that a doctor, on his first visit to a patient, ought to find out either from the patient or from

those present." For so runs the oracle of our inspired teacher: "when you come to a patient's house, you should ask him what sort of pains he has, what caused them, how many days he has been ill, whether the bowels are working and what sort of food he eats." So says Hippocrates in his work *Affections.* "I many venture to add one more question: What occupation does he follow?"[334]

The following occupations and jobs have been studied or have had reported cases of asbestos-related diseases.

6.4.1 Boilermakers (also see Section 6.4.3.12)

Breslow et al.[405] are one of the first to show that certain occupational groups, in conjunction with cigarette smoking, have higher lung cancer risks. When categorizing persons by occupational groupings they observed steamfitters, boilermakers, and asbestos workers, who worked in these occupational groups, experiencing ten lung cancers compared to one in controls. Mesothelioma has been reported in laagers, pipe fitters, and boilermakers.[406] Boilermakers made up 10.6% of the identified mesothelioma cases in the Australian mesothelioma registry between 1980 and 1985.[407] The prevalence ratio for pleural plaques greater than 4.0 for boilermakers and workers in high-exposure shops who smoked were found to have the highest prevalence of pleural plaques.[408] Canadian boilermakers exposed to both asbestos and welding fumes showed 20% with x-ray changes, 8% were circumscribed, and 9% with diffuse pleural thickening. The boilermakers with the longest service had more pulmonary function changes when compared with those working as welders. The authors say these findings are in support of and consistent with past studies which have shown boilermakers having and increase in mortality from lung cancers, x-ray changes, and asbestosis.[409] Studies among pattern makers in the Italian auto industry found three cases of colon cancer among pipefitters and boilermakers when only one was found in the control population for an OR of 10.7 (95% CI: 1.07–103).[227] Members of the Michigan Boilermakers Union were studied and it was found that interstitial fibrosis and pleural plaques were related to 10 or more years in the trade with 25% showing at least a 1/0 profusion and 30% with bilateral pleural abnormalities.[410] Boilermakers in the petro-refinery industry were show to have an excess of mesothelioma.[411]

6.4.2 Bakers

Eight malignant pleural mesotheliomas were reported among bakers and pastry cooks in the Rome and Orbassano/Turin Italy area, none of which had radiological evidence of asbestosis. Three cases were among sisters, suggesting a possible genetic role in their etiology. The other four had no familial connections. It has been found that asbestos was used in and around the ovens and other asbestos-containing products the 1980s and up though the 1990s.[412] Five additional cases of pleural mesothelioma were reported in Italy among bakery workers, however, two of which may have had other exposures in addition to their bakery work.[413]

6.4.3 Brake Repair and Instillation Workers

Mesothelioma has been reported among brake mechanics, their wives, and children.[180,182,296,414–417] Huncharek et al.[418] describes a 47-yr-old lifetime nonsmoking man whose only known exposure to asbestos occurred while he was a brake mechanic from age 30 to 41, giving him a latency of 17 yr. Langer and McCaughey[415] reported only chrysotile fibrils in the lung parenchyma tissue of a 55-yr-old brake repair worker of which 10% were longer than 10 μm. They further describe that "... besides this submicroscopic chrysotile fiber in brake drum housing there is a more significant source of free, unaltered fiber in the bevelling, refurbishing, and refitting of brake pads. There is thus ample opportunity, during brake maintenance and repair, for contact with chrysotile fibre both in drum debris (where it will usually be in a transformed state) and as long and predominantly unaltered fibres liberated by machining."[419] Langer and McCaughey also reported that pathological diagnosis of asbestos-related diseases in people exposed to chrysotile is complicated because asbestos-bodies do not form readily. Vianna and Polan[420] reported three mesotheliomas in women having exposure to brake linings. Godwin and Jagatic[421] reported two cases of mesothelioma, one in a 43-year-old man who had spent 3 years weaving brake lining made of chrysotile asbestos and the second in a 50-year-old man who worked 5 years in a Canadian asbestos mine who gave x-ray diffraction evidence of only chrysotile present in his body.

Epidemiological studies have been equivocal. For example, Rushton et al.[422] concluded that their study, while negative, suffered from small numbers of men and that follow-up time would be required to determine any definite causal mortality patterns. Teta et al.[423] reported an RR of 0.65 for automobile repair and related service when they observed six of their 220 cases found in the Connecticut Tumor Registry from 1955 to 1977. They concluded that difficulties in ascertaining occupational histories, in their study population, indicated a better need for record keeping and that lack of detailed information regarding the residual cases may obscure the true number of occupationally exposed cases.[423] Robinson et al.[319] found among the deaths observed in a textile or friction production plant 17 deaths were the result of mesotheliomas, representing 4.3% of the deaths.

Rodelsperger et al.[424] reported that approximately 300,000 mechanics in the automotive service stations, in Germany, are exposed to asbestos. In their clinic, they have observed four cases of mesothelioma. The observation of four mesotheliomas, from one clinic, is clearly not reprehensive of the overall incidence of mesothelioma among brake mechanics in Germany. Wong[425] reports that the three cases (actually four) observed by Rodelsperger et al.[424] are not over the background rate. Given there might exist a background level of mesothelioma occurring in the absence of exposure to asbestos, even though there is no proof of this, "natural level" is probably much lower than the 1–2/million/year which has often been cited,[165] therefore three or four, out of some 300,000 auto repair workers, is clearly above that number. Jarvholm and Brisman[426] reported no excess of mesothelioma, but a slight increase in lung cancer, among car mechanics. In

their cancer linkage study, using Swedish census and death register data, they conclude that because other exposures cannot be ruled out that such a study methodology cannot answer the question concerning cancers among car mechanics. Hansen[427] reported increases in pleural mesothelioma in Danish auto mechanics. In their study of malignant mesothelioma, and relying on interviews of next of kin, they found a slight excess of mesothelioma among brake lining work or repair although not statistically. They found that 90% of the incidences of pleural mesothelioma, among men, were directly attributable to past exposures to asbestos. The authors conclude that next of kin interviews may have resulted in biased responses. Spirtas et al.[428] reports 33 cases of mesothelioma in persons having stated as part of their occupational history brake repair work. One of the confounding factors preventing Spirtas et al. from calculating an RR was that an overwhelming majority of those workers had also been exposed as insulators or shipbuilders.

In a study of mesothelioma among car mechanics in Germany, the authors found no evidence of an increased risk of mesothelioma, but concluded that if there is a mesothelioma risk and if it was small it would not be detected and that the absence of fibers in the lung tissue of one of the cases does not exclude the possibility that, decades before, chrysotile fibers were active at the target cells.[429] Teschke et al.[430] did not find an excess of mesothelioma among vehicle mechanics, but because their findings were based on small numbers, judgments about any causal associations would be speculative according to the authors. However, they did conclude that most of the mesotheliomas were explainable by exposure to asbestos.

In a dose–response study with low levels of asbestos exposure in a French-based case–control study, 82% of motor vehicle mechanics had frequent exposure. The authors found a clear dose–response relation between cumulative exposures and pleural mesothelioma and that a significant excess of the mesothelioma was observed at levels that were probably below the limits adopted in most industrial countries.[431] Henderson[432] reports that 58 mesotheliomas were reported among Australian brake mechanics having no other exposures to asbestos and that only a small fraction of the total 82,827 mechanics in Australia worked with brake blocks or brake linings. Thus he concludes that these 58 cases represent 1,062,946 person-years and that if one rounds off the total mechanics to 100,000 mechanics; this represents 45 mesotheliomas per million person-years and that if one doubles this number to 200,000 mechanics to include retirees and other workers who moved to other occupations then the mesothelioma rate becomes 22.6 per million person-years, a rate substantially above the upper limit of the estimated background rate of 1–2 mesotheliomas per million person-years or around a tenfold excess.

While the results of these reports and epidemiological studies are equivocal, they by no means exonerate the brake mechanic from being susceptible to a causal relationship between asbestos exposure and mesothelioma. The presence of asbestos and fiber concentrations found in this industry is further evidence of this risk (for a more detailed analysis, see McDonald et al.[433]).

6.4.3.1 Bricklayers and Masons

Brick masons were found to have statistically elevated cancer risks for lung cancer among male construction workers in North Carolina who resided and died in North Carolina during the period 1988–1994.[434] In a survey of unrecognized sources of asbestos exposure in British Columbia, the incident of mesothelioma in bricklayers resulted in an OR of 3.5 with a 95% CI of 0.9–14 and while not statistically significant the OR was elevated.[430] Swedish bricklayers had and overall SIR of 2.23 (95% CI: 1.34–3.49), when followed from 1961 to 1998.[156]

6.4.3.2 Carpenters

In a study which identified mesothelioma patients under the age of 50 exposed predominately to amosite, construction workers predominated with carpenters and three other job titles dominating among these young patients with mesothelioma.[435] In a proportionate mortality study of North Carolina, construction workers and carpenters were found to have an elevated risk of lung cancers.[434] In a study from the Connecticut Tumor Registry between 1955 and 1977 found an RR for carpenters and cabinetmakers of 2.25 with a p value of <0.05.[423] Mesothelioma was reported among carpenters in the Australian mesothelioma register.[436] In an update of mortality among Texaco refinery workers, found carpenters and other insulation related trades to have an SMR of 411.[411] In a study of 27,362 members of the Carpenters' Union who died in 1987–1990 found asbestosis to have a PMR[§§] of 283, 95% CI: 158–457, and a total of 121 mesotheliomas.[437] A survey of 631 asbestos-exposed construction carpenters found pleural plaques and interstitial fibrosis.[438] A survey of asbestos-related mortality in Northern Ireland between 1985 and 1994 found carpenters and joiners to have a PMR of 397 for pleural cancers (mesothelioma) that was statistically significant at the 5% level [lower limit (LL) = 245 and upper limit (UL) = 607] and for asbestosis of 628 also statistically significant [LL = 329 and UL = 1095].[439]

6.4.3.3 Custodial Workers, Laborers, and Maintenance Workers

Among the statistics from the Australian Mesothelioma between 1980 and 1985 laborers represented the greatest percentage of jobs with mesothelioma (14.8%).[407] Among 11,685 members of the Laborers' International Union of North America (LIUNA), who died between 1985 and 1988 found statistically significant elevated mortality risks for lung cancer ($N = 1208$, PCMR[‖‖] = 1.06, 95% CI: 1.00–1.12) and 20 mesothelioma deaths.[440] Anderson et al.[441] x-rayed 457 school maintenance and custodial workers and found conditions consistent with asbestos-induced diseases including pleural abnormalities which could not be explained to prior

[§§]PMR = number of cases/number of people in the population.
[‖‖]PCMR = proportional cancer mortality ratio.

work before that of their present occupation. Laborers, at the schools, with more than 20 yr of school employment had the highest prevalence of abnormalities.[441] Churg and Warnock[442] found asbestos bodies in the lungs of 21 patients in the general population, who had 300 to 9000 bodies/g, which the authors claim, is a concentration frequently found in manual laborers among the general population who were not primary asbestos workers and conclude that among laborers their risk was most likely occupational in nature, thus confirming that laborers are at risk of asbestos-related disease. Almost 660 custodians, employed by the New York City Board of Education, were examined between 1985 and 1987 for asbestos-related disease and 39% of those with 35 yr of employment had abnormal films. Eighty-four percent reported removing asbestos and 89% reported working in area where asbestos was present and abated.[443] In a study of male employees of one California school district, 13.3% of custodian were found to have asbestos-related disease and because these were related to parenchymal and pleural fibrosis it would indicated rather high exposures to these custodial workers.[444] Oliver et al. (1991) found pleural plaques greater than background as well as restrictive disease among 120 white male public school custodians in the Boston school district. Among the total group, the percent distribution of pleural plaques increase with latency for those having no other outside exposure to asbestos.[445] In a multicenter (Paris, Caen, and Lyon) cross-sectional study of 227 custodian and maintenance workers in buildings containing friable asbestos-containing material and with generally low exposures (82% had fewer the 5 fibers/ml yr) found pleural thickening, particularly circumscribed pleural thickening, significantly higher in the exposed group when compared with the control group of 87 nonexposed for latency from first exposure but not with duration of exposure. No significant differences were seen between the exposed and nonexposed groups. The authors concluded as there were no differences between profusion categories between the exposed and nonexposed group that the cumulative asbestos exposures were probably insufficient as suggested by Doll and Peto[322] which found such changes at 25 fibers/ml yr or higher.[446]

6.4.3.4 Decorators

One case of pleural mesothelioma was reported in a female decorator where crocidolite sprayed on asbestos as her only known exposure to asbestos.[447]

6.4.3.5 Electricians

In a survey of materials sprayed on the ceilings of 127 buildings throughout the United States asbestos was found in some 50% of the buildings. Chrysotile was the main fiber type identified. During renovation activities average fiber concentrations, at workers' breathing zones, were less than 2 fibers/cm^3, but exceeded 0.1 fibers/cm^3 and some workers were exposed to high concentrations averaging 16.4 fibers/cm^3 and electricians were included among the workers studied.[448]

Electricians had a twofold excess of mesotheliomas in a study of national population-based registries linking cancer incidence from 1961 to 1979 with 1960 census data on industry and occupation for all employed individuals in Sweden.[443] A cross-sectional epidemiological study of a small group of nonshipyard electricians found asbestosis in 15 and 25% for those with 20 yr of service.[450] In a survey of unrecognized sources of asbestos exposure in British Columbia, the incident mesothelioma in electricians resulted in an OR of 3.0 with a 95% CI of 0.08–12, although not statistically significant.[430] In a study which identified mesothelioma patients under the age of 50 exposed predominately, from lung burden analysis, to amosite, construction workers predominated with electricians and three other job titles dominating among these young patients with mesothelioma.[435] Swedish male electrical workers followed between 1961 and 1998 had an SIR for pleural mesothelioma of 1.92 (95% CI: 1.49–2.44).[156]

6.4.3.6 Jewelers

Jewelers have been exposed to asbestos through the use of asbestos powder and have been found to develop pleural plaques and pleural plaques with asbestosis as well as mesothelioma.[449,452] Dossing and Langer[453] report on four cases, among retired jewelers, two with pleural plaques and parenchymal changes, one with isolate pleural plaques, and one with only parenchymal infiltrates.

6.4.3.7 Mechanics

Pleural plaques were found in 41 of the mechanics but in none of the referents, however, no apparent impairment was detected among 925 car mechanics and 109 referents.[454] Because pleural plaques are an indicator of asbestos exposure, the risk of asbestos disease among auto mechanics is possible. In a study of low-level exposure to asbestos, among vehicle mechanics, the authors found slight small airway dysfunction and a dose–response relationship between asbestos exposure and closing volume, a finding not reported previously. The authors suggest that such exposure initially might cause involvement of both terminal and respiratory bronchiole which thereafter develops into a diffuse interstitial fibrosis.[455] Auto mechanics and plumbers had an increased rate of lung cancer in a case–control study of welders and exposure to asbestos.[456] In a survey of cancer by occupational groups, mechanics were among a group with the highest incidence of pleural cancers over a 20-yr period in Nordic Countries.[457] Mechanics had an increase in mesothelioma in the Australian mesothelioma registry data indicating an increase within the asbestos user industries.[436] In a survey of Hungarian workers exposed to asbestos with lung tumors, 72 patients (24%) of 297 had cumulative occupational asbestos exposures assessed as below 25 fiber years (between 0.01 and 23.9 fiber years). Among this group car and truck mechanics were identified.[140]

6.4.3.8 Merchant Seamen

Merchant seamen studies have been conducted of persons involved in the building, maintenance, and repair of seagoing vessels. The majority of these studies have shown an excess of asbestos-associated diseases, including asbestosis, lung cancer, and mesothelioma. Routine maintenance at sea can result in high exposures to asbestos when the fibers are disturbed and become airborne and are of repairable size, thus putting merchant seamen at an increased risk of developing asbestos-related diseases. In fact, the United States Maritime Commission studies found that long after the vessel had been at sea, that it was not unusual to find flaking and cracking of asbestos-containing materials due to the vibration and motion of the vessel at sea. Therefore, the hazards of asbestos exposures were not confined to the shipbuilders alone, but also to the vessel's crew.[458] In some studies, asbestos-induced lung changes were detected in the x-rays of over 40% of those studied. One study of radiological abnormalities among 3324 United States merchant marine seamen found the highest prevalence of asbestotic changes among those who served in the engine department (391/920; 42.5%), when compared with other departments (deck: 301/820; 36.6%; steward: 278/981; 28.4%) or multiple departments (167/541; 30.9%).[459] Further, Selikoff et al.[459] estimated that all vessels delivered before 1975 contained extensive asbestos-insulating material aboard and that most vessels delivered between 1975 and 1978 might have some asbestos in the form of insulating cement on machinery casings, even though most other uses of asbestos aboard ship had been reduced.

In 1918, the first report of radiological change among asbestos-exposed workers included those of a marine fireman.[40] Selikoff et al. further referenced reports of subsequent incidences of parenchymal fibrosis, pleural plaques, pseudo-tumors, lung cancer, and mesothelioma. In their study of marine engineers, Jones et al.[460] reported knowledge of mesothelioma in addition to asbestotic pleural changes. Greenberg[452] reports that seamen have experienced excess mortality from cancer for the past 100 yr and that in a preliminary mortality analysis of a small population of merchant seamen that two cases of malignant mesothelioma have been identified and that in the United Kingdom's National mesothelioma register 28 cases have been reported in seamen which represents a "markedly excessive" number.[461] Two mesotheliomas were reported among Greek merchant seamen, one in a marine engineer with 35 yr service and the other in a deck department seaman with 25 yr service.[462] A mortality study of Italian merchant seamen reported one mesothelioma and an excess of respiratory cancer (36 obs. vs. 19.8 exp.), drawing the authors to conclude that because of the observation of a mesothelioma that asbestos may have been responsible for the excess respiratory cancers.[463] A 79-yr-old man was found to have pleural plaques on x-ray, 6 yr before his lung cancer appeared. He had been a farmer; the majority of his life, having served on a battle cruiser for 1 yr during World War II, at age 26 as a boiler man, his only known exposures to asbestos. He was a 26-pack-yr smoker and had 3348 asbestos bodies per gram dry lung tissue.[464] In a case–control study of merchant seamen between 1960 and 1980, cancer of the lung increase with increased employment

and after 3 yr had an OR of 1.68 (95% CI: 1.17–2.41) for engine crews while deck officers did not. Deck officers on icebreakers did have an increased OR of 3.41 (95% CI: 1.23–9.49) after 20 or more years. The same study found that mesothelioma was increased to 9.75 (95% CI: 1.88–50.6) after 20 yr latency among engine room workers. Kidney cancers were increased after 3 yr employment as deck officers (OR 2.15; 95% CI: 1.14–4.08).[279] Swedish seamen from the Gothenburg area had an SIR of 7.43 (95% CI: 3.54–13.72) in 1960 and when followed through 1970 had an SIR of 4.27 (95% CI: 0.80–12.63). Overall, Swedish seamen had an SIR of 2.83 (95% CI: 1.41–5.09).[156] Cancer incidence among marine engineers was elevated in those followed between 1955 and 1998 for both lung cancer (SIR = 1.2, 95% CI: 1.0–1.5) and for stomach cancer (SIR = 1.3, 95% CI: 1.0–1.5). When smoking was controlled for, through questionnaires on a sample of the cohort (1501), the lung cancer risk was elevated (1.4, 95% CI: 1.2–1.8) as was the mesothelioma (SIR 4.8, 95% CI: 1.3–12.3) and urinary bladder cancer (SIR = 1.3, 95% CI: 1.0–1.8) after a 40-yr latency.[465]

6.4.3.9 Painters

At the Devonport Dockyard, 53 deaths from mesothelioma were observed in workers employed since 1966. Painters were found to have affected excessively.[154] Painters were found to have a mesothelioma SIR of 199 using union record to search tumor registries.[466] In a case–control study of New York painters, members of the International Brotherhood of Painters and Allied Trades (IBPAT), a 3.6-fold excess of lung cancer was identified. Painters using spackling compounds, known to have contained asbestos, had an estimated OR of 4.33 (95% CI: 1.40–13.96) when compared with cancer controls and an OR of 6.33 (95% CI: 2.04–19.68) compared with noncancer controls.[467]

6.4.3.10 Petro-chemical Workers

The United States Bureau of Mines published an information circular in November 1936 outlining "Some Problems of Respiratory Protection in the Petroleum Industry, with suggestions for their Solution."[468] In this information circular, they specifically mention the disease asbestosis caused by breathing the "fine particles" of asbestos. They further state that the dust need not be visible to be dangerous and that no one seems to be able to state with exactness the safe size and number of dust particles that may be in the air without causing harm. The information circular provides detailed measures to protect the workers from these "fine particles" and concludes by stating that the "forward-looking employer will take steps to become fully informed."

"Because it is the duty of industry to protect its employees and because no comprehensive survey of the hazards incident to occupational dust problems had yet been made, it was felt that here was an opportunity to render a service to the petroleum industry and its employees by making such a survey." These were the

words of Willard J. Denno, MD in the forward to the survey of Dust Producing Operations in the Production of Petroleum Products and Associated Activities sponsored by the Standard Oil Company (N.J.) in July 1937.[469] This survey is a report on the use of insulation within the petrochemical industry and discusses the hazards associated with the use of asbestos-containing insulation and outlines measures for reduction on the hazards. This survey reviews the medical literature to date and found that asbestos dust did not seem to be readily handled by the protective mechanism of the lungs. The author of the survey report, Bonsib, used much of the knowledge he gained from the 1937 survey to author *Safeguarding Petroleum Refineries and Their Workers* for the International Labour Office that was published in 1943.[470] This report discusses many hazards found in the petroleum refinery, one of which was asbestos and recommends preventive methods to protect workers from asbestos-related diseases.

In 1949, Standard Oil Company (N.J.) commenced a "Summary of the Plant Industrial Hygiene Problems" authored by Berry et al.[471] The report was marked *Company Confidential Not For Publication In Present Form.* The report discussed the extensive use of asbestos in the refinery and the problem with high concentrations of asbestos dust. The report also discusses asbestos and its relationship to fibrosis and cancer of the lungs and identifies various trades at risk, that is, brick masons and helpers, insulators, laborers, and pipe benders.

Between 1949 and 1957, an industry-wide effort was sponsored by the Medical Advisory Committee of the American Petroleum Institute to assess the possible skin cancer hazard to petroleum workers, however, this study was terminated on July 1, 1956, due primarily to the lack of cooperation within the industry itself. The report did however find that the proportion of tumors of the digestive system and peritoneum was much larger than that found in the United States as a whole.[472]

In 1960, two cases of primary malignant mesothelioma of the pleura were reported in a 57- and 58-yr-old refinery foremen.[473] Many additional studies since 1960 have discussed the hazards of asbestos in the petroleum refinery industry.[474–489] In a follow-up to a 1992 study of a Canadian petroleum company,[490] with the exception of mesothelioma, no clear excesses in work-related mortally was observed. For mesothelioma, no cases were observed in females and the risk for men increased overall to SMR 3.51; 95% CI: 2.25–5.22 and an SMR of 8.68; 95% CI: 5.51–13.03 was observed in the operating segments mainly among mechanical workers and pipefitters. Cancers of the large intestine, except the rectum, were higher than expected with a significant SMR of 1.98 (95% CI: 1.24–3.00) in the marine section of employment.[491] Satin et al.[492] in an update of two California petroleum refineries between 1950 and 1995 found no excess of mortality for any asbestos-related diseases. While the study consisted of a very large number of person-years at risk,[429,462] criticism has been levied, because of the strong healthy worker effect that the study suffered from dilution which may indicate a comparison bias concealing association.[493] For those asbestos-related diseases of long latency, the inclusion of workers employed after December 31, 1980, could also dilute the cohort and mask any causal associations. In addition, the authors should attempt

to segregate those with potential exposure to asbestos from those with no potential exposure.

An update of the mortality data from a refinery from Louisiana found three mesotheliomas but could not calculate an SMR for comparison with national data as the authors said because no mortality rates are available for mesothelioma. However, when the author compared this mortality to data from the SEER program, they calculated a nonstatistical excess SMR of 2.16 (95% CI: 0.44–6.30). As the expected mortality was calculated using SEER incidence rates, this may be misleading. This study had a total of 68,881 person-yr, from the 3579 men making up the cohort and when compared with the most recent mesothelioma mortality data from Louisiana, which reports 1.4 deaths occurring out of each 100,000 population, this study's expected mortality from mesothelioma may have been overestimated thus underestimating the SMR and its 95% CI.[494,495]

6.4.3.11 Plasterers and Drywall Workers

In a survey of men applying and finishing tape and spackle at the joints of wallboard, it was found that 60% of the personal samples exceed the recommended exposure limit of NIOSH of 2 fibers/cm^3 greater than 5 μm in length per milliliter and two thirds of the 69 workers with at least 10 yr exposure had x-ray abnormalities (37 of 63; 59%). The authors suggest that asbestos disease is an important hazard in this industry.[496] Among samples of consumer spackling and patching compounds, asbestos was found in 5 of 15 of the spackling and patching compounds and in all 10 of the drywall taping compounds. The asbestos fibers ranged from 0.25 to 8.0 μm and those shorter than 5 μm in length would only be found using electron microscopic and not the PCM method. Using PCM it was found that airborne concentrations of 5 fibers/ml of air were common and that they lingered in the air at high concentrations even after 15 min. Further it was found that for every visible fiber under the PCM there were 200 to 1000 which could be seen only with the electron microscope. These findings have further implications to their use in home repair than just to the worker, but also to the family members as the fibers stay airborne for long periods of time. According to the authors, none of the samples had warning labels.[305] Fischbein et al.[497] further confirmed the risk of asbestos-related disease among drywall construction workers. Residential and commercial drywall workers were found to have exposures to concentrations of asbestos dust as high as 12.4 fibers/cm^3 from dry joint compound; mixing of a paste premix produced 1.2–3.2 fibers/cm^3; and that when sanding the drywall the highest concentrations were encountered at 2.1–24.2 fibers/cm^3. Dry sweeping of the waste resulted in concentrations of 4–25.5 fibers/cm^3.[498] In a PMR study of unionized construction plasterers and cement masons, statistically significant elevated mortality occurred among plasterers for asbestosis (PMR 1657, $p < 0.01$) and lung cancer (PCMR 124, $p < 0.01$). In cement masons, stomach cancer was statistically significant (PCMR 133, $p < 0.01$).[499] In a study of asbestos exposures during dry wall abatement work, it was found that personal time-weighted average samples range from

0.12 to 3.16 fibers/cm^3 which were above the current OSHA PEL of 0.1 fibers/cm^3.[500] Lange and Thomulka (2000), with further study, concluded that when abatement workers are trained and follow OSHA as well as by the Pennsylvania Department of Labor and Industry requirements, on friable asbestos-containing materials, that exposures may be kept low and that likelihood of exceeding the OSHA standard was less than 5%.

6.4.3.12 Plumbers and Pipefitters

Among mesothelioma cases from the Connecticut Tumor Registry plumbers and pipefitters had an RR of 3.87 with a p value of <0.05.[423] Auto mechanics and plumbers had an increased rate of lung cancer in a case–control study of welders and exposure to asbestos.[454] A cross-sectional study found plumbers and pipefitters, having had asbestos exposure, especially in the plumbers, found excesses in x-ray abnormalities.[501] In a survey of unrecognized sources of asbestos exposure in British Columbia, the incident of mesothelioma in plumbers and pipefitters resulted in an OR of 8.3 with a 95% CI of 1.5–86.[430] In a study of x-ray and pulmonary function effects of asbestos-induced pleural thickening, 19% had parenchymal fibrosis and 29% had pleural thickening and those with pleural thickening had decrements in pulmonary function with the pleural abnormalities increasing with length of exposure.[502] Small airway disease was found among 701 Copenhagen plumbers in which 23 are never smokers, who had removed asbestos insulation and intermittently been exposed to high levels of asbestos for about 25 yr without being exposed to welding fume.[503] Bilateral pleural thickening was found in 28 (18.3%) of 153 plumbers and pipefitters employed in building construction.[504] In a study of 7121 members and retirees of the United Association of Plumbers and Pipefitters in California who died between 1960 and 1979, PMRs were elevated for lung cancers (PMR = 1.41) and 16 mesotheliomas were found.[505] The SIR for pleural mesothelioma was 4.56 (95% CI: 3.42–5.95) among Swedish male plumbers followed between 1961 and 1998.[156]

6.4.3.13 Power Plant Workers

Asbestos has been used in power-generating plants for thermal insulation of steam pipes and turbines. Asbestos is found in many electric conductors such as electrodes wrapped with asbestos-containing yarn; cable and wring may also contain asbestos insulation as does field-coil wrapping used on electrical machinery.[35] Laggers (pipefitters) striping asbestos off steam pipes, which were generating clouds of dust containing asbestos were found to have pneumoconiosis.[506] Mesothelioma was reported in two refinery workers, indicating that this asbestos-related disease was not confined just to those mining or manufacturing asbestos-containing products, but also from the uses of such insulation materials containing asbestos.[473] As warned by Bonsib,[469] the use of asbestos outside of the manufacturing process could pose a problem, as reported by Eisenstadt and Wilson.[473] In 1963, another article in the

literature warned that controls for asbestos must be expanded beyond the mining and manufacturing industries to others including power stations.[336]

Fontaine and Trayer[507] noted that the Tennessee Valley Association (TVA) had been engaged in asbestos control for about 30 yr (i.e., 1945) and reported levels of asbestos, even when using controls, to reach 4.7 fibers/cm^3 and not only controls were to be used but training was a key factor in the control of asbestos. Other studies have validated the existence of asbestos use within the electric power-generating industry.[508–510] In general, the asbestos fibers counts have been low except in the areas where mixing of asbestos for insulation occurs and evidence of ferruginous bodies have been found in the sputum of workers in power plants.[511] In 1975, at the 18th International Conference on Occupational Health in Brighton England, which I attended, a paper by Dr. J. Bonnell was presented on insulation workers (laggers) from British power plants ain which eight mesotheliomas were discussed and stated that in 1949 a case of asbestosis was reported in a lagger employed at a power plant for 13 yr. He indicated that these cases of asbestos-related diseases presented in his paper were not indicative of the measure of the prevalence or the incidence of the diseases because many of the cases were only diagnosed after retirement.[512] Cammarano et al.[513] found excess mortality in an Italian thermoelectric power plant, where asbestos mainly amosite was used as an insulating material on the turbines, boilers, and pipes and where workers were exposed during periodic removal for maintenance, from cancers associated with asbestos such as lung, larynx, stomach, and colon. Forastiere et al.[514] also reported an excess of cancer in Italian thermoelectric power plants. Their excess was among maintenance workers from respiratory cancer suggesting past exposure to known respiratory carcinogens including asbestos.

Two cases of mesothelioma have been described, in detail, in a clerk and an insulator at an electric power-generating plant in Israel.[515] Another paper, from the IARC, reiterates that asbestos was used in electricity-generating plants and that it is carcinogenic.[516] Four mesotheliomas were reported among workers at three Italian power plants which were not confined to any particular work group in the plants. Additional three mesotheliomas were reported by physician records from Tuscany. The cases ranged in age from 46 to 60 and exposures ranged from 21 to 40, three of the cases were among maintenance workers, one case was an insulator, one case was handler of asbestos-containing products for insulation, one case was a cleaner, and the 7th case was a clerk.[517] In a study of active male workers of Electricite de France-Gaz de France, asbestosis was found and an OR calculated of 57.4 with a 95% CI of 17.0–194.0 in the highest exposure group. Pleural cancer had an OR of 4.8 with a 95% CI of 1.2–19.8 and lung cancers had significant ORs of 2.0 with a 95% CI of 1.3–3.2 and 1.9 with a 95% CI of 1.2–3.0 in the two highest exposure groups. The cell type most related to asbestos-exposed cases was squamous. The authors concluded that their study showed that occupational exposures to asbestos could increase the risk of pleural cancers in areas of the plant where exposures are not considered high as compared with other industrial settings.[485] Asbestos exposure accounted for significant excesses of lung and pleural cancers in men employed in Danish utility companies.[518] While a study of the geothermal

power plants at Larderello, Italy, reports no significant excess of mortality from asbestos-related cancers, two cases of mesothelioma were found among the less than 40% of the workforce with any exposure to asbestos. While one of the mesotheliomas occurred in a worker with prior asbestos exposure, before work at the power plant, the other did not and the overall mortality indicated a significant healthy worker effect and with the known use of asbestos-containing materials in the plant may have a more significant meaning than that concluded by the authors.[519] Three cases of fatal extrapulmonary neoplasm were reported among asbestos-exposed workers.[520]

6.4.3.14 Railroad Workers

The knowledge of the American Railway Association Medical and Surgical Section, pertaining to dust and asbestos exposures and disease, dates back to the 1930s. Their first entry entered is in 1932 and discusses dust as an industrial hazard which demands attention and causes pneumoconiosis, pathologically described as fibrosis of the lungs.[521] A discussion of the prevention of pneumoconiosis states the following prevention:

> Dust pathology of the lungs can be prevented in two ways, first, by the adequate and proper use of water to wet down the dust at the point of its origin; second, by forced ventilation to quickly remove the dust particles and replace this with clear air.

The next entry in 1933 also discusses ways to control dust.

> The subject of dust as an industrial hazard has been presented for consideration by the committee. The subject cannot be considered as inherently [as] a railroad problem; however, it may arise in connection with various lines of work [in the railroad industry], and when it does so, presents a problem which demands attention. . . . use of water to wet down the dust at the point of origin, or by forced ventilation to remove the dust particles. In the event that neither of these methods is practicable, respirators should be made available to employees [sic] who are required to work in the presence of the dust.

In 1935 when, at the 15th meeting of the Association of American Railroads Medical and Surgical Section, the term "asbestosis," the pneumoconiosis caused specifically from breathing asbestos fibers, was used.

> Pneumoconiosis (pneumon — lung; konis — dust) is a condition that may be caused by any kind of dust entering the lung; but we as railroad surgeons are undoubtedly more interested in silicosis and asbestosis than other types.
>
> . . . asbestosis is caused by breathing fine fibres of asbestos which consists of magnesium calcium silicate. Asbestosis is not a common condition but it causes extensive pulmonary fibrosis and takes on a more rapid course than does silicosis.

The minutes of Association of American Railroads Medical and Surgical Section continue to specifically recommend prevention methods, including education,

eliminating the dust, wetting down the dust, use of respirators, and analysis of the work air to ensure that the suppression of the dust is effective. These are specifically discussed for the years 1935, 1937, 1939, 1940, 1951, 1952, 1953, 1957, and 1958.[310,522–529]

Asbestos has been used in the railroad industry in a variety of ways, including insulation for railroad shops, wrapping around the boilers of locomotives, insulation in the driving cabins and carriages of locomotives, in asbestos cement ties, and for other heat-transfer protection.[530,531] Railroad workers at risk of exposure to asbestos include workers engaged in repair, demolition, technical control, maintenance (including machinists), handling waste materials, rail construction and maintenance; others include locomotive engineers, electricians, joiners, painters, laborers, brakeman, station maintenance, pipefitters, riggers, insulators, fitters, finishers, polishers, mechanics, and other ancillary workers in close proximity to workers directly exposed to asbestos. Numerous reports of asbestos-related diseases have been reported in railroad workers.[449,532–534] Reports on the announcement of the French railroad SNCF that 30 rail workers have died since 1988 from asbestos-related disease, while another 120 current or former employees have been diagnosed with health conditions related to on-the-job exposure to the substance. The main French rail workers' union estimates that asbestos-related health conditions kill 97 rail workers annually.[535] Railroad carriage construction and repair workers experienced elevated risks of lung cancer (26 cases, SMR 124; 90% CI: 87–172) and excesses for pleural cancer (five cases, SMR 1327; 90% CI: 523–2790); larynx cancer (nine cases, SMR 240; 90% CI: 126–420); land multiple myeloma (three cases, SMR 429; 90% CI: 117–1109). Both liver cancer and pancreatic cancers were also in excess.[536]

6.4.3.15 Roofers

Pneumoconioses and other nonmalignant respiratory diseases (NMRDs) were reported in a group of union roofers and waterproofers with a PMR of 115 with a 95% CI of 103–128 and the authors concluded that asbestos could have be a factor in their cause.[262] Lange and Thomulka[500] are among the very few to evaluate asbestos exposures to roofers, during controlled abatement activities, and concluded that, in their small study, if outlier samples are removed that there is a probability of about 30% of the 5% of those exposed to asbestos to have experienced exposures that exceed the OSHA PEL and that 95% fell within 2 standard deviations of not exceeding the PEL. Overall the study suggests, during abatement, that exposure is low, but because the airborne samples were nonnormally distributed and exhibited large variation, that additional investigations are warranted to best assess such asbestos exposures during asbestos abatement activities.

6.4.3.16 Rubber Workers

The risk of lung cancer was found significant among rubber workers exposed in the early stages of production where exposures to asbestos contaminated talc and carbon

black can occur. The authors concluded that either asbestos or carbon black could play an etiological role.[237] For carbon black, weak associations were found for lung cancers, according to the IARC which has concluded that there is inadequate evidence for the carcinogenicity of carbon black to humans while there is sufficient evidence that carbon black is carcinogenic to experimental animals. The overall IARC evaluation of carcinogenic risk places it in Group 2B (possibly carcinogenic to humans).[238] Thus, the combined role of asbestos and carbon black needs further investigation to evaluate the risk of lung cancers from asbestos in the rubber industry. Stomach cancer was also increased among rubber workers, who worked in the early production stages of mixing and weighing, which the authors concluded may point to the role of either asbestos-contaminated talc or carbon black, but their results do not support the causal role of nitrosamines.[237] The role of carbon black in the etiology of stomach cancer is not supported.[238]

6.4.3.17 Shipyard Workers

It has been known that shipyards have contributed to the increase in asbestos-related diseases because of their vast amount of asbestos use.[537,538] Data on asbestos-related diseases have been reported from around the world in jobs within the shipyard industry (see Shipyard Bibliography). Exposures within the shipyard have been measured dating back to 1946 when Fleischer et al.[340] found pipecovers doing bandsawing to experience exposures to asbestos between 1 and 73 mppcf, during cement mixing from 31 to 84 mppcf, and during installation between 11 and 142 mppcf. Harries[28] measured asbestos fibers when applying amosite thermal insulation to pipes to range from 9 to 40 fibers/cm^3; removal of the thermal pipe amosite insulation from between 29 to 1040 fibers/cm^3; and removal of sprayed on asbestos from between 112 to 1906 fibers/cm^3. In 1971, Harries[539] again did sampling for asbestos at shipyards and found removal of lagging [insulation] in the boiler room to range from 24.7 to 186.4 fibers/cm^3, during application of the pipe lagging, in the boiler room, to range from 0.13 to 5 fibers/cm^3, and while removal of pipe and machine lagging to range from 0.16 to 3021 fibers/cm^3.

6.4.3.18 Smelter Workers

Smelter workers in New Caledonia had excesses of lung cancer and nasal sinus cancers that were thought to be the result of the carcinogenicity of nickel. Langer et al.[540] speculate, the lung cancer cause, may in part be because the nickeliferous ores, from at least one major smelter in New Caledonia, come from serpentine host rocks which contain large amounts of chrysotile asbestos. Analysis indicates the ores are contaminated with asbestos and that when mined the miners are exposed.[540] In an exposure assessment of aluminum smelter workers, it was found that 40% of the smelter workers were exposed to asbestos.[541]

6.4.3.19 School Teachers

Case reports of four mesotheliomas have been reported among two male and two female school teachers, aged 60, 52, 43, and 64 who worked in buildings containing asbestos.[542] Twelve cases of mesothelioma were reported among school teachers from Wisconsin, nine of which had no other known exposures to asbestos than from asbestos-containing materials found within the buildings where they taught.[543]

6.4.3.20 Steel Workers

Analyzing asbestos bodies in lung tissue from 252 patients, over 40 yr of age, we found only 12% of white-collar men, 32% of blue-collar men not in construction or steel-mill work, and 45% among steelworkers and 65% of the construction workers had more than 100 bodies per gram of lung tissue.[442] A study of steel workers, in Belgium, found an increased prevalence of asbestos bodies particularly among maintenance workers, among production workers, and in workers reporting no asbestos exposure had increased prevalence of asbestos bodies compared with controls.[544]

Asbestos-containing materials were used in some parts of the steel mills as protective gloves, protective clothing, and refractory bricks on the hot tops, liner boards, and asbestos blankets used for covering ladles, often being discarded on the pouring pit floor. Studies of steelworkers have found elevated risks of lung cancer in areas where asbestos was used; however, the role of asbestos has not been specifically assessed because of the difficulty of separating other carcinogenic exposures within the mills.[545–547] Asbestos bodies have been found among steelworkers indicating the possible role of asbestos in the etiology of the lung cancers.

6.4.3.21 Sulfate Mill Workers

Among 2480 men between 40 and 75 yr of age at death and observed between 1960 and 1989 found that lung cancer (OR = 1.6, 90% CI: 1.1–2.3) and pleural mesotheliomas (OR = 9.5, 90% CI: 1.9–48) were significantly elevated, which the author suggests are probably due to asbestos exposure.[548]

6.4.3.22 Welders

Welders, in a shipyard, had higher rates of both parenchymal fibrosis and mesothelioma.[154] Thirteen of 306 welders, in a shipyard, had small irregular opacities of the ILO/UICC category of 1/1 or more. When strict clinical criteria were followed, 3% were diagnosed with parenchymal fibrosis as compared with 0.5% from a random sample who did not have pleural or parenchymal lesions over the same timeframe. The authors conclude that while welders are at risk of asbestos-related disease that pleural lesions may not only be merely markers of exposure

but may be a source for identifying those at risk of developing parenchymal fibrosis.[549]

Five deaths from pleural mesothelioma, unrelated to the type of welding, draws attention to the risk of exposure to asbestos in welding activities.[550] Lung cancer was increased among arc-welders in Germany (SMR = 113) as was mesothelioma.[551] Asbestos bodies were found in 40.1% of welders examining their bronchoalveolar lavage fluid and 39.5% in lung tissue and the intensity of exposure to welding increased the retention of the asbestos bodies which the authors suggest could well increase the risk of fibrotic as well as malignant lung disease.[552] Among Norwegian boiler welders, 50 cases of lung cancer were observed when 37.5 were expected (CRR = 1.3333; 95% CI: 0.99–1.76) and three cases of pleural mesotheliomas versus 1.1 expected (CRR = 2.73; 95% CI: 0.56–7.97) were observed.[553] Welders in Sweden had an SIR of 1.86 (95% CI: 1.20–2.75) from 1961 to 1998.[156]

6.5 TAKE HOME AND COMMUNITY EXPOSURES TO ASBESTOS

"It inevitably tends to lower the social status and self-respect of work people if they have to go back to their homes in the same untidy condition." (J. S. Haldane, 1908. Dust removal in factories. Delivered in a Lecture at Oxford. In W. Gilman Thompson, Ed., *The Occupational Diseases — Their Causation, Symptoms Treatment and Prevention*, 1914, D. Appleton and Company).

Take-home asbestos on workers clothes, shoes, or hair can cause household exposures as can proximate residential exposures to asbestos sources. These types of exposures and their resultant disease manifestations are outline very effectively in the NIOSH Report to Congress on Workers' Home Contamination Study,[304] which was conducted under The Workers' Family Protection Act (29 U.S.C. 671a). In this report NIOSH concludes that "... families of asbestos-exposed workers have been at increased risk of pleural, pericardial, or peritoneal mesothelioma, lung cancer, cancer of the gastrointestinal tract, and nonmalignant pleural and parenchymal abnormalities as well as asbestosis."

It has been known for many years that the best method to control diseases associated with exposure to asbestos was to control the exposure to the dust containing the asbestos fibers.[378] As early as 1897 Netolitzky, a physician, reporting on lung disease among textile workers, also observed illness among their family members.[554] In 1913, it was suggested that street clothes should not be worn in the work area and that work clothes should be removed prior to leaving the factory, thus preventing industrial poisons from being carried away from the workplace and exposing nonworkers to the industrial hazard.[555] Kober and Hayhurst[556] advised that street clothes should not be worn at work and that change rooms and washing facilities be furnished, by the employer at the workplace. The International Labour Office (ILO), in their Standard Code of Industrial Hygiene, published in 1934 recommended that "In dusty trades, cloakrooms, wishing accommodations, and eventually douche-baths, separate from the workrooms, should be provided for the workers." The Code also stated that "Such smoke, fumes and gas should

be rendered harmless prior to being passed into the outside air."[557] In 1940, the German issued "Guidelines for the Prevention of Health Hazards from Dust in Asbestos Manufacturing Plants" that specifically mentions that street garments must not be left in the working area and that the retained dust on working clothes must be removed at regular intervals.[568]

In 1943, the United States Public Health Service published in their *Manual of Industrial Hygiene and Medical Service in War Industries* the importance of cleanliness so that the worker did not carry the workplace exposures out of the workplace. The Manual stated that "[I]t is highly necessary that workers have adequate washing facilities. This implies enough washstands or showers and a sufficient quantity of hot water as well as cold. There should also be adequate time to enable thorough cleansing, change of clothes and dressing between the end of work and the time when transportation facilities are available. Many plants give too little time between the end of work and the bus home." The report further states that "The work clothes should be provided and laundered by the employer." Also, that "[T]he employer should, without expense to the employees, furnish proper boots or shoes for the use of the employees while at work in such places."[559] As can be seen from the above-cited references, concern for take-home exposure and the release of toxic materials from the factory were of major concern.

Specifically, by 1943, documentation of the effects of these take-home and environmental contamination concerns were appearing in the literature. Good and Pensky[560] reported a few cases in workers' wives of eruptions resembling their husbands' from halowax acne (cable rash). The authors suspected the cases in the wives to have been the result of contact with work clothes and from laundering shirts and underwear.[560] In 1965, two events documented asbestos take-home exposure and environmental exposure to asbestos with disease. The first was the publication of Newhouse and Thompson[180] reporting mesothelioma among persons with a history of living with asbestos workers and of cases in persons living in the neighborhood of asbestos factories. Also, at a meeting of the New York Academy of Sciences, published in December 1965, discussion of the Newhouse and Thompson findings, the Wagner et al.[300] findings of community disease in South Africa, first published in 1960 and rereported at the NYAS meeting[561] and the Kiviluoto[562] finding of bilateral pleural calcification in a 50-yr-old woman whose only known exposure to asbestos was living in the immediate vicinity of an asbestos mill and playing with asbestos as a child.

Subsequent to the events of 1965 many studies have shown the effects of take-home asbestos exposure and of community environmental exposures. Navratil and Trippe[563] in Czechoslovakia found 9 out of 155 persons living in the neighborhood of an asbestos factory to have x-ray evidence of pleural calcification, with or without other signs of asbestosis when only 0.53 would have been expected. They also found 4 out of 114 persons older than 20 yr who were relatives of factory workers when only 0.39 would have been expected. Finally, they found 28 of 8127 persons over the age of 40 yr that lived in the same district of the factory, but not in the immediate neighborhood of the factory to have pleural calcification or about 0.34%.[563] Lieben and Pistawka,[178] from the Pennsylvania Department of Health, reported several

cases of, both neighborhood and household, mesothelioma among persons exposed to asbestos. Anderson et al.[564–566] and Anderson[567] reported on familial exposure to asbestos and disease showing both nonmalignant and malignant disease occurring in family members not otherwise exposed to asbestos. Among households with at least 20 yr latency, Kilburn et al.[568] found radiographic evidence of asbestosis (profusion 1/0) in 11.3% of the wives of shipyard workers when only a 0.6% prevalence was reported among California women and 0.0% was reported among Michigan women with prevalence increasing up to 32% in wives with the longest latency period. Of the shipyard workers, 1% were insulators, however, 25% of the wives with asbestosis were of the insulators.[569] In 1991, Joubert et al. followed household contacts from one amosite factory in New Jersey and found 28% died of lung cancer, 23% died of gastrointestinal tract cancer, and 9% died from mesothelioma. The authors stated that this represented two times expected based on national estimates. Magnani et al.[570] reported that among family members of Italian cement workers that four pleural tumors (one mesothelioma) were observed when only 0.5 were expected and that six lung cancers were observed when only four were expected. This represented a significantly elevated SMR of 792.3 for cancer of the pleura among domestically exposed women. The authors reported that the plant had no laundering facilities and therefore the work clothes were laundered at home.[570]

Many other community studies,[569,571] case–control studies (Rubino et al., 1972; Vianna et al., 1978),[183,420,572–575] and according to NIOSH some 17 case reports and 22 case series reports[304] have also discussed both take-home asbestos exposure and subsequent disease development as well as neighborhood exposure to asbestos and disease. A population-based case–control study was carried out in six areas from Italy, Spain, and Switzerland. Fifty-three cases without evidence of occupational exposure to asbestos compared with 232 control found that domestic exposure was associated with an increased risk having an OR of 4.81 (95% CI: 1.8–13.1). The authors suggested that cleaning asbestos-contaminated clothes, handling asbestos material, and the presence of asbestos material susceptible to damage may have been the cause. The estimated OR for those living near sources of asbestos was 11.5 (95% CI: 3.5–38.2).[161] A meta-analysis by the IARC found RR[¶¶] of pleural mesothelioma for household exposure between 4.0 and 23.7 with a summary risk estimate was 8.1 (95% CI: 5.3–12) and for neighborhood exposures, the RR ranged between 5.1 and 9.3 (a single RR of 0.2 was reported) and the summary estimate was 7.0 (95% CI: 4.7–11). The authors concluded that while their analysis found a positive causal association between both household and neighborhood exposures to asbestos and mesothelioma that, at present, data do not allow any estimated of the magnitude of risk from general environmental exposures.[576] Placenta transfer of asbestos fibers have been reported that suggest, in the absence of maternal history of asbestos-related jobs, that environmental exposures may have played a role.[577] Additionally, one study observed 12 of 16 dogs with

[¶¶]RR = relative risk and CRR = authors calculated RR.

mesothelioma had a history of asbestos exposure. Among these, 75% of dogs had a history of exposure to asbestos, 9 were living in a house with a member having an asbestos-related occupation or hobby, five lived in households where additional insulation or home remolding had occurred, and five others were living in residential proximity to industrial sources of asbestos (Glickman et al., 1983). It is interesting that, when using a method to equate dog to human age that the mesotheliomas were occurring at similar ages in dogs as in humans. In a study of individuals not exposed occupationally to asbestos, short fibers (<5 μm in length) were predominate in the omentum-mesentary, actually only one fiber greater than 5 μm in length was found, while there was a low fiber burden in the lung. The findings were in contrast to those found in occupationally exposed persons who died of mesothelioma which were linked to the lung fiber burden, the number of asbestos bodies, the total amphibole burden, average fiber length and aspect ratio.[189] An evaluation of the residents of Da-yao, China, found lifetime environmental exposure to crocidolite asbestos found significantly higher rates of pleural plaques, asbestosis, lung cancer, and mesothelioma. The authors reported an annual mortality rate of mesothelioma that ranged from 85 to 365 per million when only 2–3 were experienced in the general population and that the lung cancer and mesothelioma ratio was very low, 1.2 to 3.0, even when the prevalence of smoking was quite high at 80%. Also, pleural plaques were prevalent in 11% of the residents 20 yr or older and 20% for those over 40 yr old.[114]

The Industrial Hygiene Foundation (IHF), first called the Air Hygiene foundation (1936–1941), was formed. The IHF was founded by the Mellon Institute with membership consisting of a group of large industrial corporations. The IHF conducted medical and industrial hygiene surveys of various industries, including the asbestos industry. It also published proceedings of its meeting and also the *Industrial Hygiene Digest* (IDH). The annual meetings were covered by various trade journals and news media like the *Wall Street Journal* and *The New York Times*, as well as wire services like the Associated Press and United Press International.[578] Starting in April 1960, the IHD published an abstract showing asbestos contamination as far as 600 m from the factory.[579,580] In July 1963, the IHD published an abstract of the results of some 500 consecutive autopsies in subjects 15 yr of age or greater. The findings suggested environmental contamination to urban residents not occupationally exposed to asbestos and that this contamination in the community might be of etiological significance in mesothelioma.[581] Subsequently the IHD continued to report the dangers of community exposures to asbestos.[561,581–587] Any company that was a member of the IHF would have received these reports. In addition, Davis, Hardy, Loeb, Austin, and Ives, a New York City Law Firm sent, on March 3, 1969, the minutes of the Health and Safety Council/Asbestos Cement Products Association meeting of February 18, 1969, to several asbestos companies many who attended the Council meeting. In these minutes, it was reported "... that mesothelioma occurred among workers as well as among people who live near crocidolite workings (so-called "neighborhood cases").[588] Finally, Dr. Homan of the Bushy Run Research Center sent, on October 4, 1982, to Mr. Sicard, Union Carbide Corporation a copy of Dr. Selikoff's paper on

"Household Risks With Inorganic Fibers" in which family contact asbestos disease is specifically discussed.[589]

6.6 HUMAN EVIDENCE OF DISEASE BY FIBER TYPE

When discussing the results of his landmark study on asbestos and its association with mesothelioma, Dr. Christopher Wagner concluded "These experiments suggest that other dusts may be 'carcinogenic' if they reach the pleural cavity. It is probable from the cases of carcinomata of the lung in patients, with asbestosis reported from overseas, and in the four cases from amosite miners, and the one from a chrysotile miner in our series, that the other types of asbestos are associated with pulmonary malignancy." (Wagner, J.C., 1964. The Pathology Of Asbestosis In South Africa. Thesis presented for the degree of Doctor of Medicine in the Department of Pathology of the University of the Witwatersrand.)

6.6.1 Anthophyllite

Anthophyllite is a member of the amphibole group with a chemical composition of $(Mg, Fe^{+2})_7 \cdot (Si_8O_{22}(OH, F)_2$ and was principally produce in Finland up 1974 where it was widely used.[17,590] Asbestos-related diseases have been reported by Meurman et al.,[207] Meurman et al.,[591] Tuomi et al.,[592] Meurman et al.,[593] Karjalainen et al.,[594] and Rom et al.[595]

Mesothelioma had not been recognized from exposure to anthophyllite until much later than in the three major commercial fiber types (amosite, chrysotile, and crocidolite). It is now clear that mesotheliomas occur among anthophyllite asbestos-exposed workers.[592,596–598] In one study, four mesotheliomas were observed when the authors expected 0.1 (SIR = 40; 95% CI: 10.90–102.42, as calculated by RAL).[593]

6.6.2 Amosite

Amosite is a member of the amphibole group with a chemical composition (Mg, $Fe^{+2})_7 \cdot (Si_8O_{22}(OH)_2$ [cummingtonite–grunerite]. It was mainly used in asbestos-cement sheet, thermal insulation and roofing products, and commonly referred to as brown asbestos.[17,18,590] Various studies have shown the causal associations of exposure to amosite and asbestosis, lung cancer, and mesothelioma.[175,300,599–606] Studies continue to confirm such associations and will not be listed here.

6.6.3 Chrysotile

Chrysotile, the most commonly used asbestiform variety accounting for some 95%+ of the asbestos ever used is found in the serpentine mineral group with a

chemical formula of $Mg_6Si_4O_{10}(OH)_8$. The nonfibrous forms of this serpentine mineral are lizardite and antigorite. As compared with the amphiboles, the chrysotile fiber is generally finer with high flexibility and good heat resistance and is commonly referred to as white asbestos.[17,18,590] The issue of chrysotile–tremolite contamination has been a matter of debate. In fact, most deposits of chrysotile do contain trace amounts of tremolite. Canadian chrysotile is said to be contaminated with fibrous tremolite[607] and considered to be less than 1%.[608] The world's largest deposits of chrysotile asbestos are found in Russia at the Bazhenovsk deposit in the town of Asbest close to Ekaterinburg City and accounts for 20% of the world production.[608] This mining area has been mined since 1889 and samples take and analyzed by phase contrast optical microscope (PCOM) and scanning electron microscope (SEM) found only chrysotile and no amphibole minerals were detected, however lung tissue analysis did find tremolite.[346] In an analysis of lung tissue of six Chinese chrysotile miners, all the bulk samples contained amphibole asbestos (measuring about 0.002–0.310 wt.% lung tissue) with tremolite fibers found in every sample. While few studies have examined impurities of Chinese chrysotile, with the exception of qualitative analyses of the Qilian mine which showed "little amount" of amphibole and the Chaoyang mine, Liaoning province which also found a small amount of tremolite.[609] Zimbabwe is also a major producer of chrysotile asbestos and has not found tremolite in samples taken for an epidemiology study.[610,611] In samples taken from another major deposit of chrysotile in a mine and mill in Balangero, Italy, no tremolite was detected in any of the samples of chrysotile.[612]

Because of the continuing controversy concerning the carcinogenicity of chrysotile, especially its ability to cause mesothelioma, this section will analyze this issue in more detail than for the carcinogenicity of the amphibole asbestos forms.

Simson[53] reported fibrosis and golden yellow bodies in the lungs of guinea pigs similar to those found in humans. The animals were exposed 2 h/day for 50 days in 1925 to chrysotile. The results from animal bioassays present a strong case for the toxicity of chrysotile. Wagner et al.[613], then with Medical Research Council (MRC), U.K., have shown that a commercial grade, predominantly short fiber Canadian chrysotile, which is used primarily for paint and plastic tile fillers, can induce mesotheliomas when injected intrapleurally into rats, and induce primary lung neoplasm when the animals are exposed by inhalation. Not only does it appear that chrysotile is as potent as crocidolite and the other amphiboles in inducing mesotheliomas after intrapleural injections,[614] but also equally potent in inducing pulmonary neoplasm after inhalation exposure.[615] In terms of degree of response related to the quality of dust deposited and retained in the lungs of rats, chrysotile appears to be much more fibrogenic and carcinogenic than the amphiboles.[615]

Epidemiologic evidence combined with the animal data supports the role that all fiber types, including chrysotile, are responsible in the etiology of lung cancer and mesothelioma as well as other cancers. While most of these studies are of cohorts of workers who were exposed to chrysotile contaminated with low levels of tremolite, an amphibole form of asbestos, several studies revealed a substantially increased risk of contracting mesothelioma from exposure to chrysotile that did not contain

any tremolite contamination. In the first study, Piolatto and his associates examined a cohort of 1094 chrysotile production workers employed at the mine and mill in Balangero, Italy, a site where no tremolite was detected in any of the samples of chrysotile.[612] Among the 427 deaths, the authors discovered two mesothelioma cases, one confirmed pathologically and one based on radiographic findings and an examination of pleural fluid.

In a similar study, Cullen and Baloyi examined the records of Zimbabwean miners and millers who had been certified as having an occupational lung disease.[610,611] Like the chrysotile ore mined in Balangero, Italy, no tremolite was detected in any of the samples. The authors estimated that 6647 Zimbabweans were engaged in the mining and milling operations at two mines: Shabani and Goths. Among the chosen cohort of 27 miners with sufficient documentation, the authors discovered one mesothelioma case proven by biopsy, one mesothelioma proven by post mortem, and one probable mesothelioma based on radiographic findings. They also reported in one case of asbestosis probable terminal mesothelioma versus lung cancer based on chest x-ray only having a pleural mass 5 yr later. Given the rarity of the disease and the size of the exposed population, and even though the authors did not report an SMR, these findings would clearly be in excess of any background or baseline level of mesothelioma in Italy when compared with a similar population of nonasbestos-exposed individuals.

Rogers and his colleagues examined 221 cases of definite and probably mesothelioma obtained from the Australian Mesothelioma Surveillance Program.[616,617] Among these cases, Rogers recorded a substantial number of mesothelioma patients in whom the only detectable type of asbestos was chrysotile (Table 9), in his paper with evidence of a dose–response effect as reflected in a trend to an increasing OR at relatively low fiber concentration of less than 10^6 fibers per gram dry lung tissue ($\log_{10} = 5.5–6$; OR = 8.67).

A 25-yr longitudinal study of workers exposed to amphibole-free chrysotile found two confirmed cases of mesothelioma among the exposed workers.[618] The RR for all cancers, adjusted for smoking and age, was 4.29 (CI 95%: 2.17–8.46). The authors reported that analysis of four commercial samples of the asbestos used in the Chongqin chrysotile asbestos plant under study were shown to contain less than the 0.001% tremolite fiber, which is less than the detection limit for amphibole contamination using the x-ray diffraction analysis and the analytical transmission electron microscopy method used in this study. It has been reported that samples of Chinese chrysotile are contaminated with tremolite; however, like the findings of the Zimbabwe UICC samples, contaminated with anthophyllite, the later findings from Chinese mines cannot be equated to those reported by the authors from their own analysis of the samples representing those taken from their study.

In addition to the studies of uncontaminated "pure" chrysotile, there have been several studies of populations who were exposed to chrysotile ore and processed chrysotile products, which contained trace amounts of the amphibole tremolite. In the mining context, Camus et al.[619] compared mortality among women in two chrysotile asbestos mining areas in the Province of Quebec with mortality among women

in 60 control areas. While focusing on lung cancer mortality, the authors discovered a statistically significant increase in mesotheliomas, as evidenced by an SMR of 7.63 with a confidence interval of 3.06–15.73.

With regard to processed products composed of principally chrysotile asbestos, Nokso-Koivisto and Pukkala[620] examined a cohort of 8391 members of the Finnish Locomotive Drivers' Association during the years 1953 and 1991. They found a statistically significant fourfold risk of mesothelioma. In another study of railroad workers predominantly exposed to chrysotile asbestos, Mancuso[621] arrived at a similar conclusion. Out of a cohort of 181, there were 156 deaths, 14 of which were identified as mesotheliomas constituting 34% of all cancer deaths in the study.

A study of workers employed in an asbestos textile, friction, and packing manufacturing facility, which utilized 99% chrysotile asbestos observed 17 deaths from mesothelioma, representing 4.3% of the deaths. Amphiboles had only been used for a few years during World War II and accounted only for a very small amount of the total asbestos used at this facility.[319]

Dement and Brown,[368] in a cohort of chrysotile textile workers, found an overall excess of respiratory cancer with an SMR of 2.25 (95% CI: 1.85–2.71) and an SMR of 2.24 (95% CI: 1.83–2.72) for pleural mesothelioma. The chrysotile fibers came exclusively fro Quebec, British Columbia, and Rhodesia. In the manufacturing process, the fibers mixed with cotton were sprayed with a light mineral oil, which saturated it to about 4% and by the time it reached the spinning looms the oil had diminished to less than 1%. Some have claimed that this study's findings might be a result of the mineral oil treatment, however, the authors found from a case–control analysis that only a slight exposure–response reduction occurred for lung cancer when the mineral oil exposures were adjusted for, thus leading the authors to conclude that the mineral oil exposures were insignificant.

Finally, Sturm et al.[622] reviewed 843 cases of mesothelioma recorded in the German Federal State of Saxony-Anhalt between 1960 and 1990. Sixty-seven cases, representing 14% of the total, were directly attributable to a sole exposure to chrysotile asbestos.

When comparing animal studies to human response, based on the epidemiology studies, Kuempel et al.[623] of NIOSH, concluded that chrysotile toxic doses (TDs) in rats compared with humans. Their analysis found that the rat-based risk estimates for lung cancer compared with humans were reasonably concordant to those for the Canadian miners and millers studies while those compared with textile workers were much higher indicating that humans may be more sensitive, however, fiber size studies were not done, but there is evidence that textile workers may have been exposed to longer fibers than those found in the Canadian cohorts.

The 1984 Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario concludes that "All fibre types can cause all asbestos-related diseases, ..."[624] This supports the finding of reported cases of mesothelioma among brake mechanics exposed to chrysotile (Langer et al., 1982).[415] Mancuso[621,626] further contends, based on his analysis of railroad machinists, that commercial chrysotile asbestos has caused mesotheliomas

and that the risk is greater than previously asserted. There is further concern that chrysotile is rarely found in its pure form and that most chrysotile deposits are contaminated with the amphibole tremolite, which is agreed by experts to be a toxic form of asbestos.[627] In a review of the evidence, scientists from the National Institute for Occupational Safety and Health conclude that "Given the evidence of a significant lung cancer risk, the lack of conclusive evidence for the amphibole hypothesis, and the fact that workers are generally exposed to a mixture of fibers, we conclude that it is prudent to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos."[349]

Two publications highlight the fact that the majority of the world medical community considers chrysotile to be a cause of peritoneal mesothelioma. In 1997, a multidisciplinary gathering of 19 pathologists, radiologists, occupational, and pulmonary physicians, epidemiologists, toxicologists, industrial hygienists, and clinical and laboratory scientists held a meeting in Helsinki, Finland, to agree on criteria for attribution of disorders of the lung and pleura in association with asbestos. Collectively, the group had published over 1000 articles on asbestos and asbestos-associated disorders. The consensus of the group was that *all types* of malignant mesothelioma can be induced by asbestos, with the amphiboles showing greater carcinogenic potency than chrysotile.[115]

The second publication was a monograph devoted specifically to chrysotile asbestos that was prepared by the International Programme on Chemical Safety in conjunction with the World Health Organization. After an extensive review of the world's literature, this body concluded that "commercial grades of chrysotile have been associated with an increased risk of pneumonoconiosis, lung cancer and mesothelioma in numerous epidemiological studies of exposed workers."[351]

Chrysotile fibers are much more chemically and biologically reactive than amphibole fibers and because of this reactivity with the tissues, they lose their structural elements and divide into smaller fibrils, making their recognition difficult by the usual analytical methods. In fact, many of the fibers are removed from the lung and exhaled back through the bronchi or removed by the lymphatic system to other organs of the body.[628–631] The concentration of dust in the lungs of rats exposed to Canadian chrysotile was only 1.8–2.2% of the dust concentration in the lungs of animals exposed to amphiboles (after 24 months of inhalation exposures). Yet the lung tumor incidence and degrees of pulmonary fibrosis were similar in all groups. These findings support the idea that chrysotile fibers cause more cellular injury, fibrosis, and lung cancer, than the amphiboles, while at the same time are less readily detected in the tissue after the damage is done. Churg et al.[632] concludes that the failure of chrysotile to accumulate in the lung is a result of preferential chrysotile clearance during the first few days to weeks after exposure and that dissolution plays no role in the clearance and that the preferential clearance may be a result of fragmentation and rapid removal of the chrysotile fibers. This is also supported by Roggli et al.,[633] in that they conclude, as do others, that chrysotile does not accumulate in lung tissue because they are broken down into smaller fibrils that rapidly cleared from the lung. Such chrysotile fibers have been missed by their technique which counted only fibers longer than 5 μm in length.

They also conclude that long, thin fibers would likewise be missed, because chrysotile content is poorly detected by the SEM and thus fiber burden is a poor indicator of total chrysotile exposure and other information must be sought in order to address the question of total body burden of chrysotile. Suzuki et al.[634] in 92 consecutive cases of mesothelioma observed that the major asbestos type identified in the mesothelial tissues was chrysotile when compared with the chrysotile fiber burden in the lungs of the same cases (79.0% versus 28.3%). It was found that dogs, with mesothelioma, had higher concentrations of chrysotile in their lungs than in the control dogs.[635] McDonald et al.[435] suggest that because of the low biopersistence, autopsy cannot be reliably used to evaluate the contribution of chrysotile in the etiology of mesothelioma, however, they contend that "... to the extent that tremolite is a valid marker, our results suggest that [chrysotile's role] is small." The question remains, as to the validity of tremolite found in the lung tissue as a valid marker for past chrysotile exposures.

Malorni et al.[636] suggest that fiber penetration can rearrange the cytoskeletal apparatus of the cell and that this could indicate an interaction between the chrysotile fibers and the normal mitotic process, as giant multinucleated cells are formed. Churg et al.[637] further believes that the short fibers may be more fibrogenic than previous animal data suggest and deserves further study.

Biologic plausibility seeks to determine if the theory of causation fits known mechanisms of injury causation. While it is impossible to have a complete understanding of the mechanisms of cancer causation, the biologic facts known about the various asbestos fibers and how they cause disease are consistent with the postulate that chrysotile asbestos fibers are capable of producing mesotheliomas. First, it has been long known that it is not the chemical composition of the various asbestos fibers that is important in their ability to produce disease, the health effects of asbestos are related primarily to their morphology, their shape, and size. Many researchers contend that the potency of crocidolite is related to its thin diameter. Similarly, chrysotile fibers have a tendency to cleave longitudinally creating extremely thin fibrils.

Second, it is universally accepted that chrysotile asbestos is carcinogenic and capable of causing or contributing to the development of lung cancer.

Third, mesotheliomas develop in the pleura, peritoneum, and other serosal surfaces of the body. It is universally accepted that chrysotile is a cause of cancer in the lung and that it also migrates to the mesothelial linings of the body (Suzuki and Kolynema, 1991).[634,638] Sebastien et al.[639] found that all the fibers in the pleural were chrysotile when there was no predominance in the parenchymal samples, leading the authors to conclude that lung parenchymal retention is not a good indicator of total body burden of asbestos retention. Translocation of asbestos fibers to other organs is also well documented. In addition, a series of 168 cases reviewed by Suzuki and Yuen of mesothelioma confirmed:

> 1. Asbestos fibers were present in almost all of the lung and mesothelial tissues from the mesothelioma cases. 2. The most common types of asbestos fibers in lung were either an admixture of chrysotile with amphiboles, amphibole alone, and occasionally

chrysotile alone. In mesothelial tissues, most asbestos fibers were chrysotile. 3. In lung, amosite fibers were greatest in number followed by chrysotile, crocidolite, tremolite/actinolite, and anthophyllite. In mesothelial tissues, chrysotile fibers were 30.3 times more common than amphiboles. 4. In some mesothelioma cases, the only asbestos fibers detected in either lung or mesothelial tissue were chrysotile fibers. 5. The average number of asbestos fibers in both lung and mesothelial tissues was two orders of magnitude greater than the number found in the general population. 6. The majority of asbestos fibers in lung and mesothelial tissues were shorter than 5 μm in length.[348]

Since chrysotile is carcinogenic and is present in high concentrations in the mesothelial linings where the mesothelioma is induced, it is biologically plausible that it causes or contributes to the cause of mesothelioma. This is also shown by many mechanistic and molecular studies that indicate how chrysotile may cause mesothelioma. Fiber penetration can rearrange the cytoskeletal apparatus of the cell and this could indicate an interaction between the chrysotile fibers and the normal mitotic process, as giant multinucleated cells are formed. These studies indicate that chrysotile penetrates the cell, enters the nucleus, and induces abnormal chromosome formations in dividing cells.[636] Some of these abnormalities include the deletion of the P53 gene growth.[640] Inhaled chrysotile asbestos induced, at the fiber deposition sites, the expression of p53 protein,[641] which suggests that the p53 protein can accumulate in the lung tissue after chrysotile exposure. Additionally a study of the phosphorylation of the p53 protein in A549 human pulmonary epithelial cells, exposed to asbestos, it was found that chrysotile asbestos, on a per-weight basis was more potent in inducing Ser15 phosphorylation and accumulation of the p53 protein than was crocidolite.[642] Another recent study has indicated particle stimulation chemiluminescence (CL) production by polymorphonuclear leucocytes has been used to evaluate the pathogenicity of mineral fibers understanding that reactive oxygen metabolites as measured by CL is etiopathogenically related to fiber toxicity. These findings may indicate that neither the total number nor the specific range of fiber dimensions are solely determinate of the CL production and thus other physiochemical factors like surface reactive characteristics of the milled fibers may play a role in the etiology of disease.[643] Pott[644] has questioned fiber dimension as a reliable yardstick for the carcinogenic dose and that inhalation studies of rats, as a surrogate for human inhalation effects, are misleading in that rats are known obligatory nose breathers. These findings bring into question the Stanton et al. hypothesis on fiber diameter and length being the only determinates of the carcinogenicity of fibers.[645] Pott[644] also addresses the use of intrapleural and intraperitoneal route in examining the carcinogenic potential of inorganic fibers, which has been criticized emphatically. Pott concludes that the consistency of such an argument is not supported when, for example, the inhalation studies with crocidolite that does not result in either lung tumors or mesothelioma, even though the fiber concentrations in the lung are very high. These epidemiological findings along with the results of the experimental studies leave no doubt that the scientific evidence supports the carcinogenicity of chrysotile alone in the induction of mesothelioma.[646]

6.6.4 Crocidolite

Crocidolite is one of the riebeckite minerals of the amphibole group with a chemical formula of $Na_2Fe_3^{2+}Fe_2^{3+}Si_8O_{22}(OH, F)_2$. It is often referred to as blue asbestos and is more brittle with harsher texture which explains why it is not used in a lot of commercial products such as friction products due to its ability to score the drums of the brake.[647,648] Studies and reports of workers exposed to crocidolite have well established its causal association with all of the asbestos-related diseases including asbestosis, lung cancer, and mesothelioma.[649–653]

6.6.5 Tremolite

Tremolite is one of the tremolite–actinolite minerals and is found in the amphibole group; even though it is often referred to only as tremolite, it has a chemical formula of $Ca_2(Mg, Fe^{2+})_5 \cdot (Si_8O_{22}(OH, F)_2$. Tremolite is often found as an contaminate of chrysotile asbestos or talc.[647] It has been suggested that milling will remove the tremolite for the chrysotile; however, this is not universally accepted.[633] Studies have established its ability to cause all asbestos-related diseases including asbestosis, lung cancer, and mesothelioma.[654–656] Persons using a pure form of tremolite to mix a whitewash, in New Caledonia, called "po" have shown a risk of pleural mesothelioma which is strongly associated with its use.[657] Other studies have shown similar associations with tremolite containing whitewashes in Cyprus, Greece, Turkey, and in Corsica where environmental exposures to tremolite deposits occur.[658,659] Associations with lung cancer have been much fewer and seem to be complicated with potential confounding factors, for example, alcohol, diet, occupational exposures, and smoking. Yarocioglu et al.[660] report excesses of mesothelioma in areas where the tremolite containing "po" is used.

6.6.6 Talc

Talc is a specific and naturally occurring mineral, described as a hydrated magnesium silicate ($Mg_3Si_4O_{10}(OH)_2$), but can occur in intergrowths where it is contaminated with the asbestos material actinolite, anthophyllite, chrysotile, tremolite, and silica.[590,661] The health effects of tremolite have been discussed earlier. Large doses of talcs have resulted in adverse inflammatory pulmonary responses, cough, tachycardia, and cyanosis.[661] Talcosis, a disease caused by the inhalation of talc, has been described in detail in many of the occupational medicine textbooks.[662] When contaminated, talc can cause diseases associated with the type of contaminate, that is, asbestos — pleural thickening, asbestosis, and lung cancer and silica — silicosis.

Epidemiological studies of talc miners and millers have demonstrated such diseases in a manner similar to the radiological patterns of silicosis — discrete opacities in the mid-lung (3–5 mm); asbestosis — diffuse, interstitial fibrosis in the lower lung zones; and mixed patterns of both diseases.[661] Dreessen[663] of the U.S. Public

Health Service published the ill effects of tremolite-containing talc among 57 workers exhibiting such effects after 10 yr of exposure. Dreessen and Dalla Valle[664] further described such findings among 66 workers in two Georgia talc mines and concluded the changes were permanent. Further epidemiological studies have confirmed the presence of talc-related diseases among New York State talc miners and millers.[93,94,665–667]

Cancers have been reported among talc-exposed workers. Kleinfeld et al.[668] reported 12 respiratory cancer deaths when 3.7 were expected in workers exposed to talc contaminated with both antophyollite and tremolite (calculated: rate ratio (RR) = 3.24: 95% CI: 1.67–5.67). Lamm et al.[669] reported an SMR for respiratory cancers of 246 among 705 male talc workers, but as the excess mortality occurred among those employed less than 1 yr the authors were unable to associate it with their exposures to talc. Thomas and Stewart[670] of the National Cancer Institute (U.S.) reported that as latency increased among workers exposed to talc and quartz, for 1 yr between 1939 and 1966, that the SMR for lung cancer rose from 250 to 364 among those exposed for 15 or more years. Other such studies have not shown such associations,[671,672] however, IARC has concluded that there is adequate evidence that talc contaminated with asbestos does cause cancer in humans, but inadequate evidence that uncontaminated talc causes cancer.[673]

Talc has had many uses in both industry and in consumer products and when it has been obtained from geographical deposits where it has become contaminated with asbestos-containing materials it will pose a significant hazard to the downstream user and result in a risk to the asbestos-related diseases.

6.6.7 Vermiculite

Vermiculite is a member of the phyllosilicate group of minerals with a typical formula of $(Mg, Ca, K, Fe^{11})_3(Si, AL, Fe^{11})_4O_{10}(OH)_2O4H_2O$ (http://www.schundler.com/techverm.htm). Like talc, vermiculite, a naturally occurring mineral, can occur in areas where other naturally occurring minerals are found and thus contaminated. One form of contaminated is from the tremolite form of asbestos. In the United States in 1981 Robert Rannie and his partner dug a 40-ft. shaft hoping to get gold but instead discovered vermiculite which was then later commercialized by Edward Alley, in 1919, who had observed its unique characteristic of expanding to a large lightweight puffy material which did not burn. The vermiculite product was then named zonolite and was found expand up to 15 times its original size when heated to 2000 °F. In 1963 it was found in an industrial hygiene study at the Zonolite Company, by Ben Wake, that samples of vermiculite found 6.2–22.5% tremolite present.[674]

Peipins et al.[675] have reported radiographic abnormalities consistent with asbestos-related pulmonary diseases as has Lockey et al.[676] who among workers in an Ohio fertilizer plant using vermiculite from the mining community of Libby, Montana studied by Peipins et al.[675] Lockey et al.[676] found workers with daily TWA exposures of 0.031–0.415 fibers/cm^3, similar to those encountered by

community residents in the mining community, to have significantly elevated radiological pleural changes as well as chest pain. Very high exposures to tremolite–actinotlite were reported in the Libby Vermiculite dry mill by NIOSH prior to 1964 to be as high as 168 fibers/cm^3 in the working areas, 182 fibers/cm^3 encountered by sweeper, and even 13 fibers/cm^3 in the quality control laboratory.[677] They also found that exposures in the mine before 1971 ranged between 9 and 23 fibers/cm^3 for drillers and less than 2 fibers/cm^3 for the nondrilling jobs.

Vermiculite contaminated with asbestos, such as found in Libby Montana, have resulted in not only the miners and millworkers developing asbestos-related diseases at an alarming rate, but also the residents in the community around the mine. NIOSH looked at 575 men hired before 1970 for at least 1 yr found SMRs of 223.2 (95% CI: 136.3–344.7) for lung cancer and 243.0 (95% CI: 148.4–375.3) for NMRD. Both lung cancer and NMRD SMRs increased with fiber-year exposures, thus showing a dose–response.[677] McDonald et al.,[678] in their most recent follow-up of a cohort from the Libby Montana vermiculite mine and community, have recorded elevated SMR for lung cancer (SMR = 2.40), NMRD (SMR = 3.09), and have reported 12 deaths ascribed to mesothelioma among 406 vermiculite mineworkers followed until 1999 and employed before 1963. They also concluded that using an all-cause linear model that a 14% increase in mortality would occur among the mineworkers exposed occupationally to 100 fibers/ml yr and a 3.2% increase for the general population if exposed for 50 yr at ambient concentration at the current OHSA PEL of 0.1 fibers/ml.

When McDonald et al.[679] had looked at another smaller cohort of vermiculite workers in South Carolina exposed to lower levels of tremolite in the ore that out of 194 men only 4 deaths from lung cancer were observed when 3.31 (SMR 121) would have been expected. PCM and ATEM fiber counts found low concentrations up to 0.32 fibers >5 μm/cm^3 and tremolite–actinolite accounted for 47.6% of the settled dust. The mortality study included those workers working 6 months or more prior to January 1, 1971, and followed through January 1, 1986. The mean duration of employment was 9.2 yr and the average mean from beginning employment to death was 19.7 yr. Since only 51 deaths had thus far occurred (26% of the cohort) and the follow-up period rather short, the resultant incidence of mesothelioma would have been difficult to ascertain until further follow-up was obtained. At the time of the study, no deaths from pneumoconiosis or mesothelioma were observed.

Hessel and Sluis-Cremer[680,681] found similar results in a cross-sectional study among black vermiculite worker exposed to "very little asbestos" at the Palabora Vermiculite Mine in South Africa. Two cases of small opacities were observed, one with a 1/0 and tt opacities in worker with 22.5 yr as an operator and the other a 1/1 with ps opacities who worked in a duster job for 19.5 yr. No dose–response trend was noted; lung function was comparable with the control groups as were respiratory symptoms; and the authors state that because of the nature of their study (cross-sectional) the risk of mesothelioma cannot be excluded.

Vermiculite contaminated with asbestos can provide significant hazards to its users and has been used in consumer products for over 80 yr. Its uses have included such generic applications as, that is, loose fill, absorbents, industrial heat insulation,

soil conditioners, asbestos substitutes, fire protection; in construction, that is, acoustic finishes, fire protection, floor and roof screed, roof insulation, gypsum plaster, loft insulation, sound deadening; in agricultural, that is, animal feed, fertilizer, pesticides, seed encapsulant, soil conditioner; and in horticulture, that is, potting mixes, root cuttings, seed germination, and sowing composts (http://www.epa.gov/asbestos/verm.html).

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CHAPTER 7

Clinical Diagnosis of Asbestos-Related Disease

Gary K. Friedman

CONTENTS

7.1 INTRODUCTION

The current medical and social importance of asbestos-related disease for the practicing clinician cannot be overstated. Because asbestos-related diseases have the potential for causing impairment, reduced life expectancy, and the necessity for costly medical care, the importance of appropriate diagnosis and management is self-evident.

In the past decade, over 650,000 reported cases of asbestos-related disease have resulted in claims for compensation, with approximately 100,000 such claims filed in the year 2003 alone. Placed in perspective, during the past 5 yr there have been more cases of asbestos-related diseases diagnosed in the United States than AIDS or cases of new onset adult asthma. The impact is not limited to the medical community. In addition to the billions of dollars that have been paid in compensation, as of June 2004, over 60 major U.S. corporations have been driven into bankruptcy. While the diagnostic criteria and clinical aspects of most illnesses are relegated to the purview of physicians and scientists, asbestos-related diseases have become a topic of heated debate for the courts, employers, insurers, and legislative bodies at the state and federal levels. The American Bar Association has broken precedent and issued a formal statement with medical diagnostic criteria for proposed federal legislation and the United States Supreme Court has attempted to address this issue without success. Recently Texas, Ohio and Florida have passed state legislation with medical criteria requiring proof of impairment before a case may be eligible to seek compensation.

7.2 A BRIEF OVERVIEW OF THE HISTORY OF CLINICAL ASBESTOS-RELATED DISEASE

It is traditional to provide a history of the use of asbestos and the chronology of the scientific advances of asbestos-related disease in chapters like this. For brevity, I leave the fine details of the history of asbestos to others without cataloguing each of the important scientific discoveries, which have occurred in the past 100 yrs, as this information is readily available from other sources.[1] A relationship between

asbestos exposure and pulmonary fibrosis has been recognized since the early 1900s. Sufficient knowledge of the relationship between asbestos and pulmonary injury existed by 1918, to cause certain insurance companies to deny life insurance to certain asbestos workers.[2] The term asbestosis was first utilized by Cooke[3] in 1927 who published a post-mortem examination of a 33-year-old woman who began working at the age of 13 in the carding room of an asbestos factory with extremely heavy exposure to asbestos. In 1930, a report from the Mayo Clinic[4] detailed many clinical aspects of asbestosis including x-ray findings, clinical symptoms, the presence of latency, the description of asbestos bodies (previously described by McDonald),[5] the potential for progression, the lack of satisfactory treatment, the relationship between pulmonary asbestosis, pulmonary hypertension, cor pulmonale, and the potentially fatal outcome of the disease.

One of the earliest reports associating lung cancer and asbestos was authored in 1935 by Lynch and Smith.[6] By 1948, Lynch and Cannon,[7] stated "carcinoma of the lung was also of such prominence as to require continued consideration as possibly inducible in a susceptible subject by severe asbestosis until disproved by further investigation." In 1955, Sir Doll[8] published epidemiologic evidence of the carcinogenicity of asbestos for lung cancer.

A few case reports of mesothelioma with asbestos exposure appeared in the late 1940s and early 1950s. Wagner et al.[9] reported 33 cases of diffuse pleural mesothelioma in patients exposed to crocidolite in the Asbestos Hills northwest of Cape Province South Africa. This was the first epidemiologic-like study on the subject and clearly established the relationship between asbestos and this uncommon tumor.

Many additional studies within the medical and industrial hygiene literature ultimately led to recommendations for standards limiting asbestos exposure (see Chapters 2, 3, 6 and Appendix). On May 29, 1969, the exposure limits previously recommended by the American Conference of Government Industrial Hygienists (ACGIH) were incorporated into federal regulation under the Walsh Healey Act, which applied to work practices of federal contractors. OSHA was established the following year with one of its first priorities being the promulgation of an emergency standard regulating the industrial use of asbestos in 1971. The passage of the permissible exposure limit by OSHA had the goal of reducing the risk of asbestosis to less than 1% during a 45-yr working lifetime of exposure. Over the next 15 yrs, progressively restrictive regulatory standards were issued, which further reduced the allowable exposures to asbestos (see Chapters 6, 8 and Appendix).[10]

A recognition of the body of medical evidence, the progressively stringent regulatory standards, and employer concerns over compensable work-related injury resulted in the decline of the utilization of asbestos in the United States by the early 1970s. Because all asbestos-related diseases have a dose–response relationship as one of the factors in their causation, an understanding of the differences in exposure which occurred during different periods of time, different occupations, and working conditions is critical for the clinician in his assessment of a given case.

7.3 ASBESTOS EXPOSURE

Between 1940 and 1979, it was estimated that 27,500,000 U.S. workers were occupationally exposed to asbestos.[14] No other occupational lung disease has been the subject of as many peer review articles. The literature has identified the occupations, industries, and other circumstances where significant exposure to asbestos may occur.[11–14] The spectrum of diseases which may result from asbestos exposure and cases where impairment, disability, and death have resulted from these diseases have been described.[14,15] Many previously reported cases resulted from high levels of asbestos exposure between 1940s and 1960s.

As asbestos utilization in the United States has fallen, since the mid-1970s, subsequent exposures were typically much lower than the historic levels which caused the diseases reported in the asbestos literature of prior years. Engineering controls, different occupations, use of respiratory protection, and other factors, which might affect exposure, must be considered. Because different asbestos-related diseases are associated with different levels of exposure and latency, each case deserves careful individual evaluation and an understanding of the evolving and dynamic nature of asbestos-induced diseases.

With reduced exposure, a substantial decrease in incidence of most asbestos-related diseases (with the exception of mesothelioma) was anticipated to have occurred by the mid-1990s. Thus, the "epidemic" of hundreds of thousands of recently diagnosed cases of asbestosis poses new challenges to the clinician. There are some within the medical and legal communities who have raised questions concerning the soundness of the methodology[16] and the accuracy of the diagnosis in some of these cases. Others point out that there may be additional cases, which have gone undiagnosed. It is unrealistic to expect that a single chapter can address all the issues. Hopefully, the following will provide some guidelines to the many physicians who will face the challenges of providing appropriate future medical care and properly addressing the questions and concerns of their patients.

7.4 HOW ASBESTOS MEASUREMENTS ARE USED IN CLINICAL PRACTICE

The measurement of asbestos levels is in the purview of industrial hygiene and is discussed in Chapters 2, 3, Appendix. However, such measurements are rarely available to the clinician. Nicholson et al.[17] utilized the levels of asbestos exposure within certain industries and occupations in an attempt to project future risks for mesothelioma and lung cancer. NIOSH has utilized job descriptions to stratify risks of asbestos exposure.[18]

Asbestos exposure is generally referred to in terms of total or cumulative dose. The dose is a product of the duration of exposure (in years) and the intensity of exposure as defined by average workplace air concentration in fibers per cubic centimeter (f/cm^3). Only fibers greater than 5 μm in length are counted. Thus, an individual exposed to 2 fiber/cm^3 for 10 yr would have a total dose of 20 fiber yr/cm^3 (fiber). At an OSHA PEL[10] of 0.2 fiber/cm^3, there is 1% risk (or less) of a worker

getting asbestosis working, 8 h per day for 45 yr at that level of exposure. The Helsinki consensus criteria report states that asbestosis "may occur" at 25 fiber years.[19] There is no compelling evidence that asbestosis occurs at less than 10 fiber years.

Some occupations such as brake repair are even more complex as consideration must be given not only to fiber counts, but also to fiber type, presence of binders, fiber size, and conversion to forsterite as a result of friction induced heat. Additional examples of specific occupational exposures are covered in the chapter on Recent Data on Selected Specific Occupations (Chapters 1, 2, 3).

7.5 LATENCY

Latency is the period of time, between first exposure to asbestos and the appearance of disease. For example, the typical minimum latency for asbestosis is 20 yr or longer for exposures of the type experienced in the past three decades.[20] The median latency period for asbestosis is in the range of 25–30 yr. The incidence of benign asbestos pleural disease is dependent on the duration of time since exposure and dose. The asbestos-related malignancies likewise only occur after sufficient latency. The unique issues relating to latency will be discussed under each disease.

7.6 DIAGNOSTIC STUDIES

7.6.1 Chest X-Ray

The chest radiograph is the most widely used among the objective studies performed for the diagnosis of asbestos-related diseases. While clinicians are familiar with the typical radiographic narrative interpretations, asbestosis and the other pneumoconiosis are frequently reported using a standardized format developed by the International Labor Office (ILO) (Figure 7.1). The system was originally developed for epidemiologic and research use in black lung disease and the radiographic reports are referred to as "B" readings. NIOSH administers an examination to certify physicians as "B" readers for proof of proficiency in reading pneumoconiosis chest radiographs.

For the purpose of ILO interpretation, only the posterior–anterior (PA) view is utilized. At this time only the standard film or screen technique should be used for purpose of ILO grading, as a consensus has not been reached on the evaluation of digital x-rays. A series of numerical values, letters, and symbols are used to characterize various aspects of the PA radiograph. The ILO publishes a set of 22 standard radiographic films some of which contain changes of the type seen in asbestosis in varying degrees of severity as measured by profusion (concentration) of small opacities. Additional standard radiographs demonstrate examples of pleural abnormalities, including pleural plaque and diffuse pleural thickening. The "B" reader must have a copy of these standard films and is instructed to compare the patient's x-ray against the appropriate standard radiographs that most closely

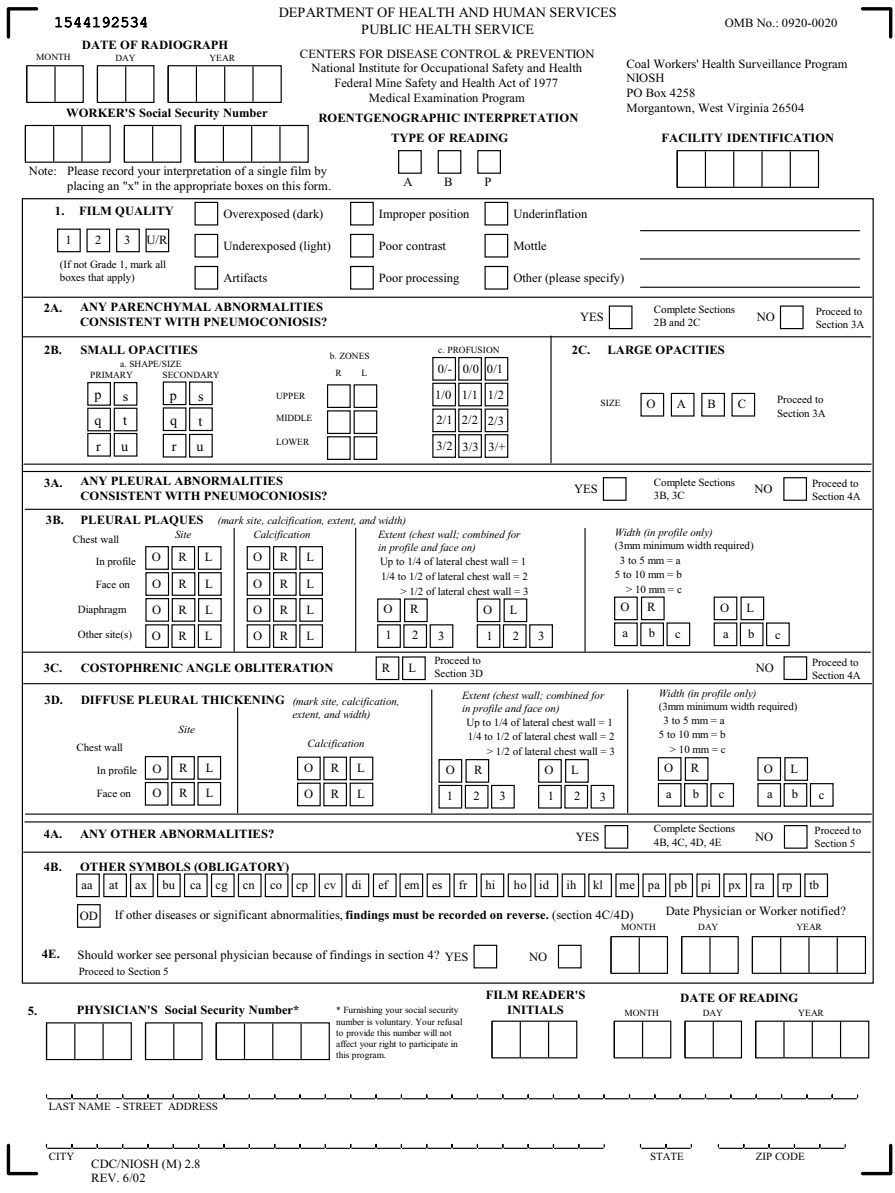

Figure 7.1 NIOSH Roentgenographic Interpretation ("B" reader) form 2000.

resemble the subject's radiograph. The results are then recorded in a systematic fashion on a special form (Figure 7.1). The ILO publishes the guidelines for interpretation of the radiographs as a handbook,[21,22] which accompanies the set of standard x-rays.

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4C. MARK ALL BOXES THAT APPLY: (Use of this list is intended to reduce handwritten comments and is optional)

Abnormalities of the Diaphragm

☐ Eventration

☐ Hiatal hernia

Airway Disorders

☐ Bronchovascular markings, heavy or increased

☐ Hyperinflation

Bony Abnormalities

☐ Bony chest cage abnormality

☐ Fracture, healed (non-rib)

☐ Fracture, not healed (non-rib)

☐ Scoliosis

☐ Vertebral column abnormality

Lung Parenchymal Abnormalities

☐ Azygos lobe

☐ Density, lung

☐ Infiltrate

☐ Nodule, nodular lesion

Miscellaneous Abnormalities

☐ Foreign body

☐ Post-surgical changes/sternal wire

☐ Cyst

Vascular Disorders

☐ Aorta, anomaly of

☐ Vascular abnormality

4D. OTHER COMMENTS

Public reporting burden of this collection of information is estimated to average 3 minutes per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. An agency may not conduct or sponsor, and a person is not required to respond to a collection of information unless it displays a currently valid OMB control number. Send comments regarding this burden estimate or any other aspect of this collection information, including suggestings for reducing this burden to CDC, Project Clearance Officer, 1600 Clifton Road, MS E-11, Atlanta, GA 30333, ATTN: PRA (09020-0020). Do not send the completed form to this address.

Figure 7.1 *Continued.*

Films are graded for technical quality. Films of very poor quality due to over- or underexposure, artifact, motion, positioning, etc., should not be used for the purpose of ILO interpretation. The fibrosis of asbestosis represented radiographically as irregular opacities is characterized by the following symbols denoting their thickness: S (fine — like a piece of thread), T (medium thickness — piece of string), and U (coarse — like a piece of heavy twine). The profusion (concentration) of the small opacities is quantified along a continuous 12-point scale. A zero indicates

the absence of small opacities or ones, which were of less profusion than those demonstrated on a Category 1 standard chest radiograph. The chest radiographs within Category 1 (e.g., standard film 1/1) indicate a mild profusion of opacities, Category 2 (as exemplified by the standard film 2/2) a moderate profusion, and Category 3 a severe profusion (exemplified by the standard film with a profusion of 3/3). An analogy for the number of "spots" on the x-ray might be made describing the number of raindrops. No drops would be (0/0), sprinkling (1/1), raining (2/2), or pouring (3/3).

As the subject's chest radiograph often does not perfectly match the standard film, two numbers are assigned to the radiograph. The first number represents the category, which the reader believes to be present and the second number represents the category to which the reader gave serious consideration as an alternative. For example, if a physician were convinced with a radiograph, which was mildly abnormal and matched a standard 1/1 radiograph, that symbol would be marked on the ILO form. However, if the subject's chest radiograph was felt to be a Category 1 profusion, but showed substantially less concentration of irregular opacities than on the 1/1 standard film and serious consideration was given to the film being normal (Category 0), the 1/0 would be utilized. The ILO indicates this would be a chest radiograph, which was "classified as Category 1 after having seriously considered Category 0 as an alternative."[21]

The 1986 ATS Statement on Asbestos, cautioned that "the prevalence of lesser degrees of interstitial fibrosis is not well known. Considerable caution has to be exercised in attributing all such phenomena to asbestos exposure either known or occult."[23] There is no ILO standard chest radiograph for 1/0 profusion that can be used for purposes of comparison. The 2004 ATS[20] statement on asbestos utilizes a 1/0 as the boundary between normal and abnormal films for asbestosis. However, the ATS qualifies the description of a 1/0 as being "presumptively diagnostic but not unequivocal." Furthermore, the positive predictive value of a 1/0 film done in diagnosing asbestosis "may fall below 30% when exposure to asbestos has been infrequent and exceed 50% when it has been prevalent."[20]

Pleural abnormalities are defined as either discrete (plaques) or diffuse areas of pleural thickening. They are characterized as to location (site), including the chest wall, diaphragm, and costophrenic angle. The left and right sides of the chest are recorded separately. Calcification of plaques is also to be noted on the forms.

Diffuse pleural thickening refers to thickening of the visceral pleura. Under the most recent ILO (2000) classification,[22] pleural thickening with a minimum width of 3 mm extending up the lateral chest wall is recorded as diffuse thickening only in the presence of continuity with a blunted or obliterated costophrenic angle.

A substantial number of obligatory symbols must also be completed. These include the radiographic presence of changes suggesting cancer, emphysema, pneumothorax, TB, pleural effusion, rib fracture, abnormality of the cardiac silhouette, and a number of other findings.[21,22]

7.6.1.1 Purpose and Limitations of the ILO Classification

The ILO classification was originally designed for epidemiologic purposes. The ILO has specifically stated that the object is to codify the radiographic abnormalities of the pneumoconiosis in a simple reproducible manner. The Guidelines for the Use of ILO Classification of Radiographic of Pneumoconiosis[21,22] states: "The classification neither defines pathological entities nor takes into account working capacity." "It does not imply legal definitions of pneumoconiosis for compensation purposes and does not set or imply a level at which compensation is payable." The importance of the differential diagnosis of the chest radiographic appearance is addressed stating, "no radiographic features are pathognomonic of dust exposure. Some radiographic features that are unrelated to inhaled dust may mimic those caused by dust."[22]

7.7 PULMONARY FUNCTION TESTS

Pulmonary function tests (PFTs) represent a battery of tests with each component assessing a different aspect of lung function. The American Thoracic Society (ATS) has published a series of official statements, which set forth criteria for the performance of spirometry, diffusion capacity, interpretative strategies and other aspects of pulmonary function testing. A detailed guide for pulmonary function laboratory management and procedures was published by the ATS in 1998.[24] An updated second edition is available for release (2005) in electronic form. PFTs are utilized in several different capacities in evaluating asbestos-related disease (Table 7.1).

7.7.1 Spirometry, Acceptability, and Reproducibility

Spirometry is the most commonly performed study and measures inhaled and exhaled volumes of air as measured over time (flow). The actual volume, which the patient can exhale with maximal effort from a maximum inhalation, is the forced vital

Table 7.1 Utilization of Pulmonary Function Testing

Diagnosis — the reduction below lower limits of normal for FVC and DLCO is of value in supporting the diagnosis of asbestosis[23]
To document impairment of lung function[25,26,35,36]
Monitoring to determine the presence of progression or improvement over a period of time (improvement suggests an etiology other than asbestos)
Preoperative evaluation for the malignant diseases
Disability determination[25,26,35,36]
Occupational evaluations — certification for respirator use, etc.
Assessment of symptoms — example: Do pulmonary function studies support a pulmonary etiology for the symptom of dyspnea or should other cause be sought, etc.?

capacity (FVC). The maximum amount, which can be expelled during the first second of exhalation, is the forced expiratory volume in one second (FEV1). Peak expiratory flows, slow vital capacities and exhaled volumes at various other increments of time can also be measured. The study provides important information concerning airflow obstruction and provides information concerning possible restriction, especially with reduced FVC in the face of normal expiratory flow.

The clinician must be aware that the results of these tests are in part dependent upon patient's effort, accuracy of the measuring device, and skill of the technician. Therefore, it is important for the clinician to determine whether or not a valid study was obtained prior to assigning clinical significance to the results. The physician should review time volume curves and flow volume loops to check for artifact, back-extrapolation, or other factors which can affect the results of the study. While it is beyond the scope of this text to review in detail the criteria for the performance of each of the studies, the following brief summaries of the ATS guidelines may prove useful in the clinician's determination of reliability of the test results[27] (Table 7.2 and Table 7.3).

Relative contraindications to spirometry include hemoptysis, pneumothorax, unstable cardiovascular status, thoracic, cerebral, or abdominal aneurysms, recent eye surgery, vomiting, and recent abdominal or thoracic surgery.[24]

7.7.2 Diffusion Capacity

The diffusion capacity (DLCO) measures the transfer of gas across the alveolar capillary interface. The test utilizes a low concentration of inspired carbon monoxide inhaled by the patient. The breath is held for 9–11 sec and an exhaled volume is collected. Pulmonary diseases, which affect the alveolar–capillary interface either by destruction of the alveolar wall, as in emphysema, or thickening of the barrier, as in interstitial lung disease, may reduce the DLCO. There are numerous factors, which can affect the diffusion capacity other than injury to the alveolar wall. Non-pulmonary factors including reduced hemoglobin concentration, reduced cardiac output, exogenous sources of carbon monoxide (such as smoking), chronic renal failure, and others may cause a decrease in diffusion capacity. Increases in diffusion capacity have been reported with polycythemia, pulmonary hemorrhage, left to right heart shunts, and exercise.

Table 7.2 Spirometry — Acceptability Criteria[27]

Acceptability
Free from artifact (cough, variable effort, leak, etc.)
Curve demonstrates a good start (back extrapolation)
Satisfactory end of study — minimum 6 sec exhalation time and/or plateau in the volume time curve
Minimum of three acceptable studies
Submission of at least three time volume curves/flow volume loops for inspection

Table 7.3 Reproducibility Criteria[27]

Two largest FVC must be within 200cc of each other
The two largest FEV1s must be within 200cc of each other
The patient should repeat these studies until either acceptability and reproducibility have been achieved or total of eight tests have been performed or if the subject cannot continue, the best three studies should be saved with appropriate notations made by the technician as to the reason that the study was discontinued

The study is effort-dependent and a summary of the ATS[28] criteria for performance of the diffusion capacity is shown below (Table 7.4).

The volume of collection should be 0.5–1 L and collected in less than 4 sec. The use of supplemental oxygen should be discontinued at least 5 min before beginning the test. Cigarette smoking affects the study in at least two different ways:

(1) Emphysema with destruction of alveolar units reduces the diffusion capacity.
(2) Cigarette smokers have elevated carboxyhemoglobin levels. This will adversely affect gas transfer and artificially reduce the DLCO. Smoking cessation is recommended for 24 h prior to the performance of this study.[28]

As with spirometry, reproducibility between the studies must be achieved. It is recommended that at least two acceptable tests meet reproducibility requirements of being within 10% or 3 ml of carbon monoxide of the average DLCO. It is recommended that there may be at least 4 min between DLCO test efforts to allow for complete elimination of the test gas prior to repeating the study.[28]

7.8 AIRWAY OBSTRUCTION

When airway obstruction is present, the ATS recommends the use of bronchodilators to determine reversibility. Bronchodilators are recommended to be utilized for disability determination when the FEV1 is less than 70% of predicted.[24] Relative contraindications for bronchodilator testing includes a known adverse reaction to a specific bronchodilator or unstable cardiovascular status such as arrhythmias, elevated blood pressure, or other diseases that could be aggravated by beta agonist

Table 7.4 ATS Criteria for DLCO[28]

Use of proper quality controlled equipment
Inspired volume of greater than 90% of vital capacity in less than 4 sec
A stable breath hold of 9–11 sec with no evidence of leak, valsalva, or Muller maneuvers
Expiration in less than 4 sec with appropriate clearance of dead space and proper sampling analysis of alveolar gas
Alveolar volumes (VA) should be measured
At least two acceptable tests must be performed
Reproducibility of the two best acceptable tests within 10% or 3 ml of CO

stimulation.[29,30] Contraindication to the use of bronchodilator should be noted in the technician's comments. Additional recommendation for the performance and interpretation of bronchodilator studies is also available.[26,31]

7.8.1 Total Lung Capacity

The total lung capacity (TLC) represents the sum of the residual volume (RV) and the FVC and can be measured as the sum of the inspiratory capacity (IC) plus functional residual capacity (FRC). TLC is used in the measurement of restrictive defect[32] (especially in the presence of obstruction) and in the alternative to demonstrate hyperinflation. FRC is the volume most frequently measured. Other measurements of volume are then computed utilizing values obtained from spirometry. FRC can be measured by gas dilution utilizing helium. It may also be measured by collecting nitrogen, which has been washed out of the lung by 100% oxygen (nitrogen washout method).

Plethysmography measures the gas volume within the thorax and is another means of measuring TLC. The subject sits in a tightly sealed specially constructed chamber (body box). The patient breathes or pants against a shutter attached to a mouthpiece. A variation of Boyles Law measures changes in the subjects' mouth pressure and the pressure in the sealed box. A "loop" is created on a graph plotting mouth pressure against change in volume (change in box pressure). The tangent of the loop is measured and corresponds to lung volume with the mouth shutter closed (FRC).[33] Plethysmography is considered to be the preferred method to measure RV, FRC, and TLC. Nitrogen and helium methods may underestimate volumes, especially when significant airway obstruction is present or if non-communicating air spaces such as cysts, large bullae, etc., prevent thorough gas distribution. Lung volumes may be estimated from the chest x-ray by planimetry using measurements taken of the perimeter of the pleural cavities of the postero-anterior and lateral views of the chest x-ray. This method is cumbersome, subject to depth of inspiration and other variants of radiographic technique and is rarely used. When available, plethysmography is recommended as the preferred method.

7.8.2 Pulmonary Function Test Interpretation

After determining that a study meets the performance criteria, the physician must then interpret the study. Guidelines have been established for selecting reference values and interpretive strategies.[32] The results of the patient's PFTs are compared against those of "normal individuals" of same height, sex, age, and race all of which have been found to be important determinants of lung function. Several reference equations are available, for predicted normal values, and the published peer-reviewed reference equations most suitable for the laboratory's patient population should be utilized. Predicted values developed by NIOSH and CDC during the NHANES III (National Health and Nutrition Examination Survey) and reported by Hankinson et al.[34] were derived for three separate ethnic groups (Caucasian,

African–American and Mexican–American, age 8–80). These values are currently utilized by certain NIOSH spirometry training programs and are available for clinical use.

The reference or "predicted normal" equations provide a method for comparing the patient to a reference population. Determination of what separates a "normal" from an abnormal study and what constitutes impairment deserves further comment.

A longstanding practice has been to classify values of FVC and FEV1 found to be below 80% of predicted as abnormal. The 1986 ATS statement on impairment and disability defined impairment as less than 80% of predicted for FVC or FEV1, or DLCO.[25] The American Medical Association (AMA) Guides to the Evaluation of Impairment adopted the same criteria through the fourth edition.[35] These guides are utilized for the purpose of impairment for worker compensation in 40 states or districts within the United States.

Further, it has been found that in aged individuals or those at the extremes of height measurement the use of 80% of predicted does not always equate to the lower limit of normal (LLN) when the latter is defined as the lower fifth percentile. In 1991, the ATS stated that the use of 80% of predicted for a lower limit in adult PFTs is not recommended[32] and normal ranges should be based on the fifth percentile. The AMA Guide to Impairment Fifth Edition[26] adopted these recommendations to use the LLN in 2001. The clinician should be made aware that some of the commercially available spirometers may not offer LLN values in their software algorithms and this may be a consideration when selecting pulmonary function equipment.

7.9 THE SPECTRUM OF ASBESTOS-RELATED DISEASES

Asbestos causes fibrosis and malignancy in the lung and pleura. Increased risk of extrapulmonic malignancy including the larynx and selected sites from the gastrointestinal tract have also been reported within the literature and have been included in the formulation of various OSHA asbestos standards.

Asbestos-induced diseases occur along a "spectrum" reflecting levels of asbestos exposure, latency, and other factors. Asbestos-related diseases, which have frequently been cited in the peer-review literature, are summarized in Table 7.5–Table 7.7.

7.10 PLEURAL DISEASES

While asbestos fibers must transverse the upper airways, the bronchial tree, the pulmonary parenchyma and its components, it is the pleura which is the most common site of clinical findings in asbestos-exposed individuals. Perhaps, this is because pleural abnormalities may occur at lower levels of exposure than those, which cause asbestosis. How asbestos reaches the pleura has been the subject of numerous investigations and some speculation. Whether the primary route is by direct mechanical penetration, lymphatic spread, or other mechanism is discussed in Chapter 3.

Table 7.5 Clinical Pleural Manifestations of Asbestos Exposure

Benign pleural manifestations of asbestos exposure:
Benign asbestos effusion
Circumscribed pleural plaques
Hyaline plaques
Calcified plaques
Diffuse pleural thickening (requires involvement of a contiguous costophrenic angle)
Rounded atelectasis
Asbestos pleuritis
Malignant pleural manifestations of asbestos exposure:
Malignant mesothelioma
Epithelial
Sarcomatoid
Mixed — biphasic

The fact that the pathogenesis and method of transport to the pleura is poorly understood has been summarized by others.[39] The typical absence of asbestos bodies and the relative paucity of asbestos fibers found in the pleural diseases likewise contributes to various theories on causation including hypersensitivity reaction. Asbestos may cause changes in the visceral and parietal pleura, involving the lateral chest walls, diaphragm, pericardium, and the mediastinum. There may be considerable overlap between the pleural diseases, and they may occur individually or in any combination with other asbestos-related diseases.

7.10.1 Pleural Plaques

Pleural plaques are discrete areas of circumscribed pleural thickening most frequently involving the parietal pleura. They most often occur on the postero-lateral chest walls in the lower-half of the chest. They frequently parallel the course of the ribs (Figure 7.2 and Figure 7.3) and typically have markedly irregular margins, which are sometimes likened to a holly leaf in appearance. They may be flat, or have a more nodular morphology which can be mistaken for a

Table 7.6 Pulmonary Clinical Manifestations of Asbestos Exposure

Benign pulmonary manifestations of asbestos exposure:
Pulmonary asbestosis
Asbestos-related small airway disease
Malignant pulmonary manifestations of asbestos exposure:
Lung cancer
Adenocarcinoma
Squamous cell carcinoma
Large cell undifferentiated carcinoma
Small cell lung carcinoma

Table 7.7 Extrapulmonic Diseases Reported to have Increased Risk Following Asbestos Exposure

Laryngeal carcinoma[a]
Gastrointestinal carcinoma
Esophageal[a]
Stomach[a]
Colon[a]
Peritoneal mesothelioma[b]
Pericardial mesothelioma
Mesothelioma of the Tunica Vaginalis

[a]Historically[12] increased risk for these tumors has been attributed to asbestos exposure. OSHA and EPA consider risks for these malignancies when formulating policy. Recent analysis has raised questions concerning the role of asbestos and the magnitude of increased risk[20] in the causation of extrathoracic malignancy other than mesothelioma.

[b]Certain pathologic entities including (a) multicystic mesothelioma[37]; (b) well differentiated papillary mesothelioma[38]; (c) deciduoid mesothelioma[38], have been reported to occur in the absence of known asbestos exposure especially in young adults and females.

pleural-based density on chest x-ray. Plaques have a unique tendency to involve the diaphragm (Figure 7.4), especially in the region of the central tendon. They may involve the mediastinal pleura and the pericardium. They tend to spare the apices and the costophrenic angles. Calcification may be a good indicator of the age of the plaque as radiographically apparent calcification usually does not appear until 20 yr or more after initial exposure. While calcification may be dramatic in its extent, it only occurs in less than 10% of plaques and by itself neither significantly increases impairment nor risk of malignancy.

7.10.2 Exposure and Latency

Pleural plaques are of interest in that they occur at substantially lower levels of asbestos exposure than does parenchymal disease (pulmonary asbestosis). Their growth and progression is dependent upon time and level of exposure.[40] Radiographically, they are rarely evident less than 15 yr from first exposure and typically are not radiographically found in most cases until at least 20 years or more after initial exposure. Thereafter, the probability of growth and developing calcification increases with time.[41]

While most pleural plaques are the result of occupational asbestos exposures in the United States, they have also been reported in household contacts of asbestos workers. This has been most commonly reported in spouses who washed asbestos-contaminated clothing over a prolonged period of time. While not seen in the United States, environmental exposures to asbestos have been reported to cause pleural disease in Turkey, Finland, and Greece where forms of asbestos occurs naturally in the soil. In Turkey, erionite, a form of fibrous zeolite (an asbestiform fiber),

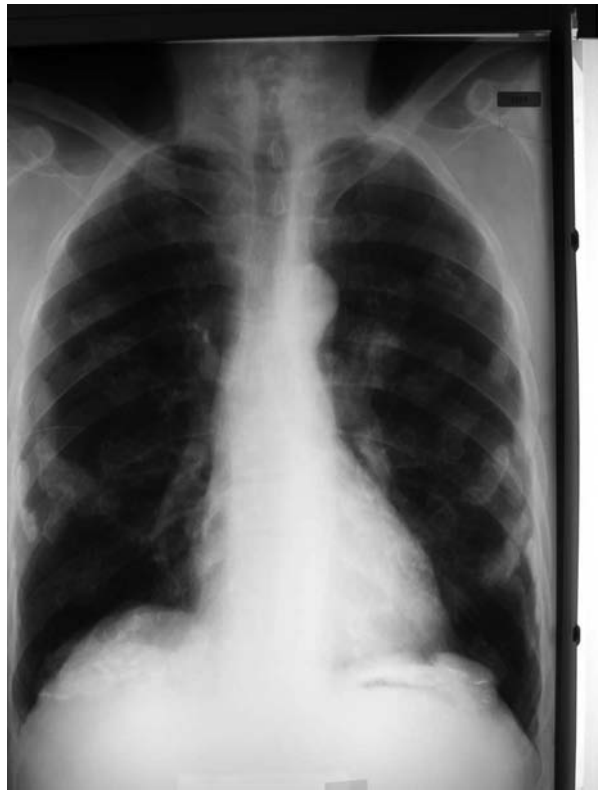

Figure 7.2 Bilateral calcified pleural plaques — both chest walls and diaphragms.

has been used in whitewash on walls of homes leading to a high incidence of pleural plaque and mesothelioma in that population.

Epler et al.[42] reported an increased incidence of plaques with passage of time with only 10% of exposed workers having plaques with less than 20 yr of latency and almost 60% by 49 yr of latency. These data probably represent substantially heavier exposure than experienced in the past three decades as the exposure periods dated back to 1933 in their study.

7.10.3 Chest X-Ray

Pleural plaques (Figure 7.2) represent the single most common radiographic findings in individuals exposed to asbestos. In surveillance studies of large groups of individuals exposed to asbestos, the occurrence of pleural plaques in the absence of interstitial fibrosis is a far more common finding than the finding of pulmonary asbestosis in the absence of plaques. In individuals with asbestosis, most studies report 60% or more to have accompanying pleural findings.[43–45]

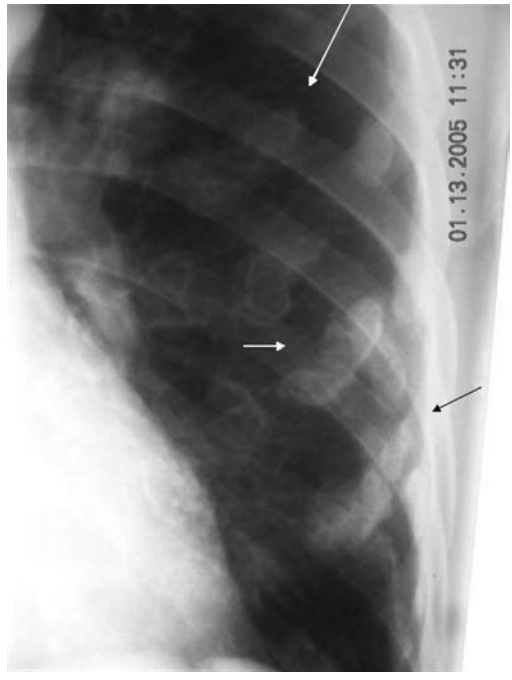

Figure 7.3 Calcified plaques paralleling the ribs (close-up).

On the PA chest roentogram, pleural plaques typically are seen as discrete circumscribed areas of pleural thickening along the lower one third of the lateral chest walls bilaterally. They typically have a flat plateau shape and may occasionally have a rounded or nodular appearance raising concern for malignancy. They

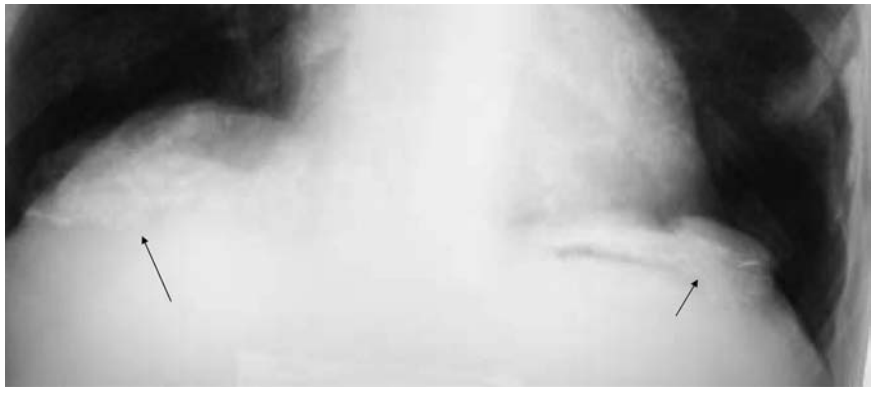

Figure 7.4 Diaphragmatic plaques — multiple punctate calcifications in plaque on right and calcified plateau-shaped plaque on the left.

typically do not involve the costophrenic angle or the apex of the lung. In the ILO classification, those seen on the lateral chest wall are described as being "in-profile" (Figure 7.2 — chest radiograph). Formation of plaques on the anterior or posterior chest wall is a less common occurrence.[46] In this position, they are perpendicular to the x-ray beam on PA projection and because of their typically thin profile, may only present a somewhat hazy or milky shadow and are described as being seen face on or "en face." To confirm the presence of such plaques, it is our policy to obtain oblique views where they are frequently seen to better advantage. CT scan may also confirm their presence (Figure 7.3).

7.10.4 Differential Diagnosis

The plaque with calcification, the plateau-shaped plaque on the diaphragm or bilateral areas of discrete pleural thickening with sparing of the costophrenic angles usually do not pose a diagnostic dilemma in the presence of an occupational history of asbestos exposure with adequate latency. However, in the absence of the classic appearance, the differential diagnosis can be more difficult.

The most common source of mistaken diagnosis is subpleural fat.[47] Subpleural fat tends to involve the apical and axillary region and may extend all the way down into the lower one third of the chest but does not involve the costophrenic angle. Serratus anterior muscle shadows have a typical saw-tooth appearance, which can mimic pleural thickening or plaque formation in some individuals. Skin folds, pectoral muscle shadows and other soft tissue shadows also must be excluded as a potential source of confusion for en face or in-profile plaque formation.

In our experience, a common source of circumscribed pleural thickening on the lateral chest wall is chest tube insertion sites. In this age population, prior coronary artery bypass and other thoracic surgery is a common occurrence. Post-operative changes from cardiac surgery, hiatal hernia or subdiaphragmatic surgery may occasionally cause diaphragmatic irregularities that can be confused with plaque. On physical examination, we carefully inspect the thorax and attempt to correlate the position of the chest tube and other surgical scars with the appearance of pleural irregularities on chest radiograph. Rib fracture and callous formation may result in adjacent pleural thickening, which must be distinguished from a pleural plaque. Penetrating chest wounds is a common occurrence in our practice. Blunt trauma often is unilateral, but occasionally may result in bilateral pleural changes. On those occasions, there are frequently associated rib fractures, which provide evidence as to the etiology of the pleural abnormality. Tuberculosis may result in pleural calcification, which may mimic asbestos-related changes. However, this is often a unilateral finding and usually is accompanied by other radiographic stigmata of tuberculosis such as upper lobe predominance, healed granulomas, and hilar adenopathy.

Silica may cause areas of pleural thickening, which are described as having a candle wax-like appearance. In these cases, however, the typical rounded opacities involving the upper lung zones, hilar adenopathy and other manifestations of silica

exposure help establish the etiology. Talc may cause pleural plaques and some of the earliest descriptions of calcified plaques occurred among talc workers.[48] However, it should be noted that talc is often contaminated with asbestos usually tremolite. Careful inquiry into these and other causes of pleural disease combined with the physical examination usually results in the proper clinical diagnosis.

7.10.5 Incidence: Pleural versus Pulmonary

In asbestos exposed populations, regardless of industry or occupation, there is a substantially higher incidence of pleural disease as opposed to pulmonary asbestosis. Kishimoto et al.,[49] studied 2951 construction workers in Japan by chest x-ray and later confirmed the findings by CT. Eighty-five patients had pleural plaques alone, nine had asbestosis alone and 74 had pleural plaques and asbestosis. In 11 subjects, pleural plaques were suggested on chest radiograph evaluation, but not confirmed on CT scan.

In 1986, 117 wives of insulation workers were screened by means of chest radiographs by Sider and Holley.[50] No women under age 40 had any abnormality. Ninety-three women were over the age of 40. Eighteen (19.4%) demonstrated pleural changes. Six of these women had diaphragmatic plaque. There was no evidence of parenchymal disease. The only significant variable predicting the finding of these radiographic changes was the elapsed time from first exposure. The mean latency was 32.8 yr. The intensity and duration of exposure appeared to be less significant.

Bresinitz et al.[51] reported on 91 elevator construction workers exposed during refurbishment work on older buildings. All had a greater than 20-yr employment in the industry. Twenty workers (22%) had evidence of pleural disease, but none had an interstitial process consistent with asbestosis. Fifteen had bilateral circumscribed plaques and five had unilateral plaque. Cases of diffuse pleural thickening or pleural effusion were not described.

Historically, there have been reports of a left-sided predominance for benign pleural disease which is unexplained. A more recent study by Gallego[52] reports on CT scans performed on 40 subjects with asbestos exposure and pleural plaque. He calculated the surface area of each plaque and the sum of these areas. He found a lack of a statistically significant predominance for either side.

Miller et al.[53] reported on 2611 long-term insulators with heavy exposure to asbestos. Those with pleural only abnormalities (633 — 24%) exceeded those with parenchymal only disease (301 — 11.5%). Miller and Lilis[54] studied 1245 sheet metal workers with at least 20 yr in the trade and compared them to insulators. They noted a substantially lower incidence of asbestosis (1/0) among sheet metal workers compared to insulators (17.5% vs. 59.5%) Also noted with lower exposure was a lower incidence of pleural disease (36% vs. 75%). The pleural findings out numbered parenchymal findings by a 2:1 ratio.

In 1994, Welch et al.,[55] investigated a larger group of sheet metal workers (9605) with 20 yr or more in the trade. The median age was 57 and there was an average of 32 yr in the industry. Radiographically, only 18.8% of them experienced pleural

disease whereas, 6.6% had parenchymal changes (1/0 or greater). Of the 2552 workers with 40 or more years, since entering the sheet metal trade, 24.2% had pleural abnormalities, 7.7% had parenchymal changes and 9.6% had both.

Oliver and Sprince[56] studied 120 public school custodians in 1991 and found that 40 (33%) had pleural plaque and 3 (2.5%) had parenchymal disease 1/0.

NIOSH[18] investigated sequelae of asbestos exposure at a petrochemical refinery at the request of a union and performed a detailed analysis stratified by occupation and length of exposure. The stratification identified those with high level of exposure such as insulators, pipefitters and boilermakers; moderate levels of exposure such as construction carpenters, riggers, welders, etc.; and those with lesser levels of exposure such as those working security, etc. Regardless of the occupation, pleural disease predominated over parenchymal abnormalities by at least a 2:1 ratio or greater. Prominence of pleural over parenchymal changes on chest radiographs was demonstrable regardless of length of employment and held true for retirees and current employees. Rosenstock[57] studied 681 plumbers and pipefitters finding 17% had pleural disease, 7% had parenchymal changes and 12% had both. Sepulveda and Merchant[58] studied 266 railroad workers (75% were over age 60) and found 49 (23%) had pleural changes, 3 (1.5%) had parenchymal changes and 3 (1.5%) had both.

Epler et al.[59] reported greater instance of pleural disease than pulmonary fibrosis in subjects with substantial asbestos exposure in all latency periods from 3 to 49 yr. Jones et al.[60] studied 5000 American Marine Engineers and found 12% with pleural abnormality either plaque or diffuse pleural thickening, whereas only 1.2% had interstitial small opacities. These authors described pleural plaque and calcification as the most common manifestation of asbestos exposure, which may be seen after relatively brief or low-dose exposures. Dement et al.[61] studied 2602 Department of Energy Workers and found 5.4% had 1/0 or greater profusion, while 23.1% had pleural changes. Of these, only 2% had parenchymal changes only (1/0 or greater), 20% had pleural changes only, and 3% had both pleural and parenchymal changes.

Substantially, more pleural plaques are found at autopsy, than are visible on chest x-ray. Hillerdal and Lindgren[62] reported a good correlation between occupational history and the radiographic observation of plaques. At autopsy, with a strict criteria utilized for plaques, only 12.5% were seen on chest x-ray. Hillerdal's criteria for definite pleural plaques included bilateral pleural changes in the chest wall or diaphragm with at least 5 mm thickness and progression in a 5-yr period if chest radiographs were available for examination. When Hillerdal utilized more liberal radiographic criteria, the number of false-positive cases exceeded the reviously undetected negatives.

7.10.6 CT Scan

Almost since its advent, CT scan has been reported to identify pleural plaques which were not readily identifiable on a chest roentogram.[63] Sluis-Cremer et al.[64] studied

19 men, eight of whom had exposure to amphiboles and concluded "CT did not consistently demonstrate either parenchymal or pleural change earlier than conventional films." Further, it was noted that pleural plaques were missed on CT when visible on conventional films and concluded that CT and conventional chest radiographs were complimentary. With the advent of high-resolution CT (HRCT) and other advanced imaging techniques, the ability to detect pleural and parenchymal diseases has improved. CT scan is useful in distinguishing the density of subpleural fat from fibrotic pleural thickening or plaque.

7.10.7 Malignancy

Sandenand Jarvholm[65] evaluated 3893 shipyard workers in an attempt to identify predictors of the risk for developing mesothelioma. They did not find any distinction between exposure parameters and pleural plaque and increased risk of mesothelioma. However, some more recent studies cite pleural plaque as a common occurrence in pleural mesothelioma. Dodson et al.[66] performed an analysis of fiber burden in lung tissue from 55 individuals with the pathologic diagnosis of mesothelioma. Fifty of these patients were reported to have pleural plaque. Forty-six had ferruginous body concentrations of over 1000 per gram dry weight of lung tissue. The majority of the ferruginous bodies had cores of amosite.

7.10.8 Symptoms

Pleural plaques are usually considered to be painless and as a rule are asymptomatic. Jarvholm and Larsson[67] studied 130 subjects having pleural plaques and compared them with a large control population who had no plaques. No difference in thoracic pain was found between the two groups. When severe pain is present, the clinician should be alerted to the possible presence of mesothelioma, cancer metastatic to the pleura, an inflammatory or infectious pleurisy, or some etiology other than pleural plaque. Unless extensive surface area is involved, plaques usually do not result in a sufficient impairment to cause dyspnea. When significant dyspnea is present, underlying interstitial disease or other etiology should be sought.

7.10.9 Smoking

There is no causal relationship between pleural plaques and smoking.[68]

7.10.10 Pulmonary Function Test

Because pleural plaques predominantly affect the parietal pleura, they either have no effect on lung function or one which is usually less than that seen with diffuse pleural thickening which involves the visceral pleura. Jarvholm and Sanden[69] investigated 202 non-smoking shipyard workers with varying degrees of asbestos exposure. The

majority had normal pulmonary function and there was no evidence that plaques alone caused impairment. They reported that 87 workers with plaques and no other radiographic abnormalities had on average, 6.9% lower FVC than those without plaques. This difference was largest for those with heaviest exposure to asbestos. Jarvholm hypothesized that this decrease was possibly due to sub-roentgenographic pulmonary fibrosis or decrease in chest wall mobility in cases where plaques covered large surface areas. Ohlson et al.[70] questioned, whether change in lung function of asbestos cement workers was due to the plaque *per se* or was the result of heavier asbestos exposure. Jarvholm opined a possible distinction between his findings and Ohlson's was reflective of levels of exposure in his shipyard workers versus Ohlson's cement workers.

Rosenstock et al.[71] studied spirometric values of 684 plumbers and pipefitters and evaluated radiographic evidence of parenchymal fibrosis and pleural thickening and cigarette smoking. In chest radiographs, pleural abnormalities only were found in 17% of cases and parenchymal abnormalities only in 7% with both found in 12%. She found that pleural abnormalities were associated with a slight lowering of FVC independent of pulmonary fibrosis at low profusion (1/0 or less). Mean values of FVC and FEV1 were 95 and 91% of predicted values, respectively. Functional changes were only slightly greater for those with diffuse pleural disease than plaque only. The population with pleural findings was small. Of 684 exposed workers, 48 patients had bilateral discrete pleural thickening while 63 demonstrated diffuse pleural thickening. Four-hundred and eighty reportedly had no pleural abnormalities. Baker et al.[72] found a reduction in FVC in sheet metal workers with greater than 30 yr employment who had evidence of pleural disease including pleural plaque after "controlling for potential confounding effects of age, smoking, and employment duration."

Most patients with plaques have well preserved lung function. Some large cohorts have shown reduction in lung function attributable to the plaques averaging about 5% of FVC even when interstitial fibrosis (asbestosis) is absent roentgenographically. However, the loss of function is not a consistent finding and longitudinal studies have not shown a more rapid decline in lung function.[20]

7.10.11 Physical Examination

There are no specific physical findings that identify the presence of pleural plaques. They are not associated with a pleural rub. A palpable mass in the chest wall should alert the physician to the possibility of mesothelioma or other malignant process as a cause for the pleural-based abnormality.

7.11 ASBESTOS PLEURAL EFFUSION AND PLEURITIS

Benign asbestos pleural effusion is one of the few pathologic responses to asbestos that occurs within 10 yr of first exposure. Epler et al.[59] reported effusions to be

bilateral or recurrent in 50% of their cases, sanguinous in one third and defined benign asbestos effusion with the following criteria:

(1) Exposure to asbestos
(2) Confirmation of effusion by radiograph or thoracentesis
(3) Exclusion of other more probable disease
(4) The appearance of no malignant tumor within 3 yr.

The latter is required to exclude those cases where the pleural effusion is attributable to mesothelioma, lung cancer, or metastatic disease, which is not detected at the time of the initial clinical evaluation. Interestingly, two thirds of Epler's patients reported no symptoms at the time, when effusion was discovered.

One of the first descriptions of asbestos-related pleural effusion came from Eisenstadt,[74] an astute internist in Port Arthur, TX, where numerous large chemical plants, refineries, and shipyards resulted in substantial asbestos exposure. In 1962, during the course of his practice, he observed "asbestos pleuritis" and asbestos pleurisy. He reported benign asbestos pleurisy was a "frequent disease" among welders, pipefitters, insulators, boilermakers, and others employed in the field of shipyards and oil refineries. He described the disease as having an acute, subacute, recurrent, or chronic course, which could be followed by mesothelioma many years later. In his series, he described effusions as clear, cloudy, or bloody.[73]

Gaensler and Kaplan[75] reported pleural effusion occurred in 21% of all asbestotics seen in their laboratory. Their paper provided the findings of pathology results from decortication in six cases and autopsy in one.

Scully in a CPC[76] from Massachusetts General Hospital in 1987 described a 48-year-old gentleman with a pleural effusion. He reported with pleural effusion, the most common asbestos-related disease during the first two decades after exposure to asbestos, which may recur on the ipsilateral or contralateral side, may be hemorrhagic or clear, and may be accompanied by rather mild symptoms. Blunting of the costophrenic angle is a common sequelae. Benign asbestos pleural effusion may be part of the pathogenesis for the development of diffuse pleural thickening, which by definition requires associated blunting of the costophrenic angle.

It is recommended that the clinician follow Epler's criteria for diagnosis of asbestos-related effusion with emphasis on exclusion of other more probable cause and 3-year follow-up.

7.12 DIFFUSE PLEURAL THICKENING

7.12.1 Description

Unlike pleural plaques, diffuse pleural thickening originates in the visceral pleura. Typically, it is a bilateral process. Because it is usually more extensive in surface area, involves the visceral pleura, and is adherent to the pulmonary parenchyma, it is more likely to cause impairment of lung function than discrete plaques. Some

opine diffuse pleural thickening represents residua from prior benign effusions.[77,78] Others suggest it is the fibrotic result of inflammatory pleuritis which may be dry and unassociated with effusion in some cases. Coalescence of pleural plaques has been suggested as another theory in the etiology of diffuse fibrosis.[77] However, this would not explain the blunting of the costophrenic angles or involvement of the visceral pleura as plaques, predominantly effect the parietal pleura. Historically, diffuse pleural thickening was felt to represent a continuation to the pleura of an underlying process of interstitial fibrosis or is frequently associated with such fibrosis histologically.[79] On HRCT scan, interstitial fibrosis (pulmonary asbestosis) is, in fact frequently associated with diffuse pleural thickening.[77] Hillerdal[80] suggested the possibility of an immunologic pathogenesis noting elevation of sedimentation rate in diffuse pleuritic reactions but not plaques. Stephens et al.[81] concluded that diffuse pleural fibrosis was a specific asbestos-associated entity "of uncertain pathogenesis" whose asbestos fiber counts fell between those with plaques and minimal asbestosis.

7.12.2 Latency

Typically, diffuse pleural fibrosis occurs after 20 yr or more from the time of exposure and the incidence increases with time.

7.12.3 Chest Radiograph

By definition,[22] diffuse pleural thickening requires blunting of at least one costophrenic angle with contiguous pleural thickening of at least 3 mm width (Figure 7.5), seen on the lateral chest wall. In the ILO classification, the extent of the pleural thickening is defined as Category 1 which involves the length of the

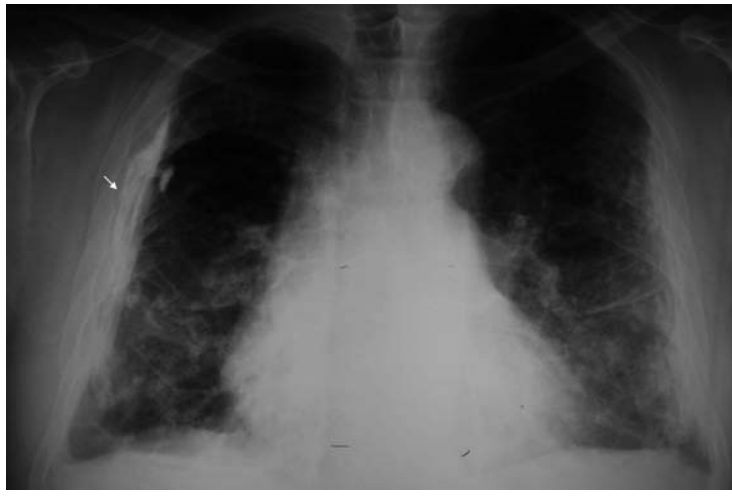

Figure 7.5 Diffuse pleural thickening with calcification bilaterally.

thickened pleura up to one fourth of the projection of the lateral chest wall; Category 2 from one fourth to one half of the projection of the lateral chest wall; and Category 3 with thickening of the pleura greater than one half of the projection of the lateral chest wall. The letters A, B and C represents the width of the pleural thickening. Recording of the width is now optional under the ILO 2000 Revision.[22] Calcification may occur usually greater than 25 yr after exposure.

7.12.4 Smoking

There is no established association between smoking and diffuse pleural fibrosis.[82]

7.12.5 Pulmonary Function Test

Thickening of the visceral pleura may affect chest wall compliance as well as impeding expansion of the underlying parenchyma, which becomes entrapped by the thickened pleura. Impairment of lung function in part is related to the extent of diffuse pleural thickening. In some cases, restrictive defect may occur in the absence of radiographically apparent pulmonary fibrosis. Reduction in diffusion capacity has been reported and attributed to possible underlying interstitial disease.[83]

7.12.6 Symptoms and Complications

Given that diffuse pleural thickening may result in impairment of lung function and in reduction of compliance, shortness of breath (especially with exertion) is the most common complaint. With active pleuritis, pain and chest wall discomfort may occur.

With diffuse pleural thickening (especially when bilateral or extensive), the degree of functional impairment may result in disability in the absence of underlying asbestosis.[84] Wright et al.[83] stated that if diffuse pleural thickening caused reduction in lung function with resulting symptoms, that disability could occur without asbestosis and that compensation might be appropriate for this complication of asbestos exposure. He studied six patients with circumferential pleural thickening and no evidence of asbestosis. Four of six demonstrated reduction in diffusion capacity and lung volumes. Miller et al.[85] described seven patients with severe chest wall restriction caused by asbestos-induced pleural fibrosis. Four had died from respiratory failure and one was near death at the time of publication. These patients either had minimal or no accompanying interstitial fibrosis and the severe impairment was attributed to the extensive pleural disease.

7.12.7 Physical Examination

The physical examination may reveal the typical findings described with pleural thickening or effusion from any cause and are non-specific. Diminished breath sounds and dullness to percussion may be present in severe cases. Diminished respiratory excursion may be apparent when there is circumferential thickening or trapped lung. When acute pleuritis is present, a rub may be heard, but in my

experience, it is extremely uncommon. Typically, the disease is diagnosed long after its inception and thus, acute findings are lacking. If a chest wall mass is palpable, malignancy must be excluded as a cause for the diffuse pleural disease. Evidence of prior blunt trauma, thoracic surgery, or penetrating wounds may be found on physical examination suggesting other more probable cause. Skin or joint manifestations of autoimmune disease, thrombophlebitis suggesting pulmonary emboli or other extrapulmonic manifestations of systemic disease causing pleural thickening may also be found on physical examination.

7.12.8 Diagnosis

The diagnosis is one of exclusion. With the exception of autoimmune disease, tuberculosis, post-operative change, and severe chest trauma, bilateral pleural thickening is uncommon. Given a history of significant asbestos exposure, with adequate latency, and the exclusion of other common causes of bilateral pleural thickening, the diagnosis can usually be made clinically without biopsy. Unilateral pleural thickening may occur, but diagnosis is more problematic as the differential diagnosis is far broader than for bilateral disease. If pleural effusion is present, thoracentesis and pleural biopsy are recommended as they would be in other cases of pleural effusion of unknown etiology. Given the increased risk for lung cancer and mesothelioma in asbestos-exposed individuals, it is recommended to aggressively approach pleural effusions in these patients and monitor their clinical course carefully.

If the pleura appears unusually thickened and has a “lumpy-bumpy” or irregular appearance, has sudden onset or if a parenchymal mass is suspected on imaging, then video-assisted thoracoscopy or open biopsy should be strongly considered in case a diagnosis is not obtained by thoracentesis, closed pleural biopsy, or other diagnostic testing.

7.12.9 Treatment

Extensive pleural thickening should be treated as in other causes of fibrothorax. In my experience, decortication has proven beneficial in select cases. However, surgical success may be limited by the technical difficulties of dissecting the adherent visceral pleura from the lung. Underlying pulmonary fibrosis may also prevent reexpansion of the lung and place limits on the benefits of decortication and thorough preoperative evaluation is mandatory. Those with diffuse pleural disease of recent onset are more likely to benefit from surgery than those with longstanding or chronic fibrothorax.

7.13 ROUNDED ATELECTASIS

Rounded atelectasis is a benign process associated with asbestos exposure, which may be difficult to distinguish radiographically from a solitary nodule of malignant

origin. It occurs as a peripheral lesion within the lung due to fibrosis of the visceral pleura which folds inward to bend or roll upon itself. Rounded atelectasis typically involves the periphery of the lung originating from thickened visceral pleura. The invaginated thickened visceral pleura causes atelectasis of the lung parenchyma producing a structure resembling a comet tail and referred to as a "comet tail sign" on imaging studies. Rounded atelectasis most commonly occurs in the inferior lobes posteriorly. This condition is often seen to better advantage on HRCT than on chest x-ray if sufficient slices are obtained to visualize the attachment to the pleura. Hillerdal[86] reported on 74 patients with rounded atelectasis. Sixty-four of these patients had been previously exposed to asbestos. Thirteen cases resulted from slowly increasing pleural fibrosis, but in 39 of the patients, rounded atelectasis was a sudden finding. Bayeux et al.[87] reported on 286 patients suffering from benign asbestos pleural disease and found a diagnosis of rounded atelectasis in 26 patients on computerized tomography. Their criteria included a rounded opacity of less than 7 cm in diameter situated at the periphery of the lung in contact with thickened pleura with reduction of lung volume on the side of the atelectasis and the presence of the comet tail sign. Doyle and Lawler[88] described eight major (Table 7.8) and five minor signs of rounded atelectasis in three patients studied with CT scan.

The primary importance of rounded atelectasis is that it must be distinguished from lung cancer, mesothelioma, or other pleural-based mass. Serial chest radiographs may be of benefit in demonstrating the evolution of the process. Recognition of asbestos as a common cause of rounded atelectasis requires its inclusion in the differential diagnosis of solitary pulmonary nodules in the asbestos exposed worker.

7.13.1 Pleural Disease and Cancer

There is no evidence that either pleural plaque or diffuse pleural thickening evolves into mesothelioma or lung cancer. The risk of developing mesothelioma and lung cancer is reported by some to be higher among asbestos-exposed workers with pleural disease than among equally exposed controls with no evidence of pleural abnormality.[72] Selikoff et al.[90] found that evidence of pleural fibrosis (even in the absence of parenchymal disease) was a "bad omen" with higher death rates from lung cancer and mesothelioma than in a group without pleural fibrosis.

Table 7.8 Major Signs of Rounded Atelectasis (Doyle and Lawler)[88]

A rounded mass of 4–7 cm in diameter in the lung periphery. The mass is never completely surrounded by lung
Mass is most dense in its periphery
Mass forms an acute angle with the pleura
Pleural scarring is usually present
Vessels and bronchi curve toward the mass
At least two sharp margins are present
"Comet tail" sign
Air bronchogram is usually seen in the central part of the mass

Hillerdal[91] reported that individuals with pleural plaque possess an increased risk for developing lung cancer and recommended surveillance for early detection. He found that, the risk of primary lung cancer was four times more than that of matched controls. Harber et al.[89] in 1987 studied pleural plaques and their relation to asbestos-related malignancy in a nested case control study of 1500 asbestos workers. They concluded that there was no association between pleural plaques and the risk of asbestos associated malignancies that were independent of other factors such as duration of exposure, age, and cigarette smoking. However, they stated that the presence or absence of plaques should not be used to allocate cancer screening resources stating that "if workers are known to have significant exposure it appears unwise to deny them appropriate examinations which they might otherwise receive simply because pleural plaque is not detected." The most recent ATS statement on asbestos[20] adopts the position that the presence of pleural plaque is associated with a greater risk of mesothelioma and lung cancer compared to subjects with comparable histories of asbestos exposure lacking plaques. The ATS identifies plaques as a "marker for elevated risk of malignancy" and that such risk may be higher than exposure history might suggest.

It is my opinion that pleural plaques are a reliable objective indicator of non-trivial asbestos exposure and that exposed individuals with pleural plaques or diffuse asbestos-related pleural thickening are at increased risk for asbestos-related malignancies.

7.14 PULMONARY ASBESTOSIS

Prior to 1986, there was considerable confusion in the application of the terminology "asbestosis." Many authors utilized the term pleural asbestosis to indicate pleural plaque, pleural thickening, asbestos pleuritis, and other stigmata of asbestos exposure.[15,92–100] In 1986, the ATS recommended the term asbestosis be reserved for the diffuse interstitial fibrosis of the pulmonary parenchyma caused by asbestos.[23] Pulmonary asbestosis is a form of interstitial lung disease which commences in the lower lobes and may ultimately progress into the mid and upper lung zones. It is caused by the inhalation of airborne particles of asbestos, which are of respirable size. The pathologic findings and grading of asbestosis are discussed in Chapter 5.

7.14.1 Exposure

Asbestosis is not caused by trivial exposures to asbestos and does not occur as a result of levels encountered in the ambient air in an urban setting. There is a dose–response relationship between the cumulative exposure and the development of disease.

It is probable that there is a threshold below which clinical asbestosis does not occur. There is no reliable evidence that clinically detectable asbestosis occurs with less than 10 fiber years of exposure. The Helsinki criteria[19] states the risk of

asbestosis detectable on PA chest x-ray may occur at a 25-fiber-yr level. The fiber burden necessary to cause microscopic change is beyond the scope of this chapter (see Chapter 3). There is a dose–response relationship for asbestosis: the greater the exposure level, the higher is the proportion of exposed individuals developing the disease. However, there does appear to be some individual variability. In part, this may be attributable to depth of inspiratory effort, minute volume, individual factors governing retention of fibers, and possibly individual immune response to the asbestos fibers. The clinical expression of dose–response relationship is mirrored in pathologic studies, which shows a substantially higher burden of uncoated asbestos fibers in patients with pulmonary asbestosis, than in exposed workers without the disease or in those with only pleural plaques.

7.14.2 Latency

Exposure levels experienced during the past three decades typically have a minimum latency of 20 yr and longer in my experience. The latency period for asbestosis is inversely related to the dose of exposure such that lower levels of exposure have substantially longer latencies.[101]

7.14.3 Symptoms

Asbestosis may be present with no respiratory symptoms or only minimal dyspnea with exertion. As the disease progresses, dyspnea becomes the most common symptom. Pain is typically not a symptom of asbestosis and suggests some other etiology. Because of the increased risk for lung cancer and mesothelioma, persistent or severe chest pain in an asbestotic, merits investigation for a malignant process. Also because of hypoxemia and pulmonary hypertension, investigation for a cardiac origin of chest pain likewise is warranted. A dry cough may be present in some patients, but in my experience this is not a prominent presenting symptom. Hemoptysis is not a feature of asbestosis and should lead the clinician to investigate for lung cancer, laryngeal cancer, or some other etiology. Hoarseness is not a typical manifestation of asbestosis, but warrants further evaluation for possible laryngeal cancer or involvement of the recurrent laryngeal nerve by a malignancy.

7.14.4 Physical Examination

Bibasilar inspiratory rales are reported to occur in approximately 40% of patients with asbestosis in earlier studies. They may precede roentgenographic findings. The rales are typically end-inspiratory, often heard in the area of the posterior axillary line immediately above the diaphragm and do not clear with coughing. They are often referred to as dry crackles. They must be distinguished from rales of pulmonary edema, rhonchi and other adventitious sounds.

While clubbing is historically a reported feature of asbestosis, in my experience nowadays it is a much less common finding than may have been observed in the remote past. It is probable that this is attributable to the reduced incidence of severe interstitial lung disease. When clubbing is present, care should be taken to exclude hypertrophic pulmonary osteoarthropathy, which may reflect a malignancy in the asbestos exposed patient. As in any patient with severe pulmonary disease, physical examination should include a careful search for elevation of the jugular venous pulse, prominent second heart sound, hepatomegaly, pedal edema, or other stigmata of current or impending cor pulmonale. Cyanosis likewise should be sought at the time of examination as a possible indicator of the need for supplemental oxygen. Stigmata of malignancy, congestive heart failure, chronic renal or liver disease, autoimmune disease, sarcoidosis, amyloidosis and other systemic illnesses known to cause interstitial fibrosis or increased interstitial markings should likewise be excluded at the time of physical examination.

7.14.5 Chest Radiograph

The PA view of the chest is used for the diagnosis of asbestosis (Figure 7.6). Bilateral increase in fine reticular (also described as linear or irregular) markings of the type seen in interstitial fibrosis in the lower one third of the lungs (Figure 7.7) are found in the early stages of the disease. If the lower lobes are spared or if there is diffuse involvement of the lungs at low profusion (especially in the absence pleural disease), a thorough search to exclude other more probable causes should be undertaken. Pleural plaque or diffuse pleural thickening is found in approximately 60% or more of the cases. Plaques may involve the lateral chest walls,

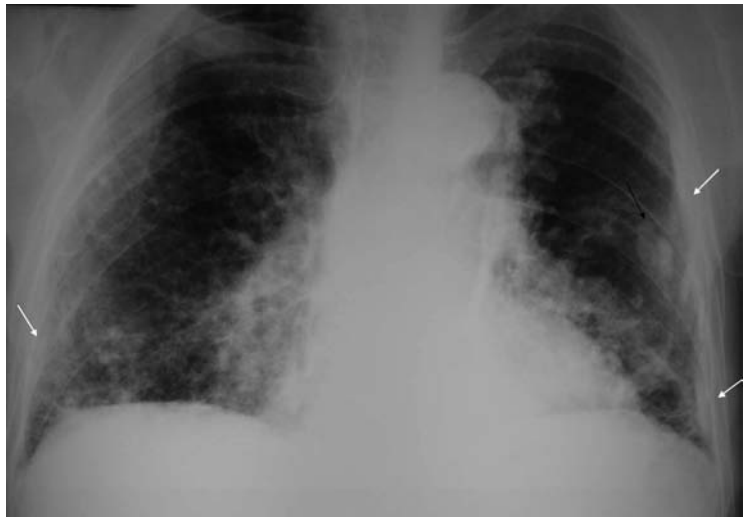

Figure 7.6 Pulmonary asbestosis: basilar fibrosis with bilateral plaques (some calcified).

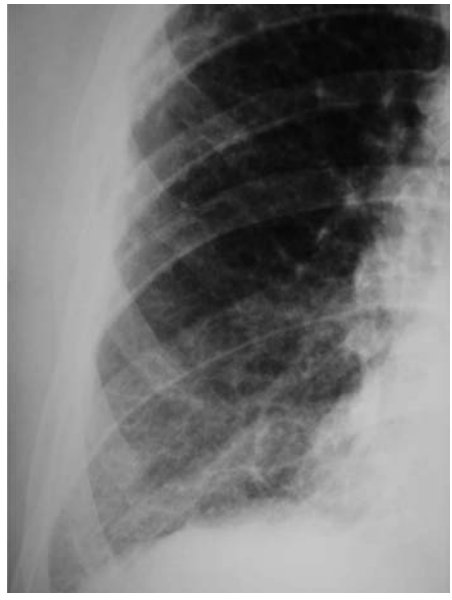

Figure 7.7 Asbestosis — lower lobe interstitial fibrosis (a close-up view).

diaphragm or pericardium. They may be hyaline or calcified. As the disease progresses, and profusion increases, middle and upper lobe involvement may occur. Rare cases of massive upper lobe fibrosis attributable to asbestosis have been reported.[103,104] The appearance of honeycombing is indicative of far-advanced disease and is usually accompanied by respiratory symptoms.

As noted previously in this chapter, the chest radiograph may be submitted to a "B-reader" for interpretation. However, the NIOSH sponsored B-reading program has come under criticism in recent years.[105] A subcommittee of the American College of Occupational and Environmental Medicine has recently suggested that, B-readings should not be used for the clinical diagnosis of a specific case of asbestosis, and that the use of that system is more appropriate for epidemiologic and research purposes.[102] Gitlin[16] has recently reported on 492 x-rays interpreted by "B"-readers involved in asbestos litigation purporting to show asbestosis. A blinded panel of six independent "B"-readers reviewed these films. The panel only concurred with a 1/0 profusion or greater in 4.5% of 2952 readings. Questions concerning the initial "B"-readings were raised as these discrepancies could not be explained by inter-reader variability. In 1988, an analysis of the practices of 23 "B"-readers interpreting 105,000 radiographs were reviewed. A marked difference was observed between "B"-readers for the frequency of perceived "definite parenchymal abnormalities." The authors felt that "B"-reader certification should not be the only quality assurance for radiographic surveillance programs, medical decision-making or related legal activities.[106] A follow-up study by Ducatman[107] suggested the formation of quality assurance panels to provide feedback and the dropping of outliers.

To date, most diagnoses have been made under the 1980 ILO system.[21] In January 2004, a newer version (2000 Revision) was instituted.[22] Inter-reader variability remains a problem and may account for a substantial number of misdiagnosed cases. Overestimation of the profusion of small opacities is encountered in obese individuals and those with elevated diaphragms due to compression of lower lobe markings. Poor inspiratory effort and underpenetration of the chest radiograph also may account for increased markings. Compression from large bullae, scoliosis and other conditions can likewise enhance markings and compress interstitium. On the other hand, overpenetration of the chest radiograph may cause a false negative interpretation. When severe pleural disease is present, it may mask the underlying interstitial fibrosis making diagnosis difficult. Histopathologic evidence of asbestosis may appear prior to radiographic evidence of the disease. Selikoff stated that, he had seen individuals who had difficulty walking across the room when little abnormality was detected in the chest radiograph.[10] However, the ATS warns that caution should be taken in diagnosing asbestosis in the face of a normal chest x-ray.[23]

The 1986 ATS criteria[23] found chest radiographic findings with small irregular opacities, which had a profusion of 1/1 or greater to be of proven value. However, these criteria came under substantial criticism.[108] The ATS committee subsequently clarified their statement[109] and Weill[110] later wrote stating that 1/1 was simply to be considered a level that was "illustrative of a film compatible with asbestosis so might also a category 1/0 film; it depends on the reader." The Helsinki criteria recommended utilizing the ILO criteria and required the use of the ILO standard films. They regard a 1/0 as an "early stage of asbestosis" for screening and epidemiologic purposes.[19] The 2004 ATS[20] statement on asbestos indicates a category 1/0 profusion on chest x-ray is "presumptive but not unequivocal" for the diagnosis of asbestosis.

Digital chest radiographs are gaining increasing popularity with improvements in technology and availability of equipment. They further have the advantage of ease of transmission from remote sites where consultants, qualified radiologists, or B-readers can have access to the films. Further, they minimize the problems of bulky storage of chest films and the risks of losing radiographs transmitted from one site to another for purposes of consultation. However, as of this writing, digital radiographs are not approved by the ILO for B-reading. The quality of the film can be manipulated as far as contrast, brightness, etc. Currently, there is no standard digital chest radiograph for the purpose of comparison for interpreting pneumoconiosis. As the use of digital radiographs become more widespread and film-plate radiographs diminish, it is possible that ongoing discussions over the use of digital radiographs will result in guidelines for their standardized use in the diagnosis of pneumoconiosis.

7.14.6 CT Scan

With the advent of CT scans in the 1970s, application of its' use for the diagnosis of interstitial and other pulmonary disease has been investigated. Initially, there were some technical limitations because of resolution. With the advent of high resolution computed tomography (HRCT), utilizing thin 1 mm sections and other technical

advances, significant improvement in clarity and diagnostic accuracy has increased the utility of the study in the diagnosis of pulmonary disease. Current criticism of utilization of HRCT for asbestosis includes the fact that there is no widely accepted standard for interpretations similar to the ILO system for the chest radiograph. There are those who have argued that such a program is not appropriate at this time because it may encounter the same problems that occurred in the B-reader program for plain films.[102] Huuskonen et al.,[111] proposed a semi-quantitative HRCT fibrosis score based on several parenchymal abnormalities graded separately. Six hundred and two asbestos exposed workers and 49 controls had HRCT findings compared to ILO interpretations for the same patients. Utilizing three radiologists, there was good inter- and intra-observer agreement in the interpretation of the scans and positive findings correlated with occupation and age. They reported specificity and sensitivity substantially greater than that reported by the ILO method and felt that application of an international classification for HRCT could possibly be adopted.

Biscaldi et al.[112] compared HRCT findings with those of chest x-rays interpreted according to the ILO classification and came to the conclusion that "high resolution chest tomography does not appear to be an indispensable test for the diagnosis," but may contribute to the evaluation of pleural thickening. Murray et al.[113] studied 49 patients exposed to asbestos and utilized HRCT in the prone position at specific pre-selected levels and found a relatively high level of accuracy could be obtained with a single prone scan. The studies were improved when additional images were utilized. They opined that using a limited number of pre-selected prone HRCT images could be applicable for screening a large patient group for asbestosis. Kraus et al.[114] proposed a classification system for CT/HRCT and opined it was practical in more than 2000 patients, which they had studied. Harkin et al.[115] studied the use of HRCT to better differentiate normal versus abnormal chest radiographs among those with low profusion scores on the ILO system, attempting to distinguish between 0/1 and 1/0 radiographs. They studied 37 asbestos exposed individuals using the ILO classification and combined it with HRCT, respiratory symptom questionnaires, PFTs and broncho alveolar lavage (BAL). A normal HRCT was an excellent predictor of normality, as demonstrated by completely normal pulmonary function studies with no evidence of inflammatory cells on BAL. When HRCT and ILO abnormalities were jointly found, there was a diminution in the FEV1/FVC ratio, diffusion capacity and an alveolitis by BAL was noted which was consistent with asbestosis.

Staples et al.[116] studied 169 asbestos exposed workers with normal chest radiographs (ILO less than 1/0) and found HRCT was normal or near-normal in 76 subjects; indeterminate in 36; and abnormal with suggestive asbestosis in 57. They found significant reductions in vital capacity and diffusion capacity in those with an abnormal high resolution CT, but a normal chest radiograph. The ATS[20] has included HRCT as an imaging study, which can be used in the diagnosis of asbestosis. They recommend its use over routine CT as it is more sensitive for detecting parenchymal fibrosis. However, it is acknowledged that because of the high degree of sensitivity of HRCT that abnormal finding may have "uncertain prognostic significance." Because of the uncertainty of the prognostic significance combined

with the lack of a standardized method for distinguishing abnormality at low levels of profusion of HRCT, I recommend caution in the utilization of HRCT at this time. In my opinion its use should be restricted to cases where there is other objective evidence (such as restrictive defect, rales, abnormal exercise study, etc.) unexplained by chest x-ray or other more probable cause.

7.15 PULMONARY FUNCTION TEST

Pulmonary function testing plays several important roles in the diagnosis and management of asbestosis (Table 7.1). First, it can provide information useful in supporting the diagnosis when used in conjunction with the history of exposure, latency, chest radiograph findings, physical examination and exclusion of other more probable cause. Impairment ratings are dependent upon pulmonary function testing, rather than radiographic findings or patient symptomatology. PFTs are useful in monitoring physiologic progression of asbestosis when serial studies are performed.

The ATS Guidelines for the Diagnosis of Non-malignant Diseases Related to Asbestos[23] states that a restrictive pattern of lung impairment with a FVC below the LLN and a reduced diffusion capacity below the LLN are of recognized value in making the diagnosis of asbestosis. While in advanced asbestosis the physiologic pattern is typically one of restrictive lung disease, early in the disease, small airway obstruction may be noted. There is no indication that asbestos causes reversible airway obstruction. When there is reduction of the FEV1:FVC ratio and in the absence of medical contraindication, bronchodilators should be administered to assess for reversibility. A dose–response relationship between asbestos exposure and impairment of function has been suggested by Weill et al.[117] who also report that small airway obstruction with impaired flow at low lung volumes may occur in pre-radiographic states of asbestosis. Other causes of small airway obstruction — especially that associated with cigarette smoking, also must be given careful consideration as etiologic factors in a given case.

Reduction in TLC is of benefit in confirming the restrictive defect — especially when airway obstruction is present.[32] If TLC is unavailable, reduction in FVC below the LLN with normal or elevated FEV1:FVC ratio is strongly suggestive of restriction. Extrapulmonic causes of reduced lung volumes including exogenous obesity, neuromuscular weakness, chest deformity, and other common causes of loss of volume should be excluded prior to attributing such abnormalities to asbestosis. Histopathologic asbestosis may occur with normal lung function.

7.16 THE PREDICTIONS FOR THE FUTURE INCIDENCE OF ASBESTOSIS

With markedly lower levels of exposure to asbestos in the 30 yr following 1973 than in the three decades preceding 1973, a significant decline in the incidence of

asbestos-related diseases was predicted. By 1978, Selikoff and Lee[118] noted that the majority of the cases he had previously reported, "had their origin in past years when dust levels generally were much higher than they are today. We would expect that with improvement in working conditions, the number of new cases would be less and that a longer time would elapse before the disease reaches the stage of being radiologically detectable." He further opined this would be especially true for asbestosis, but less apparent for pleural calcification.

In 1982, Nicholson et al.[17] opined that only the heaviest and longest exposed individuals would suffer serious non-malignant disease in the future. They projected that mesothelioma deaths would exceed deaths from asbestosis and that the incidence of asbestosis would peak in 1997 and decline, thereafter.

In 1983, Walker et al.,[119] from the Harvard School of Public Health, performed a detailed analysis attempting to project asbestos-related disease between the years 1980 and 2009. Utilizing the incidence of mesotheliomas he projected there would be 11,400 asbestotics who would be alive between the years 2000 and 2004. However, he opined, there could conceivably be many additional cases which "would include many people with few or no symptoms whose asbestosis would be detected by physical or radiologic examination only." He opined the number of future asbestotics would depend upon the diagnostic criteria, which were used and might reflect non-medical influences.

In 1990, Seidman and Selikoff[120] reported on the decline in death cases among insulation workers associated with reduction in asbestos exposure. They reported diminution of exposure between 1967 and 1986. There was a significant decline in death rate from lung cancer, peritoneal mesothelioma and asbestosis in men with less than 40 yr from onset of exposure. For those with greater than 40 yr from first exposure (1946 or earlier), these declines were not observed. The recent surge in the number of cases diagnosed with asbestosis requires further investigation.

7.16.1 Diagnosis of Asbestosis

The diagnosis of asbestosis requires the same careful, clinical assessment, which is utilized when approaching any interstitial lung disease (Table 7.9). The author for the clinical diagnosis of asbestosis utilizes the following criteria:

1. A detailed occupational history should be obtained commencing with the patient's initial employment starting from the time the individual first entered the work force. A chronologic history should be obtained of all subsequent employments and all potential occupational exposures documented. In addition to job description, details of the specific duties, which the individual performed should be recorded including intensity, duration, and frequency of exposure, use of respiratory protection and other factors which impact on exposure. In addition,

non-occupational sources of asbestos exposure should be recorded. The level of cumulative exposure should be capable of causing clinically detectable asbestosis.

2. At most levels of exposure experienced since 1973, a minimum of a 20-yr latency period is appropriate.
3. Radiographic findings supporting the diagnosis of asbestosis including the presence of bilateral interstitial fibrosis or irregular opacities in the lung bases. At low profusion (1/0 or 1/1), it is unusual to see upper lobe involvement. Bilateral pleural plaque, bilateral pleural thickening or calcified plaques, help in strengthening the probability that fibrosis is attributable to asbestos, but is not required. Because pleural change is present in over half of the cases with asbestosis, the absence of pleural change requires documentation of a diligent search to exclude other more probable cause for interstitial fibrosis. The 2004 ATS Statement[20] includes the use of HRCT as an acceptable imaging study for the diagnosis of asbestosis. My concern with, regard to the utilization of HRCT have been previously discussed.
4. The presence of impairment of lung function as demonstrated by reduction in FVC or reduction in diffusion capacity below the lower limits of normal on pulmonary function testing, serve as supporting evidence for interstitial lung disease. While impairment is not required, in my opinion such findings are helpful when minimal fibrosis (1/0 or 1/1) is present radiographically. Pulmonary function testing should be performed in all patients when diagnosed with asbestosis.
5. On physical examination, bibasilar dry inspiratory rales, which fail to clear with coughing support the diagnosis of an interstitial lung disease such as asbestosis. Their presence is of proven value in supporting the diagnosis, though it is not required. Clubbing is of historical importance. As the frequency of severe interstitial fibrosis has diminished, clubbing has become an uncommon finding. In the absence of severe interstitial fibrosis, when clubbing is present, malignancy or other etiology should be excluded.
6. The exclusion of other more probable causes of interstitial lung disease is mandatory;
   (a) A detailed medical history should be obtained for non-occupational causes of interstitial lung disease or increased interstitial markings including those which are set forth in the following section on differential diagnosis. As noted by the ILO, there is nothing pathognomonic about the chest radiograph and other illnesses may "mimic" asbestosis.

Table 7.9 Minimal Criteria for Diagnosis of Asbestosis

Asbestos-exposure sufficient to cause disease
Adequate latency
Chest radiographic findings
Exclusion of other more probable cause
The strength of the diagnosis is enhanced by:
1. Impairment of lung function especially as demonstrated by reduction in FVC or DLCO
2. Rales
3. Small airway disease (especially in non-smokers)
4. Presence of pleural plaques or bilateral pleural thickening

(b) Exclusion of other occupationally induced interstitial lung disease and exposure to other fibrogenic agents.
(c) If the patient is deceased, or unavailable for examination because of the gravity of their illnesses, it is mandatory that the physician requests all available medical records, chest radiographs and CT scans in order to obtain the above information. The same detailed occupational history should then be obtained through all available work records, interview of family members or other reliable sources of information concerning the patient's employment. The physician or a trained member of the physician's staff should obtain this information.

7.17 DIFFERENTIAL DIAGNOSIS OF ASBESTOSIS

Evaluation of asbestosis requires familiarity with the differential diagnosis of interstitial lung diseases. A detailed history from the patient should include careful inquiry into all prior pulmonary illnesses and injuries, presence or absence of autoimmune disease, such as scleroderma,[121] lupus,[122] and rheumatoid arthritis[123] which may cause interstitial lung disease; medications including the chemotherapeutic agents,[124] amiodarone,[125] methotrexate,[126] gold,[127] Furadantin,[128] and other drugs that have been implicated in causing interstitial fibrosis. Inquiry concerning use of illicit drugs including both inhaled and intravenous substances may prove rewarding.[129] Heroin and other injectables may be cut with talc or other impurities that can cause fibrosis and granulomatous reactions. Crack cocaine[129] has been associated with pulmonary sequelae. Paraquat sprayed on marijuana has caused interstitial damage.

Specific disease entities including sarcoidosis, amyloidosis[130] and other infiltrative diseases should be given due consideration. Hepatitis C,[131] and inflammatory bowel disease[132] may be accompanied by interstitial fibrosis. The group of diseases identified as idiopathic pulmonary fibrosis may likewise, cause severe interstitial fibrosis, and honeycombing as seen with asbestosis.[133,134] My policy is not to render a diagnosis of idiopathic pulmonary fibrosis in patients with an adequate history of occupational asbestos exposure with appropriate latency unless there is compelling evidence to the contrary.

Because asbestosis is traditionally an occupational disorder, the clinician must also inquire as to all other occupational exposures which may have occurred within the same setting or during a different employment. Pneumoconiosis including silicosis, talcosis, aluminum oxide, berylliosis, coal miner's pneumoconiosis, hard metal pneumoconiosis, arc welder's pneumoconiosis, and other inorganic mineral exposures should be explored. Fumes and chemicals such as vinyl chloride have been shown to cause pulmonary fibrosis. Many workers may have worked in agriculture or other industries where they may have contracted hypersensitivity pneumonitis which also may be of occupational origin.[135] Occupational and therapeutic exposures to high levels of radiation[136] also merit consideration.

Prior surgery, sepsis or shocks, resulting in ARDS, pneumonias, mycobacterial, fungal, and other pulmonary infections likewise, are routine components of our

inquiry. Lymphomas and lymphangitic spread of tumor usually are distinguishable by history or other diagnostic studies.

The preceding paragraphs gives only a partial list of examples in the differential diagnosis. There are numerous review articles and texts,[139] which provide a more detailed discussion of interstitial lung disease.

7.18 SUMMARY

Because no radiographic finding is pathognomonic of asbestosis, the physician must evaluate all other available data, including exposure history, latency, physical findings, pulmonary functions and a detailed medical and occupational history (including chronology of the disease). Review of prior radiographs and medical records when available is necessary in some cases to render a proper diagnosis.

The physician should keep in mind that asbestosis is a potentially serious disorder, which has no satisfactory treatment and can progress even after exposure ceases. Likewise, the diagnosis may adversely affect the patient's employability and insurability for both life and health insurance coverage.

Accordingly, the same diligent care should be taken in diagnosing asbestosis as would be undertaken with any other medical illness which is non-treatable and may result in disability or death.

7.18.1 Smoking

There are conflicting reports to the contributory role smoking plays in asbestosis. Some studies report a higher prevalence of interstitial disease among asbestos exposed workers who smoke.[137] Selikoff et al.[138] failed to find statistically significant increase in such changes among smokers. Barnhart et al.[140] attempted to determine the relationships between ILO roentgenographic classification of pneumoconiosis, spirometric values and effects of cigarette smoking. A positive association between smoking and level of ILO parenchymal abnormality was demonstrated — especially in those with the heaviest cumulative smoking history. There is biologic plausibility that smoking would increase the risk of asbestosis given that cigarette smoke adversely affects clearance mechanisms.[140] On the other hand, it is possible that mucous production from smoking along with chronic coughing of bronchitis may actually enhance clearance. Pulmonary injury and associated diseases caused by smoking such as desquamative interstitial pneumonia (DIP)[203,221,222] — respiratory bronchiolitis, as well as the more common complications of emphysema, and chronic bronchitis are present in asbestos exposed workers, as they are in other populations.

Cigarette smoking may cause increased bronchovascular markings and the appearance of "dirty lungs."[216] However, it is my opinion that current evidence is inadequate to opine that smoking by itself causes an increase in irregular opacities or interstitial fibrosis of a profusion necessary to support the diagnosis of asbestosis

radiographically, excepting cases where DIP or Langerhans is present. I believe, there is sufficient evidence to opine that smoking may be a risk factor for both the incidence and severity of interstitial lung disease in asbestos exposed individuals.

7.18.2 Airway Obstruction

In my opinion, both smoking and asbestos may cause small airway disease, and there is no convincing proof that asbestos causes emphysema or broncho-reactive disease. Attempting to assess the contributions of tobacco use requires obtaining a detailed smoking history including age of onset, duration, pack-years, and objective findings on chest radiograph examination, and pulmonary function testing.

The most recent ATS statement on the diagnosis of non-malignant disease related to asbestos[20] states that while the role of asbestos as a cause of airway obstruction is controversial, that small airway obstruction and reductions in FEV1:FVC ratio are reported. The magnitude of the effect of asbestos on airway function is relatively small and is unlikely to result in functional impairment or the usual symptoms and signs of chronic obstructive lung disease. However, when superimposed on other underlying disease process, the additional loss of function caused by asbestos-induced airway obstruction could be functionally significant at low levels of lung function. Short duration and low cumulative exposure are less likely to result in a significant obstructive abnormality.

The ATS recommends that, assessment of functional impairment of clinical significance should generally be based on the restrictive findings associated with asbestosis, as these are more likely to be disabling. However, the opposing effects of hyperinflation attributable to obstruction and the restrictive effect from fibrosis, which may end in a net zero change in TLC, may compromise utilization of TLC to measure restriction.[20,141]

Churg[142] has previously described asbestos-related small airway disease as an entity separate from asbestosis as a fibrotic process initially affecting the respiratory bronchioles and the alveolar ducts. He opined the abnormality was of "questionable functional significance" and was not a radiographically visible lesion. Nevertheless, he opined that small airway disease could represent a marker of "parenchymal damage even in the absence of diffuse fibrosis." The Helsinki Consensus Report includes small airway disease as one of the clinical findings, which may occur in asbestosis.[19]

7.18.3 Recommendations for the Clinician Concerning Care of the Patient Diagnosed with Asbestosis

1. Notify the patient that there is no treatment or therapy, which either cures the disease or prevents progression;
2. Secondary prevention — patient should be informed of the synergistic effects between asbestos and cigarette smoking in increasing the risk of lung cancer and should be advised to stop smoking completely and immediately;

3. Prognosis, in part, is related to age and other competing risk factors. For example, a patient of age 75 with mild asbestosis has a lower risk for future progression than does an individual of age 55. Competing risk factors for morbidity and mortality in the geriatric age group and longer potential latency to develop complications of asbestos exposure in younger individuals are considered in the clinical assessment of future risk;
4. Prognosis, in part, is related to the level of profusion on the chest x-ray at the time of diagnosis;
5. The prognosis for individuals with asbestosis in part reflects the increased risk for developing asbestos-related malignancy. Patients should be notified of increased risk of lung cancer, mesothelioma, laryngeal cancer and other asbestos related malignancies;
6. Patients are advised to undergo yearly checkup by their treating physicians with emphasis on the respiratory and GI tract in keeping with OSHA recommendation;
7. Chest radiographs: OSHA recommends yearly chest radiographs over the age of 40.[10,14] The ATS[20] recommends chest x-ray every 3–5 yr. Chest x-ray should be performed more often if there is a clinical change such as the appearance of unexplained increase in dyspnea, the appearance of hemoptysis, persistent cough or chest pain;
8. Screening for colon cancer should be performed according to the criteria established by the UICC International Workshop on Facilitating Screening for Colorectal Cancer,[183–185] as well as the guidelines of the American Cancer Society[186] for early detection of cancer. Annual fecal occult blood tests with flexible sigmoidoscopy every 5 yr commencing at age 50 are recommended, or double-contrastbarium enema every 5–10 yr starting at age 50 or colonoscopy every 10 yr starting at 50. Change in bowel habit or detection of blood in the stool would call for additional testing;
9. Screening for lung cancer and mesothelioma — there is no proof at this time that either chest x-ray or sputum cytology materially alters survival and currently, no major health organization recommends routine screening for lung cancer or mesothelioma.[186] Low dose CT scan has shown some promise and improvement over routine x-ray, but there is insufficient data at the present time to recommend for or against its use in screening.[186]
10. Patient should receive appropriate inoculations for:
    (a) Influenza vaccine;
    (b) Pneumococcal pneumonia vaccine.
11. Individuals with asbestosis should be advised to avoid any future exposure to asbestos or other fibrogenic dusts including coal, silica, etc.;
12. Individuals with asbestosis should be advised to exercise caution in the use of pharmacologic agents known to cause interstitial fibrosis such as bleomycin, furadantin, amiodarone, etc.;
13. If there is evidence of household or environmental asbestos exposure, patient should be properly informed so as to avoid future exposure;
14. The patient should be notified that he has a condition, which may be compensable;
15. The patient should be notified of pulmonary function results. If appropriate criteria are fulfilled, the patient should be notified of disability;
16. The physician should report to the appropriate state agencies as required by law;

17. For the patient who is found not to have asbestosis, strong reassurance should be given as to the absence of the disease. Appropriate information should be provided as to the need for proper follow-up and that smoking cessation is mandatory.

7.19 LUNG CANCER

Asbestos has long been recognized as a human carcinogen. McDonald[182] stated that it has been established "beyond reasonable doubt" that asbestos of the type used commercially is a cause of human lung cancer. Lynch and Smith[6] (1935) initially raised possible associations between asbestos and lung cancer. In 1955, Doll[8] reported 11 deaths in a cohort of British asbestos textile workers where 0.8 were expected for an SMR of 14.0. Subsequent to that time, numerous studies of various designs conducted on asbestos exposed workers in a variety of industries have reconfirmed carcinogenicity of asbestos for lung cancer. In 1986, OSHA[10] stated "lung cancer constitutes the greatest health risk for American asbestos workers" noting the agencies and organizations, who concluded that there is a causal relationship between asbestos exposure and the development of lung cancer including the International Agency for Research on Cancer (IARC), NIOSH, Environmental Protection Agency (EPA), Advisory Committee of the Health and Safety Commission of the United Kingdom, The Chronic Hazard Advisory Panel on Asbestosis (CHAP) and others.

Hammond et al.[143] reported approximately a five-fold increase in cancer risk among insulators. While carcinogens in asbestos and cigarette smoking may each independently cause lung cancer, exposures to both results in an increase in risk that is greater than the additive sum of the lung cancer risks. This is referred to as multiplicative synergism. For example, if asbestos increased the risk of lung cancer five-fold in a non-smoking insulator and smoking increased the lung cancer risk 11-fold in a smoking non-asbestos exposed individual, the synergistic effects in a smoking insulator could result in a 55-fold (5×11) increase in risk.

In 1964, Selikoff et al.,[144] studied 632 insulators who entered the trade before 1943 and were followed through 1962. Forty-five had died of cancer of the lung or pleura (mesothelioma), whereas only 6.6 such deaths were expected.

Occupational exposure to asbestos is associated with increased risk of all major histological types of lung cancer. The cell type cannot be used as an argument for or against the involvement of asbestos in a given case. Churg[145] reviewed eight different studies with a total of 471 patients and determined squamous carcinomas accounted for 43% of the tumors, small cell for 28%, adeno for 19% and large cell for 10%.

Dr. Weill[146] likewise noted that there was no specific histologic type of lung tumor linked to exposure to asbestos nor could the location of the tumor within the lung be used to support or exclude causation by asbestos. A review of the literature does not demonstrate any epidemiologic confirmation of increased risk for carcinoid tumors attributable to asbestos.

Amosite, crocidolite and chrysotile are all considered as carcinogens for lung cancer. While there is evidence for greater carcinogenicity of amphiboles over chrysotile with respect to mesothelioma, the establishment of a clear gradient in the carcinogenicity of fiber types is unproven at this time as it relates to lung cancer.

7.19.1 Exposure

A linear relationship between cumulative asbestos exposure and the development of lung cancer has been described. However, at low levels of exposure, there is some question, whether a threshold exists below which excess risk does not occur.[147] At ordinary environmental or ambient levels of exposure there is no objective data, which demonstrates increased risk for lung cancer. At very low levels theoretical risk assessments have been developed which assume a linear, no threshold model extrapolating from health effects at higher levels such as those reported in occupational settings. Hughes and Weill[148] assessed theoretical risks at low level asbestos exposure for students with 6 yr average enrollment in schools containing asbestos products. The students' cancer risks were substantially less than other risks of activities of daily living such as riding a bicycle or playing high school football. Governmental agencies and regulatory bodies erring on the side of caution assume a zero threshold when developing public policy. For example, the Department of Labor Asbestos Work Group stated that, there was no level of exposure to asbestos below which clinical effect did not occur and recommended a PEL[10] based on the limits of current technology for measuring airborne concentrations of asbestos without distinction of fiber type.

Because of the linear dose–response relationship between asbestos exposure and the development of lung cancer, efforts have been made to quantify the relationship between the fiber years of cumulative exposure and relative risk of lung cancer. The Helsinki criteria[19] states the increase in risk is estimated to be between 0.5 and 4% for each fiber year of cumulative exposure. Using the upper boundary of this range, cumulative exposure of 25 fiber years would double the risk of lung cancer. At this level, clinical asbestosis may likewise occur. This equates to tissue fiber burden of approximately 5000–15,000 asbestos bodies per gram of dry tissue. Because asbestos fibers undergo clearance with time especially chrysotile, some experts feel that for chrysotile, occupational history is a better indicator of lung cancer risks than is fiber burden.[19] According to the Helsinki criteria, attribution to asbestos as a substantial contributing factor in a specific case of lung cancer could be stated with probability at the 25-fiber year exposure level. Lower levels of exposure may be associated with an increased risk of lung cancer, but to a lesser extent.

The risk of asbestos-related lung cancer may vary between occupations or exposure settings as the intensity and duration of asbestos exposure may vary by occupation. For example, the risk of lung cancer is dramatically different for an insulator than it is for a brake mechanic.[17] Thus, a detailed exposure history is essential in determining risk or attribution.

7.19.2 Latency

Some authorities cite a minimum of 10 yr from first exposure prior to attributing lung cancer to asbestos.[19] In my opinion, a 15–20-yr or longer latency period is more appropriate. The latency can be affected by level of asbestos exposure, synergy and co-carcinogens. The risk increases with time and is highest after approximately 30 yr.[181] It then diminishes 35–40 yr following exposure.

7.20 CLINICAL APPROACH TO ASBESTOS-RELATED LUNG CANCER

There is nothing unique about the cell type or tumor location, growth pattern, metastatic tendencies or response to therapy, which distinguishes an asbestos-related lung cancer (Figure 7.8). Therefore, the clinical approach to these tumors is similar to that of non-asbestos exposed individuals with some exceptions including the necessity to distinguish between lung cancer and mesothelioma. The presence of underlying asbestosis may affect lung function to an extent that impacts on decisions concerning resectability. Underlying interstitial fibrosis may also enter into decision-making concerning the selection of chemotherapeutic agents, which may be fibrogenic and the use of radiation therapy.

7.20.1 Attribution and Apportionment of Lung Cancer to Asbestos

In 2001, Haus et al.[177] reviewed excess risk of lung cancer attributable to occupational and environmental causes. He stated that, as much as 4% of all lung

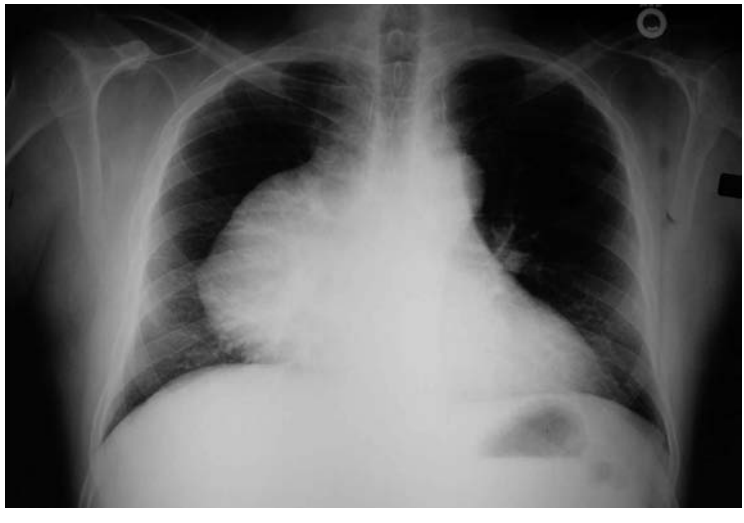

Figure 7.8 Non-small cell lung cancer with lengthy history of heavy asbestos exposure.

cancer diagnosed annually in the U.S. is attributable to asbestos. In 1996, Steenland et al.[178] at NIOSH reviewed 20 asbestos exposed cohort studies. The combined relative risk for lung cancer was 2.0 compared to an unexposed population. Six of these studies identified the combined relative risk of individuals with asbestosis (rather than just exposure) for developing lung cancer as 5.91.

The clinician is sometimes called upon to render an opinion concerning the causation of lung cancer in a given patient. There are no specific clinical features or radiographic characteristics of the tumor itself, which can aid in this determination. Thus, in the individual case, the probability that asbestos was a contributing factor, in large measure relies upon the dose–response relationship between cumulative exposure and development of lung cancer. Because the cumulative levels of exposure which cause asbestosis in some patients is similar to that which causes lung cancer, some authors require the presence of asbestosis[149,150] prior to attributing causation to asbestos in a given case. Other authors have argued that asbestos is a carcinogen and that fibrogenicity as an intermediate process is not required.[151–153]

In an occupational setting, exposure to other established human carcinogens also must be considered if causation of a lung cancer is in question. The following are known carcinogens for lung cancer in humans: arsenic, cadmium, bischloromethyl ether (BCME), chromium, nickel, silica and radon.[174]

Roggli et al.[154] found the asbestos body content in patients with lung cancer to be variable. Roggli, Greenberg and Pratt[155] demonstrated substantially higher fiber counts in 48 patients with lung cancer and asbestosis as compared to 25 patients with pleural plaque and lung cancer or 70 patients who only had histories of asbestos exposure. They reported a separate group of six non-smoking asbestos workers without plaques or asbestosis with lung cancer. Four of these demonstrated tissue content above the range of normal for their laboratory with a fiber analysis demonstrating approximately 30,000 uncoated fibers per gram of wet lung. They opined that in these individuals asbestos was a substantial contributing factor to the development of lung cancer in the absence of asbestosis.

Warnock and Eisenberg[156] attempted to distinguish asbestos-related lung cancer from unrelated ones. They studied 75 men with lung cancer, all but eight of them had some history of asbestos exposure. After measuring fibers per gram of dry lung, they reported that a substantial number of the subjects with the highest fiber burden did not have asbestosis. It was their opinion that because large burdens of asbestos do not always cause pulmonary fibrosis, that asbestosis may in fact be a poor marker of fiber related lung cancer. They opined that a concentration of 1000 or more asbestos bodies per gram of dried tissue or a combined fiber count of amosite and crocidolite totaling 100,000 or more per gram of dried tissue could be used as an indication of a relationship between lung cancer and asbestos exposure.

Wilkinson et al.[157] reviewed chest x-rays for fibrosis and obtained occupational and smoking histories from 271 lung cancer patients compared to 678 controls. After correction for age, sex and smoking, the O.R. was 2.03 for those with an ILO score of 1/0 or greater and 1.56 for an ILO score of 0/1 or less. They opined

that workers from occupations with high probability of exposure to asbestos were at increased risk of lung cancer even in the absence of radiographically apparent asbestosis. IARC[158] cited Edge and others concluding that an excess incidence of bronchial carcinoma existed in those exposed to asbestos without concomitant radiologic signs of asbestosis. Kannerstein and Churg[159] in 1972 stated that, they were unable to accept fibrogenesis as an intermediate essential causal phase in the development of lung cancer in asbestos exposed individuals. While Kipen et al.,[160] found pulmonary fibrosis histologically in their patients with lung cancer, they reported that 10–15% did not have radiographic findings of asbestosis and stated that the probability that interstitial fibrosis will not be radiologically detectable in a sizeable proportion of cases of cancer is of considerable significance. Whether or not asbestosis histologically always preceded lung cancer was unresolved.

The clinician may be called upon to render an opinion concerning causation in the absence of pathologic specimens, asbestos fiber or asbestos body counts. The physician must therefore, reach a conclusion only after taking into careful account the exposure history including nature of the exposure, the duration and intensity of exposure, the presence of objective evidence of asbestos exposure in the form of non-malignant disease, and weigh these factors against an accurate smoking history. If possible the medical records of the treating physicians should corroborate the latter. Likewise, the presence of other recognized pulmonary lung carcinogens must be factored into the determination.

I utilize the following as part of my decision-making process for the major cell types of lung cancer (squamous cell, adenocarcinoma, small cell, large cell undifferentiated carcinoma, large cell neuroendocrine carcinomas and mixed tumors of the above cell types). It does not include carcinoid tumors and certain other rare histopathologic variants. The following also assume a 15-yr or greater latency unless there is compelling evidence of unusually heavy exposure.

1. If clinical or pathologic asbestosis is present, I attribute lung cancer to asbestos.
2. If there is unequivocal radiographic evidence of bilateral pleural plaques or bilateral diffuse pleural thickening (not caused by the tumor, surgery or other therapeutic intervention), it would be my opinion that, asbestos played a contributory role in the causation of the tumor with supportive exposure history.
3. In the absence of objective clinical evidence of asbestos exposure and if no pathology is available for review, if the patient has a documentable, significant, history of asbestos exposure that reasonably can be shown to be 25 fiber yr/cm^3 or greater, I would state that asbestos was a contributing factor in the causation of the lung cancer.
4. If there is no clinical evidence of a non-malignant asbestos-related disease, but there is pathologic evidence of findings of asbestos bodies on H&E or iron stains sufficient to cause an asbestos-related disease, I would consider asbestos a contributing factor in the causation of the cancer.
5. If there is no clinical evidence of asbestosis or pleural plaque and pathologic material is available (other than a transbronchial or needle biopsy) and fails to

show evidence of interstitial fibrosis, asbestos bodies or asbestos fibers, I do not attribute the cancer to asbestos regardless of exposure history.

6. If there is no radiographic or other clinical evidence of asbestosis or pleural disease and pathology specimens are unavailable and there is a significant smoking history and a 25 fiber yr/cm^3 exposure history cannot be reliably documented, I do not consider asbestos a contributing factor in the causation of the tumor.
7. If there is a necessity to apportion causation, the relative risk attributable to asbestos must be compared to the relative risk attributable to smoking along with consideration of any other carcinogens or co-carcinogens.

7.20.2 Future Risk of Lung Cancer

When confronted with a patient who had significant exposure to asbestos or had been recently diagnosed with asbestosis, the physician should be prepared to answer questions concerning future risk of cancer. It is often easier to make broad statements that apply to large groups based on information gleaned from epidemiologic studies, than it is to provide specific information concerning the individual patient sitting in the examination room or consultation office.

The future risk of cancer in the asbestos exposed patient is more complex than simply stating that asbestos is a proven human carcinogen capable of causing lung cancer. In order to properly counsel the patient who has asbestos exposure or an asbestos-related non-malignant disease, the assessment of cancer risk is multidimensional. The physician must take into consideration the level of asbestos exposure, the presence or absence of benign asbestos-related diseases that might help quantify prior exposure, the presence of risk factors from other carcinogens, the potential for the synergistic interaction between asbestos and such carcinogens, the patient's age and other competing risk factors.

An "increased risk" of cancer suggests that the physician has some knowledge or understanding of the background risk of lung cancer in the absence of asbestos exposure. The estimate for new cases of lung cancer during 2004 is 173,770 with 93,110 occurring in men and 80,660 in females with 160,440 of these cases resulting in death.[161] Estimates suggest that tobacco smoking causes or contributes to at least 85% of the lung cancer deaths. There has been a slight decline in lung cancer death between 1990 and 2000. Some have attributed this decline to reduction in smoking, which commenced in the 1960s following warnings from the Surgeon General's office.[162] Given the population in the United States in the year 2000 at 265,306,000, with approximately 2,410,000 deaths per annum, the lifetime odds of dying of lung cancer are approximately 6.0% with approximately 85% of such cancers attributable to smoking. After 10 years of smoking cessation, there is a decrease in the risk of lung cancer with significant further diminution of risk as the duration of smoking cessation increases. After 15–20 yr of smoking cessation, the risk of lung cancer approaches that of a non-smoker.[166]

The age at which smoking commences effects the risk of lung cancer. People who start smoking in teenage years have a higher incidence of lung cancer than those starting in later life. While there is a dose–response relationship between cumulative cigarette smoking measured in pack-years and lung cancer risk, the duration of smoking may be a contributory factor independent of total pack-years.

Liddell[163] has reviewed the additive and multiplicative models for lung cancer risk due to the interaction of asbestos and smoking. After analyzing the imprecision and statistical challenges of comparing risk of smokers and non-smokers exposed to asbestos, he concluded the relative risk of lung cancer from asbestos exposure was approximately twice as high in non-smokers compared to smokers.

In 2004, Berry and Liddell[180] published a study on the interaction of asbestos and smoking in causation of lung cancer. They used the term modified relative asbestos effect (RAEm) as the ratio of the excess relative risk in non-smokers to that of smokers. They concluded the RAEm was 3.19 with 95% CI (1.67–6.13).

7.20.3 Occupations, Asbestos Exposure and Risk of Lung Cancer and Non-Malignant Disease

As previously noted, there is an estimation that the risk of lung cancer increases from approximately 0.5% to 4% per fiber year of exposure.[19] In addition, a latency period of 20 yr or more is required before significant increase in lung cancer risk occurs. Historically, many references cite Dr. Selikoff's study[164] on cancer risk in 17,800 United States and Canadian asbestos insulation workers. A group of 9590 men who were cigarette smokers had 25 deaths predicted and 134 observed (relative risk 5.34). Among a select group of 370 New York–New Jersey insulation workers there were 87 non-smokers with only one death from lung cancer and 283 smokers with 41 deaths occurring from lung cancer (relative risk 12.39). Kleinfeld et al.[165] reported on 152 asbestos workers with more than 15 yr exposure prior to 1965, finding that ten out of 46 deaths were due to lung cancer as compared with the expected 1.43. Selikoff and Lee[164] noted a ratio of observed versus expected deaths with a relative risk of 6.29 for workers in an amosite factory and 3.21 for those working in a chrysotile factory. Others have reported higher risks with chrysotile exposure. In 1979, Hammond et al.,[143] studied insulators and found that asbestos workers who were non-smokers had a mortality ratio of 5.17 for lung cancer, while those who smoked had a mortality ratio of 53.24. Statistics for insulators who traditionally have histories of heavy exposure to asbestos may not always be applicable to other trades.

In 1982, Nicholson et al.[17] projected mortalities from asbestos-related diseases covering the years 1980–2030. The authors estimated future cancer projections attributable to prior asbestos exposure for a significant number of different occupations and industries. They identified fiber contents of various products, and potential exposure levels in different occupational settings. They also reviewed lengths of employment within the occupations, primary source of asbestos exposures and estimated indices of relative asbestos exposure between selected occupations and

industries. By example, in primary manufacturing, they estimated that the average fiber concentration to be 20–40 fiber per ml of air, insulation work 15, ship building and repair (exclusive of insulators) 2; with auto maintenance 0.1–0.3 fibers/ml. From these numbers, they determined a relative risk of lung cancer in primary manufacturing to be up to 6.1, among insulators to be 4.8 and among chemical plant and refinery maintenance workers, to be 1.5. They did not attribute any increased risk of lung cancer or mesothelioma to automotive maintenance workers. Minimum employment was 20 yr for all industries except automotive maintenance which was calculated at 10 yr because of employee turnover. Comparing the relative risk of lung cancer between other occupations to insulation work after 25 yr of employment revealed that shipbuilders and repair workers (except insulators) had half the risk and the construction trade (except insulators) had between 0.15 and 0.25 the risk of lung cancer. Stationary engineers and fireman, chemical plant and refinery maintenance workers also only had 0.15 the risk of lung cancer as compared to insulators. Auto maintenance workers had a 0.04 relative risk of malignancy compared to insulators. These opinions were based on the prevalence of non-malignant chest radiographic abnormalities among these populations when studied.

Miller et al.[167] compared insulators and sheet metal workers (a trade recognized as having substantial risk of asbestos exposure) observing that the radiographic findings of sheet metal workers of asbestosis were only 29% of insulators. Their risk of pleural disease was less than half that of insulators and the authors concluded that despite having similar age, duration of exposure and smoking histories, the sheet metal workers had less severe radiographic findings which were "consistent with a less intense exposure to asbestos as may be expected from the nature of their work compared with insulators."

Koskinen et al.[168] conducted a study of asbestos induced occupational diseases in Finland between 1990 and 2000 for the Finish Institute of Occupational Health. They analyzed the significance of specific occupations with descriptions of actual job duties, an expert evaluated cumulative asbestos exposure index and x-ray abnormalities as indicators of asbestos-related cancer risk among construction workers. They assigned different weights, to asbestos exposure occurring prior to 1976 and following 1977. For example, in 1976 they weighted pipe insulation work with an exposure of 10, whereas construction work in building repair was a 2, asbestos spraying and asbestos insulation work was 20 and brake or clutch repair, a 1. Following 1977, they reduced the risks in various categories. Of 16,696 male Finish construction workers, 249 cases of lung cancer were observed with a normal SIR in non-smokers and an SIR of 3.74 in smokers. Of the 249 lung cancer cases, 150 had pleural plaques and 32 had an ILO profusion of 1/0 or greater. There was a dose–response relationship based on the cumulative exposure index. The Standard Incidence Ratio (SIR) for lung cancer was calculated in comparison to the Swedish population. The SIR for lung cancer among insulators was 3.03, whereas for plumbers it was 1.24, electricians 0.9, painters 1.13 and carpenters 1.00 with age and smoking adjusted relative risk of lung cancer. Using univarite analysis, insulators had a relative risk of 5, plumbers 2.4 and electricians 1.8. A strong relationship between an asbestos exposure index and malignancy was

seen. The authors opined that pleural plaques alone did not identify a group with an elevated risk of lung cancer while lung fibrosis, category 1/0 or higher, identified a two-fold risk and the expert evaluated cumulative exposure index imparted a three-fold relative risk of lung cancer.

The above data are presented to remind the reader of the importance in identifying not only job title, but specific duties, duration and chronology of employment. Further, they document the potential errors in attributing risk factors, which are applicable to insulators to other asbestos exposed professions.

7.20.4 Presence of Non-Malignant Respiratory Disease

The relationship between pleural plaque and risk of lung cancer was discussed previously in this chapter. It is widely accepted that when pulmonary asbestosis is present, the risk of lung cancer is significantly increased with an SMR of 2.0 or greater. Historically, those with asbestosis resulting from high cumulative levels of exposure, experienced greatly elevated lung cancer risks. In Great Britain, asbestosis was a compensable disease by 1948. In 1965, Buchanan[169] performed a study for the medical branch of Her Majesty's Inspectorate of Factories of the Ministry of Labor. The study involved workers, who had been previously diagnosed with asbestosis and who had expired prior to 1964. Over 50% of males with asbestosis dying between 1961 and 1963 also had an intrathoracic neoplasm as found in 42 cases of 77 asbestotics. Four of these were recorded as mesothelioma. However, lesser death rates were recorded during other time periods.

Berry[170] reviewed workers registered with a British pneumoconiosis panel between 1952 and 1976 as having been certified as suffering from asbestosis. Of 665 men, 283 had died, 39% from lung cancer and 9% from mesothelioma. The SMR for lung cancer was 9.1. The incidence of lung cancer was related to the severity of the underlying asbestosis at the time of initial reporting as measured by percentage disability.

It should be noted that these studies are of historic interest demonstrating the carcinogenicity of asbestos with exposure levels prevalent during the time of the above cohorts' employment.

The studies which have been performed in more recent years reflecting reductions of exposure to asbestos which occurred in the 1970s may be more appropriate for many patients with newly diagnosed asbestosis. Hillerdal[171] studied 1596 men with pleural plaques from 1963 through 1985. The relative risk for lung cancer among individuals with pleural plaques and asbestosis (when adjusted for smoking) was 2.3, whereas those who only had plaques, the relative risk was 1.4.

There is a decline in the risk of development of lung cancer approximately 35–40 yr after first asbestos exposure.[172] A recent report from Poland[173] assessed the risk of asbestos-related malignancies in 907 men and 490 women previously diagnosed with asbestosis between 1970 and 1997. They were followed through December 1999. Of the 300 male deaths, 39 were attributed to lung cancer (13%). The authors opined that increased risk of lung cancer and mesothelioma occurred in persons exposed to a dose above 25 fiber yr/ml. Males had an SMR

of 168 for lung cancer while females had an SMR of 621. In addition to lung cancer, three mesotheliomas were found in males and three in females.

Seidman and Selikoff[120] who in 1990 reported a reduction in mortality associated with diminished occupational exposure, observed a decline in death rates among insulators in recent years.

Hughes and Weill[149] performed a prospective mortality study on 839 men employed in manufacturing asbestos cement products in 1969 and followed up through 1983. Workers were studied for lung cancer risk in relation to radiographic evidence of pulmonary fibrosis, controlling for age, smoking and asbestos exposure. Twenty or more years after hire, no excess cancer was found among those without radiographically detectable pulmonary fibrosis. Workers with a 1/0 or greater profusion had an SMR of 3.6.

Thus, in counseling the patient concerning lung cancer risk, it is important to document a detailed occupational history as it relates to job duties, frequency of exposure, and the point in time when such exposures occurred. A detailed smoking history and exposure to other potential carcinogens also must be considered.

The age of the patient is important, as an individual at age 50 has a far greater potential latency period for developing a future malignancy than does an individual at age 80. Also, the length of time since initial exposure is important as there is some reduced risk of lung cancer at 35–40 yr following exposure. Finally, as in any other clinical determination, other competing risks for mortality are essential. For example, in an individual with asbestosis who also has hypertension, diabetes, a prior history of coronary artery disease and/or cerebrovascular disease, is less likely to die from a future lung cancer than is an asbestotic of similar age who lacks any such competing factors. Prostate cancer and other malignancies likewise pose significant competing risk in this population.

7.20.5 Other Risk Factors

Because of the cancer risk, some have argued for a ban on asbestos regardless of fiber type.[175] Camus[176] argued for a distinction by fiber type suggesting a lower risk of asbestos-induced lung cancer in chrysotile industries than in amphibole industries. Distinction between carcinogenicity of fiber type in causing lung cancer is not as well defined as that for mesothelioma. OSHA does not distinguish between fiber types in their risk assessments for lung cancer.

Oksa et al.[179] reported that, radiographic progression of asbestosis is a predictor for the development of lung cancer. He studied 85 asbestotics who were followed radiographically between 1978 and 1987. Those who progressed one major or two minor categories were identified as having progressive disease. Of 24 males with radiographically progressive small opacities, 11 (46%) developed lung cancer. Five (9%) of 54 males without progression developed lung cancer. The SIR for lung cancer was 37 (95% CI 18–66) for the progressors and 4.3 (95% CI 1.4–9.9) for the non-progressors. Oksa concluded that progression of pulmonary fibrosis may be an independent risk factor for lung cancer risk in addition to smoking history and intensity of asbestos exposure.

7.21 MALIGNANT MESOTHELIOMA

Malignant mesothelioma is a rare malignancy arising from the serosal surface. The most common origin is from the pleura followed by peritoneal mesothelioma with rare mesotheliomas reported to arise from the pericardial surface or the tunica vaginalis. The association between asbestos exposure and the occurrence of mesothelioma is so well established that the finding of a pleural mesothelioma may act as a "sentinel tumor" or as a "signal malignancy" serving as an epidemiologic marker for asbestos exposure[187] (see Table 7.10).

Dail and Hammar[188] reviewed the association between asbestos exposure and the incidence of mesothelioma. They cited 14 studies where the incidence of asbestos exposure ranged from 13% of cases to 100%. In 11 of the 14 studies, over 50% of the mesothelioma cases had experienced asbestos exposure. The Helsinki consensus statement[19] indicates asbestos exposure can be identified in approximately 80% of mesotheliomas. The incidence of mesothelioma in women is approximately one to two per million, which some suggest may reflect the background risk of the tumor. However, it is probable that some of these cases represent household exposure or other non-occupational exposure to asbestos. In males, the incidence has varied from 0.65 per million[189] to 17 per million. The difference in incidence of occurrence between men and women is largely attributable to the male dominance in occupations where asbestos exposure is most likely to occur.

The number of mesotheliomas reported annually has been increasing. Possible explanations include:

(1) True increase in incidence due to length of latency from heavy exposures in the remote past;
(2) Improvement in immunohistochemical and other pathologic techniques resulting in increased recognition of the disease;
(3) Increased awareness of the public and physicians due to litigation and articles published in the peer-reviewed literature.

7.22 LATENCY

While mesotheliomas have been reported in an isolated number of pediatric cases, the occurrence below the age of 50 is rare. The latency for mesothelioma while

Table 7.10 Asbestos Exposure and Mesothelioma

80% of pleural mesotheliomas are attributable to asbestos exposure
Understanding the relationship between asbestos exposure and mesothelioma requires an assessment which is multidimensional:
Latency — risk increases exponentially with latency
Dose-response relationship
Fiber type — amphiboles are substantially more carcinogenic for mesothelioma than chrysotile
Location — peritoneal mesotheliomas are usually the result of lengthy high dose exposures to amphiboles
Histologic characteristics

rarely as short as 15 yr, usually exceeds 30–40 yr. The occurrence of mesothelioma with latencies of less than 15 yr, and some cases reported in young adults, raise the possibility of deciduoid mesothelioma, multicystic mesothelioma, and well differentiated papillary epithelial mesothelioma of the peritoneum which have been reported in the absence of asbestos exposure.

7.22.1 Pleural Mesothelioma Clinical Manifestations

Typically mesothelioma presents with symptoms of chest pain, shortness of breath, and pleural effusion.[190] The effusion is often sanguinous and has high protein content. The diagnosis may be difficult to establish and reliance upon cytology, cytologic evaluation of pleural fluid, fine needle aspiration biopsy specimens and Tru-Cut needle biopsy specimens may be fraught with difficulty.[191] The tumor grows in a contiguous fashion along the pleural surface encapsulating the lung resulting in reduced lung volume. Involvement of the mediastinum and pericardium is common and may result in pericardial effusion, extrinsic compression of the esophagus, and compromise of other mediastinal structures.

The patient often experiences marked weight loss, cachexia, and hypoxia in the later stages of the disease. The pain associated with mesothelioma may be severe and unrelenting requiring significant amounts of analgesics including narcotics. While the growth of the mesothelioma is usually contiguous, it may exhibit metastatic spread and frequently may grow through the diaphragm to involve the liver or peritoneum. Conversely, peritoneal mesotheliomas may penetrate upward through the diaphragm causing pleural effusion.

7.23 CHEST X-RAYS

Chest radiographic findings in cases of mesothelioma may begin with evidence of unilateral pleural effusion, minimal non-specific pleural thickening, or blunting of the costophrenic angle. Often the initial finding is described as a pleural-based density or pleural-based mass (Figure 7.9). As the disease progresses, the chest radiograph typically shows marked pleural thickening which may begin anywhere along the pleural surface, but in some cases may extend to circumferentially surrounding of the lung resulting in compression and areas of atelectasis of the involved lung. The pleura typically has an irregular or nodular surface and is sometimes described as having a “lumpy-bumpy” (Figure 7.10) appearance. As the disease progresses, there is a frequent loss of lung volume. Opacification of a hemithorax may occur either as a result of pleural effusion or tumor growth complicated by atelectasis or underlying pneumonia. Radiographic evidence of pleural plaques or asbestosis may be seen on x-ray or CT scan, but are not mandatory.

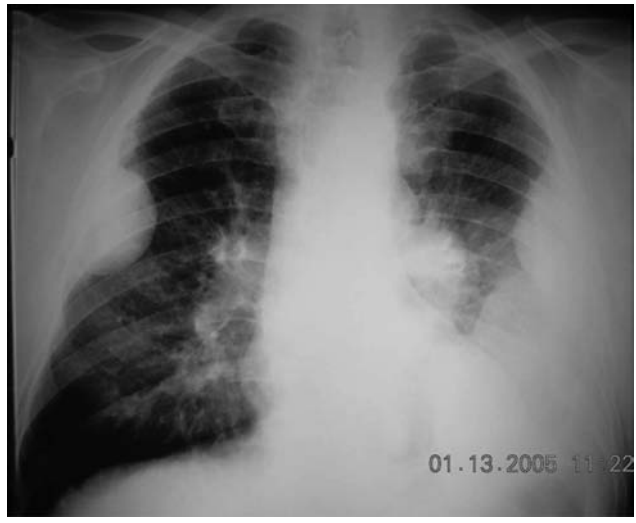

Figure 7.9 Malignant mesothelioma with bilateral pleural based masses.

7.24 DIAGNOSIS

The diagnosis of pleural mesothelioma requires pathologic confirmation. The pathologic distinction between mesothelioma and lung cancer (especially adenocarcinoma) metastatic to the pleura may be difficult and requires the use of histochemical, immunohistochemical and rarely, electronmicroscopic evaluation, as set forth in Chapter 5. The U.S./Canadian Mesothelioma Panel[191] stresses the importance of being familiar with the gross features of the tumor either as seen radiographically or as described by the surgeon. Because small pleural biopsies and cytology may be misleading, specimens obtained by video assisted thoracoscopic surgery (VATS) or thoracotomy provide a more reliable diagnosis. At the time of surgery, the surgeon often describes extensive pleural thickening, or tumor studding of the visceral and parietal pleura. Tumor invasion of parietal and visceral pleura may make dissection of the lung from the chest wall virtually impossible.

Care must be taken in distinguishing benign pleural reactions from mesothelioma.[192] Many immunohistochemical stains, while helpful in identifying pleural cells, are of little value in distinguishing benign from malignant processes. This is especially true in differentiating reactive mesothelial hyperplasma from invasive epithelial mesothelioma and desmoplastic mesothelioma from fibrosing pleuritis (see Chapter 5). Here a pathologist's familiarity with mesothelioma may be essential in making the distinction. Documentation of tumor invasion is the most important pathologic feature separating benign from malignant processes. Further complicating this issue is the fact that mesothelioma may present with a variety of pathologic patterns. Dail and Hammar[188,193] discusses the spectrum of benign and malignant pleural diseases and identifies the various pathologic presentations of mesothelioma and the difficulties in differentiating pseudomesotheliomatous carcinoma from mesothelioma.

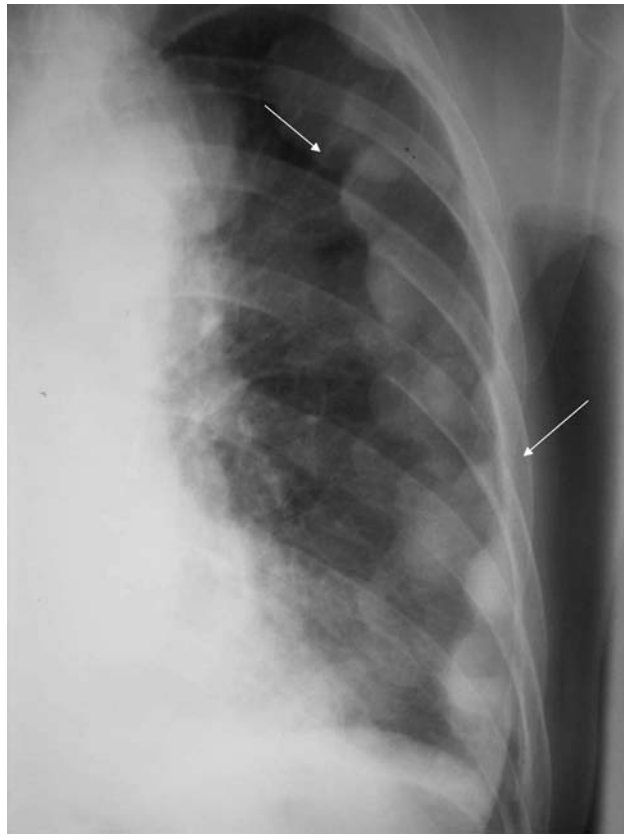

Figure 7.10 "Lumpy-bumpy" appearance of mesothelioma (a close-up appearance, see Figure 7.11).

In some cases, there may be recurrent episodes of chest pain accompanied by pleural effusion with negative bronchoscopy, thoracentesis, and other studies making the diagnosis difficult. In most cases, the diagnosis is made after VATS or thoracotomy is performed and sometimes the diagnosis is not made until autopsy.

7.25 PROGNOSIS

In my experience, the prognosis for mesothelioma (both pleural and peritoneal) is grim, and life expectancy for pleural mesothelioma is typically 9–18 months from the time of presentation with symptoms. Ribak and Selikoff[194] reported a mean time of 11.4 months from presentation until death for pleural mesothelioma and 7.4 months for peritoneal mesothelioma in 457 consecutive fatal cases of mesothelioma in asbestos insulation workers.

7.26 PERITONEAL MESOTHELIOMA

Peritoneal mesothelioma arises from the serosal surface of the abdomen. The diagnosis requires pathologic confirmation. Sugarbaker et al.[195] reported on 51 patients he had treated with mesothelioma. The typical presenting symptoms are abdominal pain or distention either with ascites or tumor mass. It is an extremely rare tumor representing approximately 10–20% of all mesotheliomas. Like pleural mesothelioma, it may cause severe symptoms while the diagnosis defies detection. Because the tumor involves the serosal surface of the abdominal cavity, gastroesophagoscopy, colonoscopy, barium and other diagnostic studies performed to evaluate the symptoms, are normal or non-diagnostic. CT scan may be of benefit in visualizing the extraluminal tumor. Often the diagnosis is not made until the patient develops ascites, bowel obstruction, palpable abdominal mass or other sequelae of the tumor. At that time, laparoscopy or laparotomy is performed and the diagnosis is rendered. In females, clinically distinguishing mesothelioma from ovarian carcinoma and certain other tumors of gynecologic origin may be difficult.

The fact that asbestos fibers can be recovered from the omentum and mesentery has been reported by Dodson et al.[196] Twenty individuals with mesothelioma had tissue from lung, omentum and mesentery studied for asbestos bodies and asbestos fibers. Uncoated fibers were found in the lungs of 19 and 17 of them had fibers in at least one extrapulmonary site. Dodson found amosite to be the most common fiber type in his study and stated the presence of fibers in the peritoneum could be predicted based on characteristics of the fiber burden in the lung.

Peritoneal mesotheliomas are typically associated with lengthy exposures to amphiboles. There is little proof that chrysotile causes peritoneal mesothelioma. Because peritoneal mesotheliomas are associated with high cumulative levels of amphibole exposure, they are more frequently accompanied by pleural plaques and pulmonary asbestosis than are pleural mesotheliomas.

Peritoneal mesotheliomas in individuals below age 40 require careful pathologic review to determine, whether the tumor represents multicystic mesothelioma, well-differentiated papillary mesothelioma, or deciduoid mesothelioma, which have been reported to occur in the absence of asbestos exposure. Pancreatic cancer, ovarian cancer and other intraperitoneal extraluminal cancers should be excluded through appropriate pathologic review.

7.26.1 Household and Environmental Exposure

Mesothelioma may occur with relatively low levels of asbestos exposure (Figure 7.11). Non-occupational sources of asbestos exposure have been reported among household contacts, environmental pollution, and community contamination. In 1965, Newhouse and Thompson[204] reported on 76 cases of mesothelioma in the London area. Nine of these occurred as household contacts of family members and there were 11 cases whose only known source of exposure was living within half-a-mile of an asbestos factory. In 1978, Chen and Mottet[205] reported a malignant

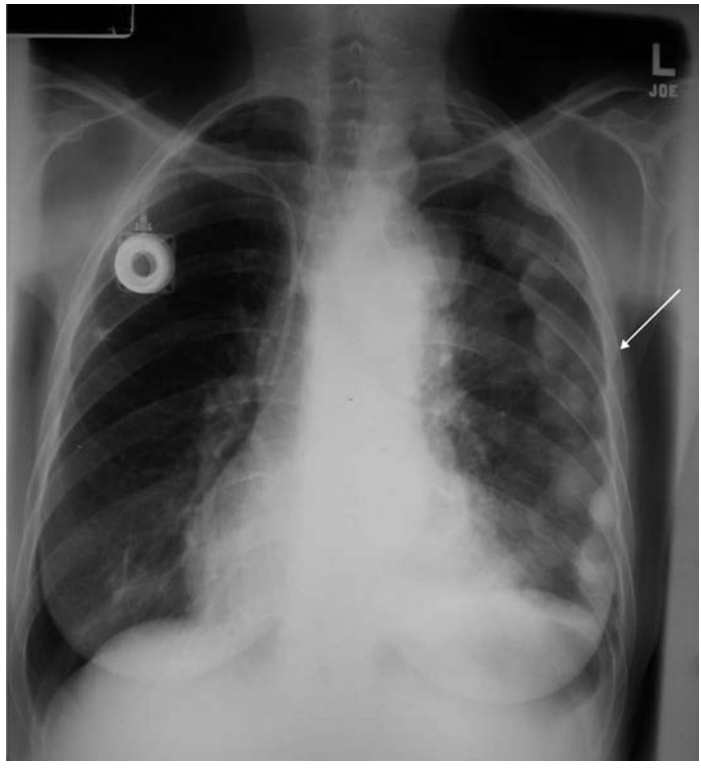

Figure 7.11 Malignant mesothelioma in the wife of an insulator (household contact).

mesothelioma in a 50-year-old executive with minimal asbestos exposure. He utilized energy dispersive x-ray analysis to confirm the presence of asbestos bodies and fibers.

In 1979, Anderson et al.[206] reviewed the literature from nine countries and reported a series of 37 cases of mesothelioma attributed to household exposure. They also studied radiologic findings in 326 household contacts of asbestos workers finding that 16% had pleural change as the only abnormality, 11% had parenchymal fibrosis of low profusion, and 8% had combined pleural and parenchymal change. Anderson suggested that non-malignant asbestos-related findings observed on x-ray might provide supportive information for appearance of malignant disease among household contacts. Epler et al.[207] in 1980, reported four individuals with asbestos-related disease attributed to household exposure. Three had benign pleural disease and one developed malignant pleural mesothelioma. In 1978, Vianna and Polan[208] studied a series of 52 females who were residents of New York State and had developed mesothelioma between the years 1966 and 1977. When compared to controls, they found a ten-fold increased risk of mesothelioma in those with household exposure to asbestos. Occupational histories revealed that six of the patients may have had occupational exposure to asbestos. The majority of the household contacts had worked as insulators and all the female patients had routinely hand-laundered their fathers and husbands clothing.

Dodson et al.[209] studied the asbestos burden in women with mesothelioma utilizing autopsy material in 15 women with a pathological diagnosis of mesothelioma. Exposures ranged from direct work with asbestos containing products to household exposure from contaminated work clothing. Two of the fifteen women had confirmed asbestosis. Seven had over 1000 ferruginous bodies per gram of dry weight while no ferruginous bodies were found in two. Analysis of the ferruginous bodies confirmed that 55 contained an amosite core while 4 had crocidolite and 3 had tremolite. The ratio of asbestos fibers to ferruginous bodies demonstrated great variability ranging from 19:1 to 2686:1. Dodson compared these 15 females to a prior group of 55 males with mesothelioma whom he had studied. Fourteen of the female cases had asbestos burdens, which fell in the lower one third of the male concentrations for asbestos bodies and uncoated asbestos fibers.

Roggli et al.[210] reported on malignant mesothelioma in women reporting that 86% had pleural mesotheliomas. Pleural plaques were found in half of the women for which that information was available. Asbestosis was only found in 16%. Over half had household contact with asbestos workers, while 19% had occupational exposure. In those women for whom fiber analysis was available, 70% had demonstrated increased asbestos burden with the primary fiber type being amosite followed by tremolite and chrysotile.

While mesothelioma may occur at low levels of exposure, dose-response relationships have been documented and those with the highest levels of exposure have the greatest increased risk of disease.[211]

Questions concerning genetic predisposition to development of mesothelioma have been raised. Hammar et al.[213] reported two families with familial mesothelioma and cited five reports from the literature of familial mesothelioma which had occurred in two or more family members. Hammar reported on three brothers who worked with asbestos insulation and developed mesothelioma. He also reported on a father who was occupationally exposed to asbestos and died of peritoneal mesothelioma and whose son later died from the identical histologic type of peritoneal mesothelioma (tubulopapillar). In 1978, Li et al.[214] reported on familial mesothelioma in which a father who installed asbestos insulation in shipyards developed asbestosis and lung cancer. His wife, who hand-washed his clothing, developed mesothelioma at the age of 50 and his daughter, developed mesothelioma at the age of 34.

There are multiple references within the literature to mesothelioma arising from environmental exposure among inhabitants living near asbestos mines, asbestos manufacturing plants, shipyards and similar industries. Magnani et al.[215] opined that household exposure to asbestos or in the general environment carries a measurable risk of malignant pleural mesothelioma.

The risk of asbestos exposure in schools was widely debated in the 1980s. In 1987, the Committee on Environmental Hazards for the American Academy of Pediatrics[217] reported that mesothelioma risk is proportional to a power of time since first exposure. Such risk significantly increases when time since first exposure exceeds 40 yr. Therefore, the committee expressed concerns about early childhood exposures and cited an Environmental Protection Agency (EPA) risk estimate that, between 100 and 7000 excess deaths were anticipated to occur as a result of

exposure to asbestos in schools over the next 30 yr (1980–2010). They stated that, "the most reasonable estimate is approximately 1000 premature deaths." It was opined that 90% of those deaths were expected to occur among persons exposed to asbestos as school children. Asbestos Health Emergency Response Act (AHERA) became federal law requiring that schools conduct inspections in May 1988 and implement management plans for removal or abatement of asbestos by July 1989.[218] At least three other risk assessment studies provided evidence that a major health threat was not present in building exposure.[218] The Helsinki Criteria Consensus Group identifies potential for environmental and household exposure in the causation of mesothelioma.

The occurrence of mesothelioma in pediatrics and young adults raises special questions concerning latency and causation. McDonald et al.[219] described 115 men and 13 women who were age 50 or less and diagnosed with malignant mesothelioma. They obtained occupational histories on these individuals and related the occupation to lung tissue concentration of asbestos fiber by type. They found that the predominant occupations were carpenters, plumbers, electricians and insulators in the construction industry, and that the mesotheliomas were predominantly attributable to amphibole exposure.

Mesotheliomas in children are so rare that they are usually presented as case reports. Brenner et al.[220] from Memorial Sloan-Kettering Cancer Center reported seven cases of pediatric mesothelioma and conducted a review of the literature revealing 49 cases of malignant mesothelioma which had been reported by 1981. Of 148 patients seen between 1950 and 1980 with mesothelioma only seven (5%) were younger than age 20.

7.27 TREATMENT

Multiple different modalities of therapy have been attempted for both pleural and peritoneal mesotheliomas. While some recent chemotherapeutic advances have appeared promising, they have only extended life expectancy by a few months. Radiation may provide palliative relief when there is intercostal nerve and bone involvement, but is not a curative measure.

Extra pleural pneumonectomy (EPP) is an aggressive surgical procedure which typically involves removal of the involved lung, parietal pleura, portions of the chest wall, portions of the pericardium, and portions of the diaphragm requiring reconstruction. While there have been some reports of success with this procedure,[212] most cases in my experience, have resulted in unfortunate outcomes. Sugarbaker et al.[197] is a proponent of EPP and described prevention and management of complications he observed in 496 patients. In a subset of 328 patients, 198 (60.4%) experienced major or minor post-operative complications. A post-operative mortality rate of 3.4% was noted. This group of patients only had a median age of 58 yr. Treasure and Sedrakyan[198] have raised questions concerning the effectiveness of this approach and caution to avoid "futile and distressing treatment."

Trimodal therapy with radiation, chemotherapy and surgery have been advocated. With the exception of the occasional case report, I can find little convincing evidence of long-term success. Weder et al.[199] recently reported on 19 patients who pre-operatively were considered to be "completely resectable" and underwent complete extrapleural pneumonectomy including pericardium and diaphragm. Neoadjuvant chemotherapy with Gemcitabine and Cisplatin was given. EPP was performed on 16 patients with major surgical complications occurring in 6. Thirteen received post-operative radiotherapy. The median survival time was 23 months.

Janne and Baldini[200] recently reported a 45% five-year survival rate for patients with "early stage" disease with epithelial histology and absence of mediastinal nodal involvement who were treated with EPP. They note that unfortunately most patients present with more advanced disease and optimum treatment has yet to be defined. They stated that adjuvant therapy with radiation, intrapleural and intravenous chemotherapy and brachytherapy fail to show consistent benefit. New approaches with radiation and chemotherapy including heated intrapleural Cisplatin are discussed.

Chang and Sugarbaker[201] are currently investigating intraoperative, intracavitary chemotherapy with high dose Cisplatin. Pistolesi and Rusthoven[202] have published a review on current knowledge and recent discoveries in malignant pleural mesothelioma. They cite various new markers such as folic acid receptor alpha, cyclooxygenase 2 and others suggesting a potential avenue for new therapeutic approaches.

It is my opinion that historically, most therapeutic interventions whether surgical, external beam radiation or chemotherapy have failed to show significant clinical benefit in the majority of malignant mesothelioma patients.

The complications of these treatment modalities are well known. Given that most mesothelioma patients have less than a year to live, I believe that their quality of life is more important than extending their lives a few months while they experience not only the consequences of their disease, but the iatrogenic complications of our well-intended attempts to render treatment. In most cases, I recommend only palliative treatment and support. In the case where early or localized disease can be documented after thorough staging workup, I recommend referral to a cancer center with experience in treating these cases.

7.28 RECOMMENDATIONS FOR THE CURRENT APPROACH TO THE ASBESTOS-RELATED DISEASES

The asbestos-related diseases are dynamic and their clinical presentation and our diagnostic criteria have evolved over the years. The medical literature that was applicable to malaria prior to mosquito eradication and the advent of anti-malarials would paint a far different picture of malaria than is seen in 21st century America. Likewise, the medical literature on polio prior to the 1950s does not reflect the current status of that disease in the United States. The more recent asbestos literature reports changes in incidence of disease and clinical presentation reflecting the

reduced levels of asbestos exposure experienced by most workers in the past 30 yr compared to that experienced by their predecessors of the 1930s through the 1960s. The CDC[223] has recently reported an increase of asbestos-related deaths during the past two decades. This has been attributed in part to changes in ICD 9 Coding, remote exposures to asbestos in an aging population reaching the end of life expectancy, increased awareness of the disease due to litigation, and more sensitive diagnostic techniques.

In evaluating the asbestos-related diseases, the physician must consider multiple variables in each case. Studies have shown that cumulative exposures experienced by insulators may be very different than that experienced by other trades. Latency has significant impact on the timing of the appearance of the various asbestos-related diseases. Many other fibrogenic agents within the workplace are well known to medicine, and the non-occupational causes for interstitial fibrosis and pleural disease can consume an entire text. Smoking and occupational carcinogens may either enhance the effects of asbestos or act independently.

The impact of OSHA regulations on mandatory respiratory protection and safeguards during abatement and removal have effected workplace exposure. New scientific approaches in attempts to treat or slow progression of disease are in their infancy. The criteria for diagnosing the non-malignant asbestos diseases has recently changed. During the year that this chapter was written, the ATS published new guidelines for the diagnosis and management of the non-malignant asbestos diseases and the ILO has revised the guidelines for the interpretation of pneumoconiosis x-rays. During the past decade, the ATS has issued new guidelines for the performance of pulmonary function testing and the AMA has redefined the criteria for pulmonary impairment. Whether all these changes will withstand scientific scrutiny remain to be seen.

The diagnosis of thousands of cases of non-malignant asbestos-related disease made during mass screenings outside of the traditional doctor–patient relationship may lead many to seek second opinions in the future. Recent and proposed future legislation will impact physicians treating these patients. The level of the skills of the clinician required to properly evaluate the asbestos-related diseases must be matched by the level of dedication to provide scientifically sound information and the best care for their patients.

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CHAPTER 8

Core Curriculum for Practicing Physicians Related to Asbestos

Jeffrey L. Levin and Paul P. Rountree

CONTENTS

8.1 INTRODUCTION

There have been thousands of publications in scientific journals and other venues regarding asbestos. In spite of its recognized health hazard, like so many other occupational causes of illness and injury in the United States and around the world, asbestos is frequently overlooked in the clinical setting. There are many complex factors and explanations that account for this rather routine oversight. The chief among them is the relative lack of emphasis that occupational causes of disease command in medical training programs at the graduate and postgraduate levels.

The American Board of Preventive Medicine (ABPM) is a Member Board of the American Board of Medical Specialties.[1] The Board was created in 1948 and authorized to certify specialists in occupational medicine in 1955. In spite of a long history of certifying physicians, in 1990, it was estimated that occupational medicine specialists numbered fewer than 1500 with a deficit of physicians having special competence in the field of almost 5500.[2] In 2000, the Council on Graduate Medical Education (COGME) noted that in-depth data on physicians in the public health workforce were in short supply.[3] In addition to proposing the collection of more comprehensive data, a second recommendation focused on increased funding for training physicians in preventive medicine. The Institute of Medicine (IOM) likewise concluded that "the continuing burden of largely preventable occupational diseases and injuries and the lack of adequate occupational safety and health (OSH) services in most small and many larger workplaces indicate a clear need for more OSH professionals at all levels."[4]

The deficiency of educating health care professionals, particularly physicians, may be more fundamental. In 1991, the IOM reported that only 66% of U.S. medical schools specifically teach occupational medicine as a part of the required curriculum.[5] Approximately half of these dedicate an average of 4 h over 4 yr. Among departments of internal medicine, roughly 20% offered clinical occupational medicine experience to residents, mostly on an elective basis.

It is not surprising that health care providers, particularly physicians, have little comfort with occupational and environmental issues such as asbestos-induced disease. This is also true of postgraduate trainees embarking upon residency programs in preventive medicine and occupational medicine. It is incumbent upon such programs, and textbooks such as this one, to impart essential and practical knowledge to these individuals as reference tools and in achieving a level of competence that will permit quality practice in this arena.

In addition to general clinical competencies required by the Accreditation Council for Graduate Medical Education (ACGME), the Residency Review Committee for Preventive Medicine specifies a number of academic core content areas, which must also address health services administration, biostatistics, epidemiology, clinical preventive medicine, behavioral aspects of health, and environmental health.[6] The study of pragmatic issues related to asbestos is in keeping with those academic knowledge content areas and practicum competencies that should be achieved for effective practice in occupational medicine. These are listed in Table 8.1.

As it relates to asbestos, what then constitutes pragmatic and essential knowledge and skills for the residency trainee and practitioner? An understanding of the scope of asbestos-induced diseases and asbestos' impact on future human health are critical. Some might suggest that the topic is passé and hardly worth the effort. There are numerous ongoing attempts to pass legislation at the federal and state levels to curtail the legal implications of injury associated with a history of occupational and environmental contamination and human exposure to asbestos. Yet, the number of asbestos claims continues to mount and its widespread implications continue to grow. Stallard, for example, estimated that 400–500 thousand personal injury claims would be filed during 2000–2049.[7]

Table 8.1 Occupational Medicine Knowledge Content Areas and Competencies

Occupational medicine knowledge content areas
Disability management and work fitness
Workplace health and surveillance
Hazard recognition, evaluation, and control
Clinical occupational medicine
Regulations and government agencies
Environmental health and risk assessment
Health promotion and clinical prevention
Management and administration
Toxicology
Occupational medicine competencies
Manage the health status of individuals who work in diverse work settings
Monitor or survey workforces and interpret monitoring or surveillance data for prevention of disease in workplaces and to enhance the health and productivity of workers
Active participation in several surveillance or monitoring programs, for different types of workforces, is required to learn principles of administration and maintenance of practical workforce and environmental public health programs. Residents must plan at least one such program.
Manage worker insurance documentation and paperwork, for work-related injuries that may arise in numerous work settings
Residents should first learn worker insurance competencies under direct supervision of faculty and demonstrate competency to "open," direct, and "close" injury or illness cases
Recognize outbreak events of public health significance, as they appear in clinical or consultation settings
Report outcome findings of clinical and surveillance evaluations to affected workers as ethically required; advise management concerning summary (rather than individual) results or trends of public health significance

Source: Accreditation Council for Graduate Medical Education, Program Requirements for Preventive Medicine, effective July 2003, available at: http://www.acgme.org/downloads/RRC_progReq/380pr701.pdf, 2004.

Paramount is some understanding of the basic pathophysiology of the diseases caused by asbestos along with the fundamentals of diagnosis and treatment strategies, particularly of a preventive nature. Finally, residents and practitioners who deal with asbestos-exposed patients should develop a facility with regulatory requirements associated with medical surveillance of exposed workers and with the essential medical–legal considerations that face the individual serving as an expert.

8.2 BACKGROUND

Asbestos is a generic term applied to a group of six naturally occurring fibrous silicate minerals that have been used extensively in commercial products.[8] These minerals are more commonly found in their nonfibrous form. The crystalline fibrous minerals are grouped into two categories: serpentine and amphibole. Chrysotile is

serpentine asbestos made up of flexible fibers, which can be woven. Amphiboles are made up of brittle fibers and include amosite, crocidolite, and fibrous forms of tremolite, anthophyllite, and actinolite. Both categories may give rise to separable, long, and thin fibers, which may persist in lung tissue. The vast majority of the asbestos commercially utilized in the United States has been chrysotile. The physical and chemical properties of these minerals have resulted in their widespread applications and distribution in construction and industry, including their important use as a thermal insulating material. **Al**though use of asbestos has steadily declined over the last two decades in the United States due largely to health reasons, the circumstances of prior exposure and its rather ubiquitous persistence create the need for ongoing health concerns. Disturbance of asbestos-containing materials may result in the release of fibers, which can be suspended for long periods and which may travel long distances.

The earliest uses of asbestos date back to ancient times.[9] However, the first death due to pulmonary asbestosis was not described in the scientific medical literature until 1924, when Cooke reported on the death of Nellie Kershaw from fibrosis of the lungs due to inhalation of asbestos dust from work in asbestos factories in Britain.[10] In 1930, Merewether and Price conducted an investigation of the condition of workers in asbestos textile factories in Britain.[9] They demonstrated a direct relationship between exposure intensity and the speed of onset and severity of fibrosis. By 1955, Doll showed convincing evidence of the relationship between asbestos exposure and lung cancer[11], and in 1960, Wagner et al.[12] published on pleural mesotheliomas in individuals associated with crocidolite asbestos in South Africa. Selikoff and others demonstrated the relationship between asbestos exposure and neoplasia among building trades insulation workers in a landmark article in 1964.[13] The association between asbestos and nonmalignant and neoplastic diseases among insulation workers in the United States and Canada has been confirmed in subsequent analyses.[14] In spite of the "early" and clear recognition of occupationally induced disease, unprotected exposure was ongoing as illustrated in Figure 8.1 and Figure 8.2.

Asbestos production continues in many countries throughout the world, particularly in developing countries, where extensive commercial utilization of asbestos is ongoing.[15] The majority of asbestos is currently consumed in Eastern Europe, Latin America, and Asia. Despite a decline in use in the United States, the U.S. Department of Labor estimates that there are 3.2 million workers who encounter asbestos as a function of building renovation, maintenance, custodial work, and similar activities and who are subject to the requirements of the current construction standards of that agency. These circumstances of exposure give rise to the notion of a "third wave" of asbestos disease.[16] The first phase of asbestos disease was associated with work in the mining and milling of ore and the manufacture of asbestos products. The second phase of disease was recognized among users of these products such as insulators. The third wave of disease relates to exposure to asbestos in place. The potential for bystander exposure exists for each of these circumstances (e.g., in the households of these workers). Although many applications have been phased out of production, a partial list of uses is included in Table 8.2.[17]

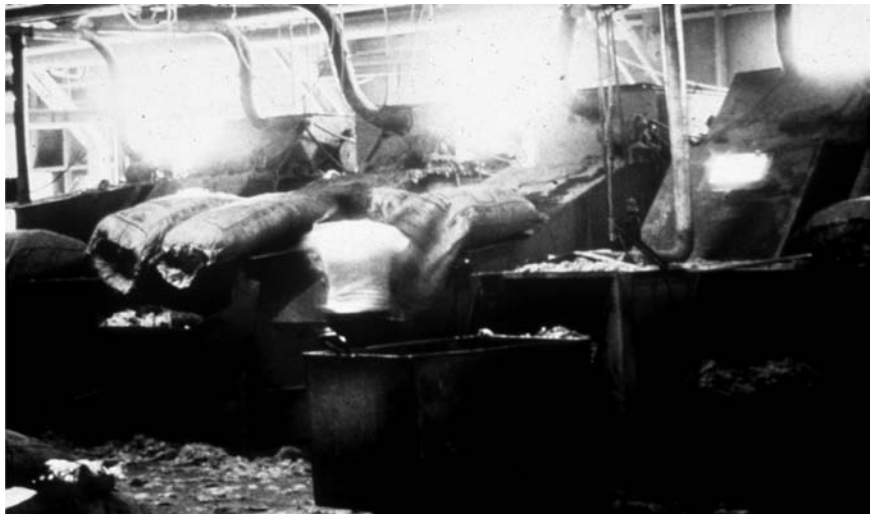

Figure 8.1 Worker in pipe insulation manufacturing facility operating from 1954 to 1972. Note the lack of respiratory protection and the qualitatively visible haze as he opens and empties burlap bags containing amosite asbestos.

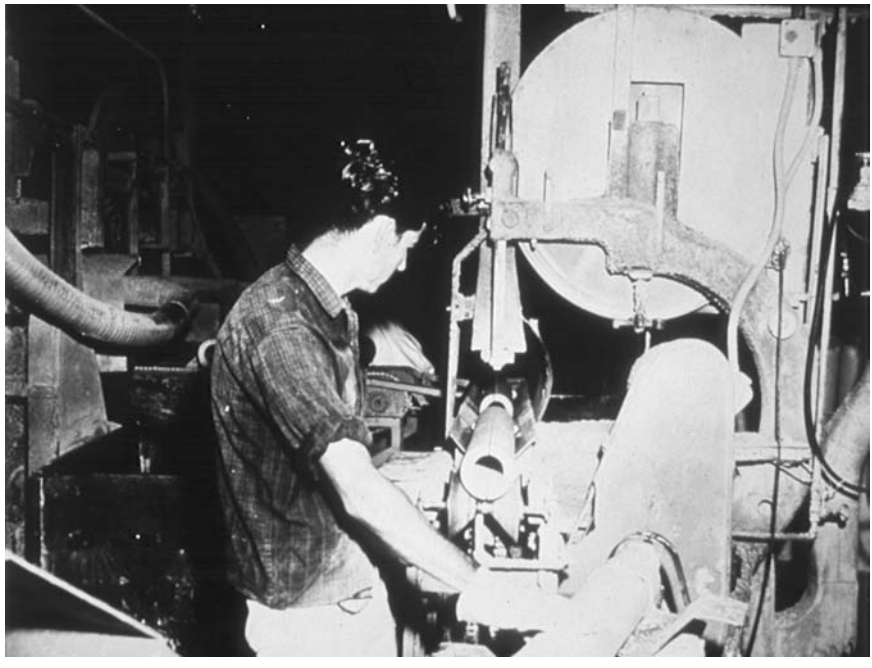

Figure 8.2 Worker in same facility as in Figure 8.1. Again note the absence of respiratory protection as he prepares to cut the cured pipe insulation in half along its length.

Table 8.2 Applications and Uses of Asbestos

Commercial
Boilers and heating vessels
Cement pipe
Clutch, brake, and transmission components
Conduits for electrical wire
Corrosive chemical containers
Electric motor components
Heat-protective pads
Laboratory furniture
Paper products
Pipe covering
Roofing products
Sealants and coatings
Textiles (including curtains)
Homes and buildings
Duct and home insulation
Fire protection panels
Fireplace artificial logs or ashes
Furnace insulating pads
Fuse box liners
Heater register tape and insulation
Joint compounds
Patching plaster
Pipe or boiler insulation
Sheet vinyl or floor tiles
Shingles
Textured acoustical ceiling
Underlayment for sheet flooring

Source: Gehle, K., Nastoff, T., and Rush, V., Case Studies in Environmental Medicine: Asbestos Toxicity, ATSDR Publication ATSDR-HE-CS-2002-0005, Atlanta, Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, available at: http://www.atsdr.cdc.gov/HEC/CSEM/asbestos/Asbestos.pdf, 2000, 1–40.

It should also be noted that asbestos could be a contaminant of other products such as vermiculite (used in gardening or landscaping products and home insulation) and talc (used in cosmetics).

On a worldwide basis, asbestos is being utilized increasingly in countries where there has been previously little use or manufacture.[18] This is not an unusual pattern of events where developing countries "import disease" as a function of their industrialization. This is a matter of particular concern as it relates to cancer where the disease is considered to be epidemic in nature with mortality projections in the millions.[19] Some have suggested that banning use often does not occur until after the costs exceed profitability. In developing countries, the lack of control measures to prevent disease is such that the equation remains profitable, at least for now.

8.3 BASIC PATHOPHYSIOLOGY

Any discussion of human exposure to a toxic substance merits a brief review of route of entry and factors that may determine dose. Inhalation is, no doubt, the primary route of entry for asbestos fibers, although there is transfer of inhaled fibers from the lung to the gastrointestinal (GI) tract as well as ingestion of fibers from drinking water. Concern for asbestos exposures in the GI system is mostly related to the suspicion of increased risk for gastrointestinal cancers.[8] This remains a controversial matter. Dermal exposure in and of itself appears to be of lesser import in that the only adverse health effect associated with this route of exposure is the formation of small "warts" or corns, presumably associated with skin penetration by macroscopic spicules.

Fibrous particles (e.g., asbestos) are those whose length substantially exceeds their diameter.[20] The so-called aspect ratio of length-to-diameter is variably defined for fibers, but 3:1 has been widely adopted by pathologists and researchers. Certainly, aerosols are rarely monodisperse, but are made up of a range of compact and fibrous particles. The deposition of particles is largely determined by mean aerodynamic diameter and distribution of particle diameter. Deposition in the respiratory tract occurs when a particle comes in contact with an airway or alveolus. Other factors such as size, density, and shape of particles as well as respiratory volume are important determinants of deposition. Larger particles tend to inertially impact within the large airways. In the smaller airways and alveoli, flow velocity is low and gravitational sedimentation plays a greater role for those particles and fibers that are small enough to reach this level. Fibrous particles such as asbestos are particularly affected by interception, where aerodynamic diameter is especially important. Fibers that are long with a high aspect ratio, but of sufficiently narrow diameter (<3.5 μm), are axially entrained in the air stream and avoid impaction and sedimentation until reaching the walls of terminal and respiratory bronchioles, particularly at bifurcations. Not all fibers that are deposited, however, are retained. Many are efficiently eliminated by cough, mucociliary clearance, and acinar clearance (Figure 8.3). These clearance mechanisms may be altered by a number of factors, particularly cigarette smoking.

Particles larger than 10 μm in diameter are mostly removed in the nasal chamber.[21] The penetration of particles and deposition in the respiratory tract from sedimentation occurs mostly in the diametric range of 0.5–5 μm, with those penetrating to and deposited in the pulmonary airspaces having a maximum value between 1 and 2 μm. Some of these fibers may be quite long (Figure 8.4).

The clearance, fate, pathologic effect, and implications of various coated and uncoated fiber types and sizes within the lung and sputum are described in detail elsewhere in this textbook. Relocation of fibers occurs to lymph nodes, pleura, and omentum and mesentery, presumably by way of the pulmonary interstitium or lymphatics.[22,23]

A brief discussion of the asbestos body (AB) is worthwhile. The AB represents an asbestos fiber that has been phagocytized by pulmonary macrophages and partially or completely coated by an iron-rich protein.[24] Their shape is variable

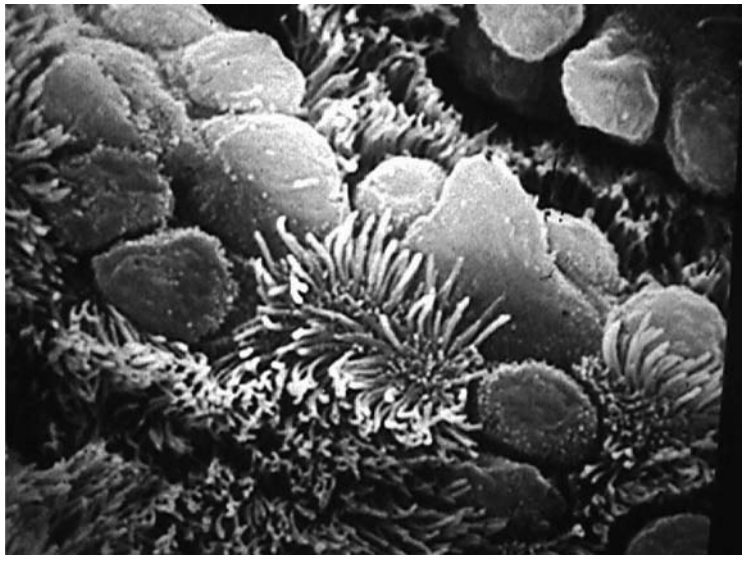

Figure 8.3 View of bronchiolar ciliated columnar epithelial surface by scanning electron microscopy. (Courtesy of Ronald F. Dodson, Ph.D.)

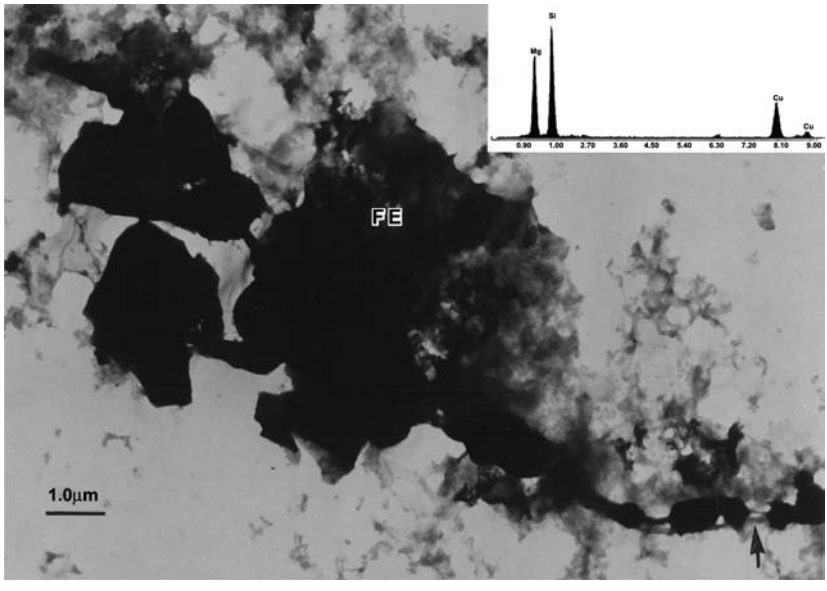

Figure 8.4 Long coated chrysotile asbestos fiber from digested lung tissue of an exposed individual. This is a transmission electron micrograph of a ferruginous body on a chrysotile asbestos core. The inset demonstrates a characteristic x-ray energy dispersive analytic spectrum of chrysotile asbestos fibers. FE, ferruginous material; arrow, fiber core. (Courtesy of Ronald F. Dodson, Ph.D.)

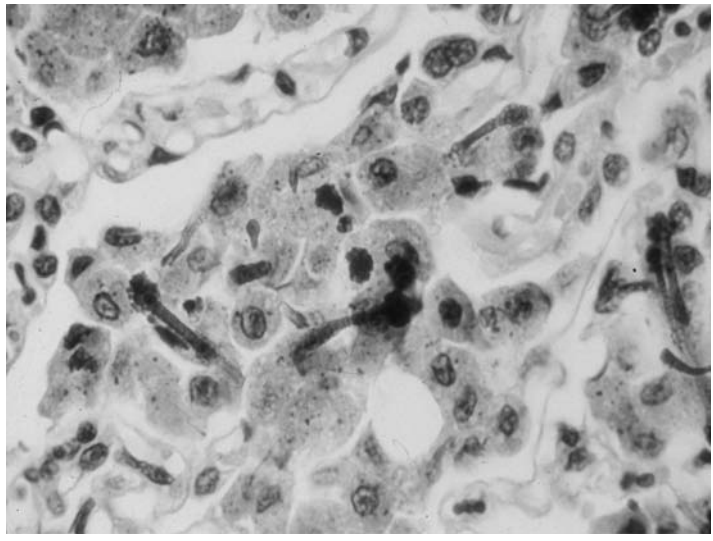

Figure 8.5 Alveolar architecture disrupted by the presence of inflammatory cells and fibrosis. Note also the presence of numerous coated asbestos fibers of variable size and shape, some resembling a dumbbell or drumstick. (Courtesy of Ronald F. Dodson, Ph.D.)

and classically appears like a dumbbell or drumstick by light and electron microscopies (Figure 8.5 and Figure 8.6). An important feature of the AB is its controversial implication for tissue diagnosis of asbestosis using light microscopy. There are people who argue "the minimal features that permit the diagnosis are the demonstration of discrete foci of fibrosis in the walls of respiratory bronchioles associated with accumulations of ABs."[25] Although ABs confirm past asbestos exposure, they typically form on asbestos fibers that are ≥ 8 μm in length, with other fiber characteristics also determining which of the longer fibers will be coated.[26] In most studies, the majority of cores analyzed are amphiboles.[27–31] Theoretically, due to physical characteristics of the fibers, chrysotile has a larger aerodynamic diameter than amphibole fibers. As a result, the opportunity for entrapment of chrysotile in the upper airways combined with the view that it may fragment or "dissolve" over time[32] would support the idea that presence of ABs indicates exposure to amphiboles[33] or correlation with amphibole exposure.[34]

Clearly, the physical and chemical properties of asbestos fibers are important in environmental and occupational exposures in relation to the pathophysiology of penetration, retention, and tissue response. This may be particularly true in the case of pleural malignancy as demonstrated by Stanton and Wrench in the early 1970s.[9] Their experiments involving the placement of refined and sized asbestos and man-made mineral fibers into the pleural space of laboratory animals led to Stanton's hypothesis suggesting that the diameters and lengths of the fibers or fibrils were largely responsible for the development of cancer.

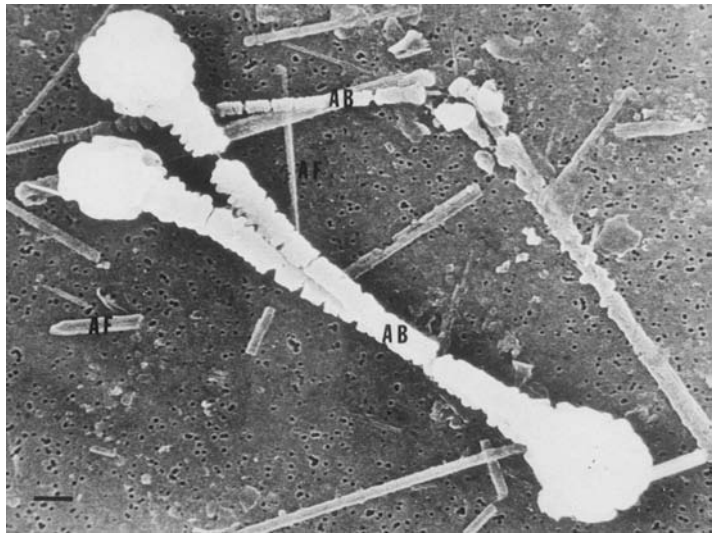

Figure 8.6 Scanning electron micrograph of coated asbestos fibers or ABs from digested lung tissue of an exposed individual. Note that exposure of limited portions of the long thin fibers would permit their identification as asbestos through use of sophisticated identification techniques. (Courtesy of Ronald F. Dodson, Ph.D.)

8.4 FUNDAMENTALS OF CLINICAL DIAGNOSIS

As with most clinical diagnoses, much emphasis should be placed on obtaining medical history. This includes occupational and environmental history taking, a measure that is frequently overlooked in clinical practice.[35] "Because many environmental diseases either manifest as common medical problems or have nonspecific symptoms, an exposure history is vital for correct diagnosis. By taking a thorough exposure history, the primary care clinician can play an important role in detecting, treating, and preventing disease due to toxic exposure."[36] This component of history taking can be pivotal in appropriately uncovering an etiology. An exposure history, taking only a few minutes, should be obtained on every patient. There are many important areas to cover including an exposure survey and a work history (Table 8.3). Exposures and their effects may be acute or chronic. The latency period from exposure to manifestation of symptoms or disease can range from immediate to delayed (hours to days) to prolonged (years). Therefore, exploring past as well as current exposures is important. Elucidating a chronology of work and examining temporal and activity patterns related to occupational and environmental disease is the key. It should also be emphasized that listing of job titles alone is inadequate, but a description of work activities offers potential exposure information. Hobbies should not be overlooked for their potential exposure concerns. Additional information concerning the exposure history is available from the Agency for Toxic Substances and Disease Registry (ATSDR). A case study

Table 8.3 Occupational Profile
Fill in the table below listing all jobs you have worked including short-term, seasonal, part-time employment, and military service. Begin with your most recent job. Use additional paper if necessary.

Dates of Employment	Job Title and Description of Work	Exposures*	Protective Equipment

*List the chemicals, dusts, fibers, fumes, radiation, biologic agents (i.e., molds or viruses), and physical agents (i.e., extreme heat, cold, vibration, or noise) that you were exposed to at this job.

Sources: Gehle, K., Nastoff, T., and Rush, V., Case Studies in Environmental Medicine: Asbestos Toxicity, ATSDR Publication ATSDR-HE-CS-2002-0005, Atlanta, Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, available at: http://www.atsdr.cdc.gov/HEC/CSEM/asbestos/Asbestos.pdf, 2000, 1–40;
Carter, W., Harkins, D.K., O'Connor, R., Johnson, D., and Tucker, P., Case Studies in Environmental Medicine: Taking an Exposure History, ATSDR Publication ATSDR-HE-CS-2001-0002, U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry, Atlanta, available at: http://www.atsdr.cdc.gov/HEC/CSEM/exphistory/index.html, 2000, 1–64.

program is available on the Internet at http://www.atsdr.cdc.gov/HEC/CSEM/exphistory/pdffiles/exposure_history.pdf.

In relation to asbestos, it is important to consider the range of commercial products previously noted to contain this material (Table 8.2) and the many trades and construction or maintenance occupations where exposure may occur (e.g., insulating, sheet metal work, pipefitting, firefighting, custodial work, etc.).[15] Routine medical history regarding dyspnea, cough, sputum, chest pain, and respiratory infections may be nonspecific. A smoking history is particularly important in the case of asbestos, where exposure interactions relative to disease are known to exist. Asbestos-related conditions often manifest themselves for the first time 20 yr and more after first exposure. Military service may be especially important given the historical and vast application of asbestos in this arena. Reviewing the work history of family members living in the home (parents, spouse, etc.) may be pertinent to uncover bystander exposure.[16] A physical examination focused on the respiratory, cardiovascular, and gastrointestinal systems targets the organs most likely affected by asbestos and is included in the medical surveillance requirements of various regulatory standards (e.g., 29 CFR 1910.1001 for asbestos exposure in general industry and 29 CFR 1926.1101 for asbestos exposure in the construction trades). The asbestos diseases of the lung are generally separated into nonmalignant and malignant categories. Each category can affect the pleural surfaces or the lung parenchyma and bronchiole tree.

8.4.1 Nonmalignant Diseases

In 1986, the American Thoracic Society (ATS) outlined the criteria for the diagnosis of various nonmalignant diseases related to asbestos. This organization suggested that it was necessary to include a reliable history of exposure, an appropriate latency period, and clinical criteria including chest x-ray evidence, pulmonary function changes, and physical findings.[37] The guidelines for diagnosis and management of these disorders were recently updated.[38] The nonmalignant processes affecting the lung are largely fibrotic in nature. Asbestosis is a pneumoconiosis characterized by diffuse interstitial fibrosis of the lungs caused by the inhalation of asbestos fibers.[8] All fiber types are considered to be fibrogenic, although there may be some differences in potency. Like the other asbestos-related diseases, there is an extended period of latency from the time of first exposure to the onset of disease. Although the period of latency may vary inversely with the intensity of exposure, the severity of the disease varies proportionately. It is notable that asbestosis is the only major pneumoconiosis to demonstrate increased mortality over the period 1982–2000.[39] This is largely explained by the fact that peak asbestosis mortality occurs 40–45 yr after initial occupational exposure. Asbestos consumption in the United States increased substantially during and after World War II, reaching its height in 1973.[40] Consequently, it is anticipated that asbestosis-related mortality will continue to climb for the next decade.

Cugell and Kamp recently provided a review of asbestos-related pleural diseases.[41] The most common nonmalignant pleural changes are lesions referred to as pleural plaques. These are discrete areas of collagen deposited on the pleural surface. Diffuse thickening and fibrosis of the pleura may also occur, as can benign pleural effusions and rounded areas of atelectasis.[15]

8.4.2 Malignant Diseases

Undoubtedly, it is now well accepted that asbestos can lead to increased risk of lung cancer and pleural mesothelioma.[8] As both are associated with chronic exposure, there is evidence to suggest that shorter exposures may also induce these neoplasms. Asbestos exposure may also pose a risk for cancers of the gastrointestinal tract and laryngeal cancers. The latter remain controversial.[8,14]

Although case reports of lung cancer among asbestos-exposed workers surfaced in the 1930s, an association was firmly established by Doll, who reported the first epidemiologic study in 1955. Later investigators noted that 17.6% of workers with more than 20 yr of asbestos exposure died of lung or pleural cancer.[13] LaDou estimated that 5–7% of all lung cancer is due to asbestos exposure.[19] Currently, about one of every seven individuals (14.3%) with asbestosis will develop lung cancer.[42] The latent period between exposure and disease onset is about 20 yr.[15] All major lung cancer cell types have been noted, very similar to the general population with no history of exposure to asbestos. Although lung cancers occur with increased frequency throughout the lung following asbestos

Table 8.4 Synergistic or Multiplicative Interaction between Asbestos and Smoking in Lung Cancer Mortality

Group	Standard Mortality Ratio from Lung Cancer
Controls	1.00
Asbestos workers only	5.17
Smoking only	10.85
Smoking asbestos workers	53.24

Source: Hammond, E.C., Selikoff, I.J., and Seidman, H., Asbestos exposure, cigarette smoking and death rates, *Ann. N.Y. Acad. Sci.*, 330, 472–490, 1979.

exposure, they have been reported to occur with greatest frequency peripherally in the lower lung zones. Recent studies of lung cancer distributions found no difference in anatomical site between those associated with asbestos exposure and those related to cigarette smoking. A synergistic or multiplicative relationship between smoking cigarettes and asbestos exposure has been identified, which greatly increases the risk for development of lung cancer as demonstrated in Table 8.4.[43]

Mesothelioma is a tumor that typically involves the pleura and less frequently occurs in the peritoneal cavity or in other locations such as the pericardial cavity and tunica vaginalis. Mesothelioma is most often associated with exposure to amphibole forms of asbestos, but may occur after chrysotile exposure. An estimated 2000–3000 new cases are diagnosed each year in the United States,[44] and it is believed that approximately 250,000 will die of this disease in Western Europe during the next 35 yr.[19] Patients typically complain of chest pain and dyspnea, but have other systemic symptoms such as weight loss, night sweats, and fever. The cancer is locally aggressive and may metastasize. In most reported case series, survival averages vary from 4 to 18 months.[45] Multimodality treatments may include surgery, chemotherapy, and radiation therapy, but the overall results are poor and the prognosis is grim. Several authors have recently reviewed various therapeutic strategies.[44,45]

8.4.3 Diagnostic Tools

As previously discussed, a thorough history with a focus on occupational and environmental exposures and a careful physical examination are the cornerstones in the diagnosis of asbestos-related health problems. The physician may employ a variety of tools in order to recognize diverse forms of disease due to asbestos. It must be remembered that measurable abnormalities will not necessarily be present in early or mild cases. Ohar et al.[46] noted that nowadays, patients are more likely to have fewer radiographic changes, long latent periods, and a normal or obstructive pattern on pulmonary function tests. Explanations for obstructive

physiologic abnormalities have been offered elsewhere.[38] Some patients may have an entirely normal examination. In more advanced disease, however, the clinician may recognize symptoms and signs of severe pulmonary effects, such as cough, dyspnea, rales, or clubbing of the fingers.

Radiography is an essential component in the evaluation of an asbestos-exposed patient. Asbestos is capable of causing numerous changes in the lungs and pleura, which can be detected by either chest x-ray or computerized tomography (CT). These findings most commonly include pleural thickening, plaques, or effusions, but atelectasis and parenchymal fibrotic changes may also occur. In asbestosis, patients may have interstitial disease characterized by small, irregular opacifications of variable profusion. In addition, as noted, a variety of neoplasms are associated with exposure.

In an effort to standardize discussions about the x-ray abnormalities that are associated with various dust diseases of the lungs, the International Labor Organization (ILO) established a system for reporting abnormalities. For a physician to demonstrate competence in the use of this ILO classification system, the National Institute for Occupational Safety and Health (NIOSH) administers a test, called the NIOSH B-Reader Certification Examination, to interested physicians.[47] The certified B-Reader examines films and specifically grades the size and type of parenchymal opacities (e.g., fine, medium, and coarse opacities may be termed as s, t, and u, respectively), their location, and their profusion or extent (graded 0 for normal, 1 for mild, 2 for moderate, and 3 for severe). Comparison is made to a standard set of chest radiographic films. A similar approach is taken with regard to pleural changes and the presence of calcification. The B-Reader then issues a standardized report concerning all abnormalities. In this report, he or she includes an opinion about the types of small parenchymal opacities that predominate (primary) and those that are present in lesser degree (secondary). Along with this assessment, two profusion scores are provided: the first indicates the extent of disease compared with the standard set of films and the second represents a possible score for the film. For example, a patient may have t and t opacities with profusion of 2/1 (Figure 8.7).

The revised edition (2000) of the Guidelines for the Use of the ILO International Classification of Radiographs of Pneumoconioses has been released and NIOSH is in the process of updating the entire B-Reader Program to reflect these changes.[47] A new Roentogenographic Interpretation Form is available from NIOSH, reflecting the changes in the Guidelines. Regarding the comparison standard set of images, a new "Quad Set" consisting of 14 radiographs of enhanced quality is now available as of March 2004.

There can be considerable variability among B-readers' interpretations. Gitlin et al.[48], for example, performed a study comparing the reports of "B" readers retained by plaintiffs' attorneys with the results from independent consultants who reviewed the same films. The findings suggested that the magnitude of differences was too great to be attributed to interobserver variability. In spite of this variability, the ILO reading is widely accepted and its use is required in mandatory medical surveillance programs.

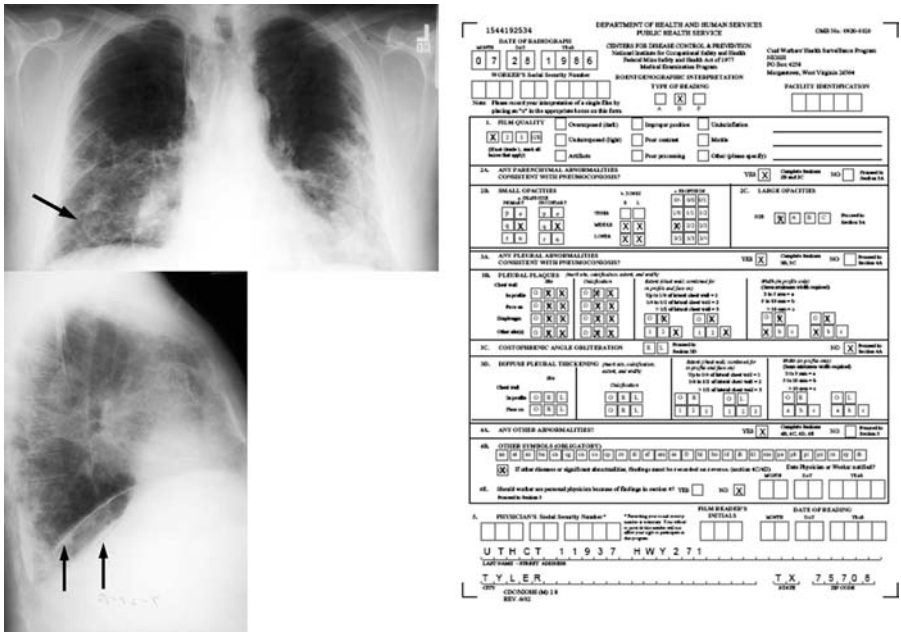

Figure 8.7 PA and lateral chest x-ray views of a patient with asbestosis and bilateral calcified pleural plaque disease. The arrow in the PA view demonstrates irregular opacities in the lower lung zones while the arrows in the lateral view demonstrate bilateral calcified diaphragmatic plaques. An accompanying B-reading has been conducted on an ILO form showing small parenchymal opacities of "t" size and shape and profusion score of 2/1. (ILO reading courtesy of Dr. David Finlay, Professor and Chair of Radiology, The University of Texas Health Center at Tyler.)

Patients with little or no change on chest radiograph are not necessarily proven to be free of disease.[49] Other investigators have estimated that 10–20% of cases of asbestosis are reported to have normal chest radiographs.[50] The use of a film "triad" including a postero-anterior view with right and left lateral oblique films increases validity and reliability.[51]

There is a good deal of evidence to suggest that smoking enhances the presence and profusion of small irregular opacities on chest radiograph.[15] However, the ability of smoking to independently produce such a radiographic appearance has been debated.

CT and high-resolution computerized tomography scans are considered to be the most sensitive radiographic methods of detection[52,53] and are associated with less variability of interpretation.[49,54] However, they are too expensive and time consuming for routine surveillance purposes. The CT scan can also be useful in the diagnosis of malignant disease (Figure 8.8 and Figure 8.9).

Pulmonary function tests are extremely important in the evaluation of the patient with asbestos exposure. Pulmonary function test results are effort dependent and in order to be credible, these tests should be performed with appropriate equipment

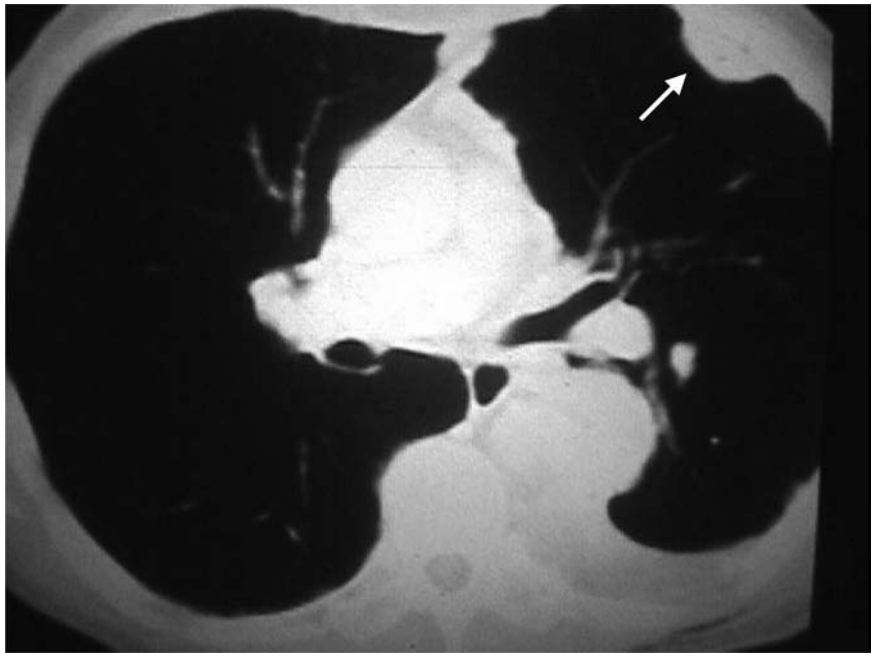

Figure 8.8 CT scan of asbestos-exposed patient with pleural plaque disease. Arrow, circumscribed pleural plaque, left anterior parietal pleura.

operated by a technician who has successfully received NIOSH-certified training, with strict adherence to guidelines published by the ATS.[55] The ATS has suggested that asbestosis is a restrictive lung disease characterized by a decline in the forced vital capacity (FVC), with a preserved ratio of the forced expiratory volume at 1 second (FEV1) to the FVC. (FEV1/FVC or FEV1%).[37] More recent published studies[46], however, suggest that nowadays, patients are likely to be older and have reduced levels of exposure. More are found to have normal pulmonary function, and when abnormalities exist they are more likely to reveal obstruction rather than restriction. Pulmonary function studies typically include measurement of the forced expiratory flow rate at mid-expiration (FEF 25–75), and may also include a diffusion study (D_LCO) to detect gas exchange abnormalities.

Bronchoalveolar lavage (BAL) has been employed in order to identify ABs. ABs are considered a marker of exposure to asbestos and may be a diagnostic aid. However, the absence of an AB in BAL fluid does not exclude the diagnosis. There is considerable variability between the ratio of AB and parenchymal fiber burden. Such studies may be of limited usefulness in the clinical evaluation of exposed patients.[56] Spontaneous or induced sputum examination may be useful in detecting ABs and is less invasive.[57] Their identification in sputum is specific for significant tissue burden, but not sensitive.[58]

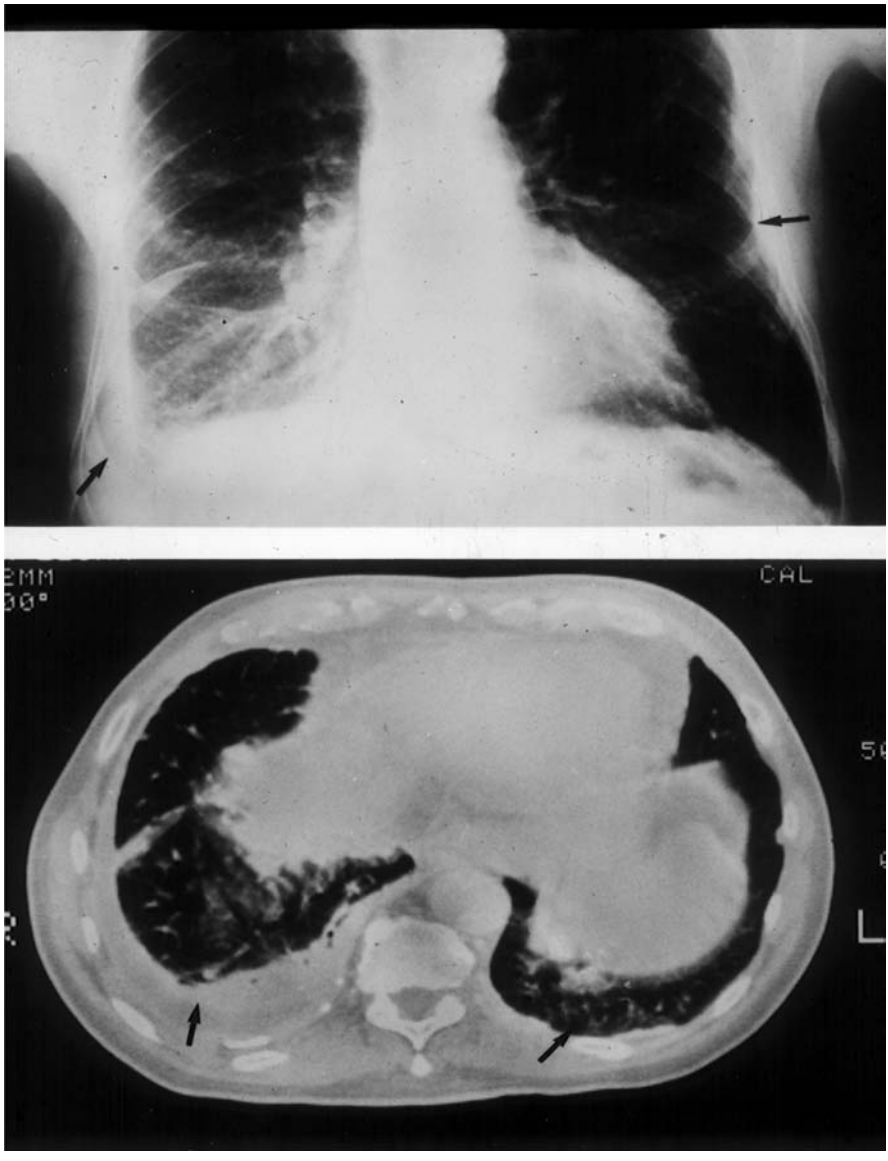

Figure 8.9 Patient with military and occupational exposure to asbestos, diagnosed with pleural mesothelioma. Upper image is a PA chest radiograph with diffuse pleural changes and blunting of the right costophrenic angle (arrow) and left-sided pleural plaque disease (arrow). The lower image is a CT slice showing interstitial fibrotic changes (asbestosis) at the left base (arrow) and thickened pleural rind on the right (arrow) consistent with the diagnosis of pleural mesothelioma.

8.5 TREATMENT

Unfortunately, there is limited effective treatment for the patient with asbestosis. Prevention of exposure to the mineral, and early identification of affected individuals is primary. Corticosteroids and immunosuppressants have had little effect on symptoms or survival.[59] Prevention of infectious complications through appropriate vaccination should be considered. It is extremely important for the physician to warn the asbestos-exposed patient of the dangerous synergism that exists with concomitant exposure to tobacco smoke. The approach to the management of cancer is uniform regardless of the contribution of asbestos. Unfortunately, an occupational history is frequently overlooked when new cases of cancer are diagnosed.[60]

8.6 CONSENSUS ITEMS AND CONTROVERSIES

Although a number of issues remain unresolved, there is a general agreement between scientists and health agencies regarding several health effects from asbestos.[8] These consensus items are outlined in Table 8.5 along with key unresolved issues. There are efforts underway attempting to reach consensus on several unresolved issues in the diagnosis of asbestos-related diseases. Studies sponsored by the American College of Chest Physicians employ an expert panel and a process developed by the RAND Corporation (the Delphi Technique) to aid in reaching consensus on contentious issues (http://www.sh.lsuhsc.edu/medicine/delphi/). The physician who becomes engaged as an expert in these matters should become very familiar with these consensus items and controversies and the conclusions, discussions, and scientific literature surrounding them.

8.7 MEDICAL SURVEILLANCE AND ESSENTIAL REGULATORY ISSUES

Until now, this chapter has focused on the diagnosis of disease, mostly when it has become clinically manifest in individual patients. In contrast, medical surveillance is "the systematic collection, analysis, and dissemination of data on groups of workers and workplaces for the prevention of illness and injury."[61] This prevention (secondary prevention) frequently takes place at a sub-clinical level resulting in early disease intervention and potential application to the larger group of workers. A component of this surveillance activity is the Sentinel Health Event Occupational or SHE(O). The SHE(O) is "a disease, disability, or untimely death that is occupationally related and whose occurrence may provide the impetus for evaluations and interventions to prevent future cases."[61] Mesothelioma serves as a SHE(O) or heralding event given its unique association with asbestos exposure and its accompanying morbidity and mortality.

As with many other regulatory standards under the Occupational Safety and Health Administration (OSHA) and similar federal agencies, medical surveillance

Table 8.5 Consensus and Unresolved Issues Regarding Health Effects from Asbestos

Consensus issues
Exposure to any asbestos type (i.e., serpentine or amphibole) can increase the likelihood of lung cancer, mesothelioma, and nonmalignant lung and pleural disorders
Important determinants of toxicity include exposure concentration, exposure duration and frequency, and fiber dimensions and durability
Fibers of amphibole asbestos such as tremolite asbestos, actinolite asbestos, and crocidolite are retained longer in the lower respiratory tract than chrysotile fibers of similar dimension
Pulmonary interstitial fibrosis associated with deposition of collagen, progressive lung stiffening and impaired gas exchange, disability, and death occurred in many asbestos workers
Most cases of asbestosis or lung cancer in asbestos workers occurred 15 years or more after their initial exposure to asbestos
Asbestos-exposed tobacco smokers have greater than additive risks for lung cancer than do asbestos-exposed nonsmokers
The time between diagnosis of mesothelioma and the time of initial occupational exposure to asbestos commonly has been 30 years or more
Cases of mesotheliomas have been reported after household exposure of family members of asbestos workers and in individuals without occupational exposure who live close to asbestos mines
Unresolved issues
Does exposure to asbestos increase the risk for gastrointestinal cancer?
Are chrysotile fibers (or amphibole asbestos fibers) primarily responsible for mesotheliomas in certain groups of workers predominantly exposed to chrysotile?
Are amphibole asbestos types more potent than chrysotile in inducing asbestosis and lung cancer?
Should the U.S. regulatory definition of an asbestos fiber (length ≥ 5 μm with aspect ratio $\geq 3{:}1$), established for purposes of quantifying exposure levels, be changed?
What are the molecular events involved in the development of asbestos-induced respiratory and pleural effects and how are they influenced by fiber dimensions and mineral type?
What are the actual risks for malignant or nonmalignant respiratory disease that may exist at exposure levels below air concentrations (0.1–0.2 fiber/ml) established as recent occupational exposure limits?
Can lung cancer be attributed to asbestos exposure (regardless of fiber type) in the absence of pulmonary fibrosis?

Source: Syracuse Research Corporation, Toxicological Profile for Asbestos (Update), Contract 205-1999-00024, prepared for U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, September, 2001, Appendix F.

is an important component of monitoring the individual worker while monitoring the workforce. Surveillance is driven by risk and in the case of asbestos regulations, workers who are subject to medical surveillance activities are those who are exposed at the action level which presently, is equal to the permissible exposure limit (0.1 fibers/cm^3, 8 h time-weighted average or TWA). Although there are subtle differences in the requirements surrounding and content of preplacement, periodic, and termination examinations, they are similar for general industry, the construction trades, the shipyard industry, and those categories of government employee or municipal and other workers covered under rules set forth by the U.S. Environmental Protection Agency (EPA). Conformance with OSHA's respirator standard

Table 8.6 Medical Surveillance for Asbestos: Relevant Federal Regulatory Standards and General Content of Examinations

Relevant federal regulatory standards with medical surveillance components for asbestos
29 CFR 1910.1001 — OSHA, general industry
29 CFR 1926.1101 — OSHA, construction industry
29 CFR 1915.1001 — OSHA, shipyard industry
40 CFR 763 — EPA, state and local government employees (like schools)
General medical surveillance examination content for asbestos
Medical and work history
Standardized questionnaire (initial or periodic)
Physical examination with emphasis on respiratory, cardiovascular, and digestive systems
Spirometry
Forced vital capacity
Forced expiratory volume in the first second (FEV1)
Calculation of FEV1/FVC ratio (FEV1 percent)
Comparison with predicted values
Chest x-ray
Postero-anterior film
At physician discretion; General Industry — at preplacement and periodically based upon age and years since onset exposure
Reviewed in accordance with ILO
Other tests at physician discretion

(29 CFR 1910.134) is essential. Table 8.6 outlines the applicable federal regulatory standards and the general content of examinations required for asbestos medical surveillance. Individual states may have additional state-specific rules.

8.8 THE CLINICIAN IN THE COURTROOM: ESSENTIAL MEDICAL–LEGAL CONSIDERATIONS

Since the 1993 landmark Daubert decision by the U.S. Supreme Court, trial courts have evaluated scientific evidence with greater rigor. U.S. courts are now required to evaluate for themselves whether testimony or evidence is relevant and reliable rather than depending solely upon the credibility of purported experts. In other words, they must determine whether the scientific methodology is reliable and the science valid.

On the matter of reliability, the U.S. Supreme Court offered a list of factors to guide lower courts when judging a "novel" scientific theory or methodology (Table 8.7).[62] However, it has now become a standard procedure for defendants to seek this analysis in toxic and occupational exposure cases even when classic rather than novel approaches have been used. The trial courts have become "gatekeepers" and judges "junior scientists" to block "junk science" from entering into the courtroom. As to relevance, the determination to be made is that the methodology used by the expert must "fit" the type of scientific inquiry at hand. If one accepts the premise that an expert's opinion has a reliable basis in the knowledge and experience of his or her discipline, then the focus relies on the "fit" of the

Table 8.7 U.S. Supreme Court in Daubert, Non-exclusive List of Factors to Determine Reliability of "Novel" Scientific Theory or Methodology

Nonexclusive List of Factors
Testability
Peer review
Known error rate
Operational standards and controls
General acceptance of method or theory in the profession

Source: Guidotti, T.L. and Rose, S.G., Eds., *Science on the Witness Stand: Evaluating Scientific Evidence in Law, Adjudication and Policy*, OEM Press, Beverly Farms, MA, 2001, p. 81.

methodologic approach and the reliability as judged by the guidance given by the Supreme Court. This is a complex matter beyond the scope of this book, but it is worth mentioning two specific methodologic considerations as they relate to asbestos and drawing conclusions about causality.

First is the matter of concluding a causal link between exposure and chronic disease using traditional epidemiologic and public health principles (Table 8.8). The reader should consider these factors carefully in determining whether he or she can conclude a causal link between asbestos, the circumstances surrounding exposure, and the disease endpoint in question. Secondly, the use of differential diagnosis is considered an acceptable methodology assuming that techniques such as history and physical examination, reliable laboratory data, and consideration of alternative causes were employed. The clinician should ascribe to ethical principles outlined by established bodies of peers and be prepared to answer the question at hand by explaining why and offering the evidentiary basis for reaching that conclusion in the citable scientific literature.

Table 8.8 Epidemiologic Criteria for Judging Causality in Public Health

Criteria
Strength of the association or high relative risk
Dose–response relationship
Consistency of findings
Biological plausibility, including experimental evidence
Temporal cogency
Control of confounding and bias
Specificity
Overall coherence

Source: Guidotti, T.L. and Rose, S.G., Eds., *Science on the Witness Stand: Evaluating Scientific Evidence in Law, Adjudication and Policy*, OEM Press, Beverly Farms, MA, 2001, pp. 60–62.

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APPENDIX

Understanding Asbestos Regulations and Their Applications

Fredy Polanco

CONTENTS

There are two primary federal agencies that regulate asbestos and asbestos-containing materials in the United States, the first agency is the Occupational Safety and Health Administration (OSHA), whose main focus is to protect employees from harmful working conditions, and the second is the Environmental Protection Agency (EPA) whose main focus is to protect human health and the environment.

The OSHA regulations for asbestos protection were first issued in 1972 and then modified in 1976, 1986, and 1994. The final changes to the standards amend the

Asbestos General Industry Standard 29 CFR 1910.1001, the Asbestos Construction Industry Standard 29 CFR 1926.1101 (previously 1926.58), and include a separate standard covering occupational exposure to asbestos in the Shipyard Industry 29 CFR 1915.1001. Major revisions in 1994 to these standards include a reduced permissible exposure limit (PEL) to 0.1 fiber/cm^3 (f/cm^3) for all asbestos work in all industries, a new classification scheme for asbestos construction, and Shipyards industry work which ties mandatory work practices to work classification, a presumptive asbestos identification requirement for "high-hazard" asbestos-containing materials, limited notification requirements for employers who use unlisted compliance methods in high-risk asbestos abatement work, and mandatory methods of control for brake and clutch repair. The following is a brief description of the major provisions of the three asbestos standards by the OSHA.

A.1 OSHA — ASBESTOS GENERAL INDUSTRY STANDARD (29 CFR 1910.1001)

This section applies to all occupational exposure to asbestos in all industries covered by the Occupational Safety and Health Act of 1970, except for construction work as defined by 29 CFR 1910.12(b) and asbestos exposure work in all shipyards employment as defined in the 29 CFR 1915. Examples of operations covered by the General Industry Standard includes manufacturing of gaskets, roofing materials, sealants, and other products; building occupants not associated with construction, cleaning activities not associated with construction. This standard was issued in 1972, which established the first PEL by the agency (5 f/cm^3).

A.2 OSHA — ASBESTOS CONSTRUCTION INDUSTRY STANDARD (29 CFR 1926.1101)

This section regulates asbestos exposure in all work as defined in 29 CFR 1910.12(b), including demolition or salvage of structures where asbestos is present; removal or encapsulation of materials containing asbestos; construction, alteration, repair, maintenance, or renovation of structures that contain asbestos; installation of products containing asbestos; asbestos spills and emergency cleanup; transportation, disposal, and storage on the site or location at which construction activities are performed.

The work practices and procedures as well as the engineering controls are based on the nature of the asbestos operation involving asbestos exposure. Under this standard, there are four classes of asbestos work. "Class I Asbestos Work" is defined as the activities involving the removal of insulation that contain asbestos applied to pipes, fittings, boilers, tanks, ducts, or other components to prevent heat loss or gain, and the removal of sprayed applied asbestos-containing material on acoustical plaster ceilings, and fireproofing materials on structural members. "Class II Asbestos Work" is defined as the activities involving the removal of materials not covered

under Class I Asbestos Work. "Class III Asbestos Work" involves maintenance operations, where asbestos-containing materials are disturbed or likely to be disturbed. The disturbance is limited to the amount of waste to be generated during the activity, and "Class IV Asbestos Work" involves cleaning activities of asbestos-containing material debris generated by a construction activity.

The main provisions of this standard include exposure assessment and monitoring, methods of compliance, respiratory protection and protective clothing, hygiene facilities for employees, communication of hazards, medical surveillance, and record keeping.

The Asbestos OSHA Construction Industry Standard was issued for the first time under a different section (29 CFR 1926.58) in 1986 and amended totally in 1994 (29 CFR 1926.1101).

A.3 OSHA — ASBESTOS SHIPYARD INDUSTRY STANDARD (29 CFR 1915.1001)

This section regulates asbestos exposure in all shipyard employment work as defined in 29 CFR 1915, including the same operations as in the construction industry but applied to vessels. This standard was issued in 1994.

A.4 EPA — ASBESTOS WORKER PROTECTION STANDARD (40 CFR 763 SUBPART G)

This rule under section 6(a) of the Toxic Substances Control Act (TSCA), extends protection to State and Local government employees not covered by the Occupational Safety and Health Act of 1970. Initially this rule, issued in 1985 and 1987, applied only to asbestos abatement projects, in contrast to the OSHA construction standard, which applies generally to any construction activity involving exposure to asbestos.

In November 2000, the "EPA Worker Protection Standard" was amended to apply not only the OSHA Asbestos Construction Industry Standard but also the Asbestos General Industry Standard to State and Local government employees who are not protected by the Asbestos Standards of the OSHA. States seeking to implement their own asbestos worker protection plan may apply for an exemption to the EPA.

A.5 EPA — THE ASBESTOS HAZARD EMERGENCY RESPONSE ACT (AHERA) OF 1986, ASBESTOS-CONTAINING MATERIALS IN SCHOOLS RULES 1987

On October 22, 1986, President Reagan signed into law the "Asbestos Hazard Emergency Response Act" (AHERA) that enacted, among other provisions, Title II of the

"Toxic Substance Control Act" (TSCA), requiring the EPA to propose and promulgate final rules for the control of asbestos in schools (K-12).

In October 1987, the EPA issued the final rule (40 CFR 763 Subpart E) under Title II of TSCA to require all "local education agencies" covered under the Act, to identify asbestos-containing materials (ACM) in their school buildings and take appropriate actions to control release of asbestos fibers. The local education agencies are required to describe their activities in management plans, which must be made available to all concerned persons (building occupants or legal guardians, short-term workers) and submitted to State Agencies designated by the State Governors.

The ACM in school rule requires the local education agency to use specially trained persons (EPA or State Approved Accredited) to conduct inspections for asbestos, develop the management plans, and design or conduct major actions to control asbestos. Appendix C of this standard has the specific training and accreditation requirements (The Model Accreditation Program — MAP).

The Asbestos "Model Accreditation Plan" (MAP) was effective in June 1, 1987, and amended last in 1994. The MAP requires persons seeking accreditation to take an initial training course, pass an examination, and participate in continuing education. The local education agencies have the option of hiring accredited contractors to conduct asbestos work or having in-house personnel receive accreditation. Accredited personnel are not required to conduct operations and maintenance activities under the MAP. EPA-accredited States may exercise their authority to have accreditation program requirements more stringent than the Model Plan. As a result, some EPA-approved training courses may not meet the requirements of a particular State's accreditation program.

A.6 EPA — MANUFACTURE, IMPORTATION, PROCESSING, AND DISTRIBUTION IN COMMERCE PROHIBITIONS: "THE ASBESTOS BAN AND PHASE OUT RULE"

In July 12, 1989, the EPA issued the final rule under Section 6 of TSCA to prohibit, at staged intervals, the future manufacture, importation, processing, and distribution in commerce of asbestos in almost all products, as identified in the rule. The objective of this rule was to reduce the unreasonable risks presented to human health by exposure to asbestos during activities involving these products. This rule also requires that the products that are subject to the bans be labeled to promote compliance with and enforcement of the rule. The rule provides exemptions in very limited circumstances.

This rule imposed a three-stage ban. First stage: the manufacturing, importation, and processing of flooring felt, roofing felt, pipeline wrap, asbestos cement flat sheet, A/C corrugated sheet, vinyl asbestos floor tile, asbestos clothing by August 27, 1990. The second-stage: gaskets, clutch facing, automatic transmission components, drum brake lining, disc brake pads by August 25, 1993. The third stage: A/C pipe, commercial and corrugated paper, roll board, millboard, A/C shingle, non-roof

coating, brake blocks, and new asbestos containing products as described by the standard by August 26, 1996.

However, on October 18, 1991, the United States Court of Appeals for the Fifth Circuit vacated and remanded most of the "Asbestos Ban and Phase out Rule" (Corrosion Proof Fittings V. EPA). The court agreed with the EPA's determination that asbestos is hazardous and presents similar risks throughout different industries. It also affirmed EPA's authority to issue rules that ban all uses of toxic substance under TSCA. The court, however, held that parts of the rule were not supported by substantial evidence because the EPA failed to sustain its burden under TSCA Section 6(a) of showing that the products banned by the rule present an unreasonable risk, and that a less burdensome regulation would not adequately protect against that risk. The court also found that the EPA failed to give adequate notice and opportunity to comment on the use of analogous exposure data to support some parts of the rule. Although, the Court vacated and remanded most of the rule, it left intact the portion of the rule that regulates products that were not being manufactured, produced, or imported when the rule was published in July 12, 1989.

A.7 EPA — THE NATIONAL EMISSION STANDARDS FOR HAZARDOUS AIR POLLUTANTS (NESHAP), ASBESTOS NESHAP 40 CFR 61 SUBPART M

These rules were issued under Section 112 of the Clean Air Act (CAA) for asbestos emissions and are based on the EPA's determination that asbestos presents a significant risk to human health as a result of air emissions from one or more source categories and is therefore, a hazardous air pollutant. This rule was published for the first time in 1973 and amended last on November 20, 1990.

Demolition and Renovation (40 CFR 61.145) — The main provisions under The EPA-NESHAP demolition and renovation include: no visible emissions during those activities, inspection of affected facility, or part of the facility where demolition or renovation will occur for the presence of asbestos, requirement to the owner of a facility to give the NESHAP Administrator 10-day notice prior to any demolition or notification that disturb regulated asbestos-containing materials (RACM), and the disposal of the waste containing asbestos in the appropriate waste disposal site.

This section classified ACMs into three different categories: Category I — nonfriable ACM meaning asbestos gaskets, resilient floor covering, and asphalt roofing products containing more than 1% asbestos by polarized light microscopy; Category II — non-friable ACM meaning any material containing more than 1% asbestos excluding the materials included in Category I non-friable ACM; and RACM meaning materials that are friable by nature or that were not friable but have became friable.

Under the EPA-NESHAP, materials containing asbestos have to be adequately wet before disturbance to prevent the release of particulates to the outside air, and a person trained in the provisions of this rule and the means of complying with

them is required to be on site. The provisions of this rule require vehicles used to transport asbestos-containing waste materials to be marked with a warning sign during the loading and unloading process. For all asbestos-containing waste material transported offsite, this standard requires that a waste shipment record ("Waste Manifest") be provided to the waste site operator at the time that waste is delivered to the waste disposal site. The waste generator is required to receive a copy of the Waste Shipment Record within 35 days from the time the waste was accepted by the first transporter. The waste packages or containers are required to be labeled with warning labels required by OSHA and the name and location of the generator of the waste.

Active waste disposal sites are also regulated by the EPA-NESHAP for asbestos. The owner or operator of an active waste site is required to maintain the Waste Shipment Record and report in writing the receipt of a significant amount of improperly enclosed or uncovered waste to the EPA Administrator by the following working day, and send a copy of the Waste Shipment Record back to the waste generator. Also, the owner or operator of an active disposal site is required to maintain records of the location, depth and area, and volume of asbestos-containing waste material within the disposal site on a map or diagram of the disposal area. Upon closure, the owner or operator must comply with all the rules applicable to inactive waste disposal sites.

The Asbestos EPA-NESHAP also regulates milling, manufacturing, fabricating, inactive waste disposal sites, and the asbestos conversion processes. Many States enforce and implement the requirements of the Asbestos-NESHAP for the EPA.

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Environmental and Occupational Health and Safety

ASBESTOS

Risk Assessment, Epidemiology, and Health Effects

Edited by
Ronald F. Dodson • Samuel P. Hammar

While there are hundreds of books available on the many different aspects of asbestos, none contain the encyclopedic, comprehensive coverage you will find here. Edited by leading authorities, with contributions from specialists and leaders in their respective fields, ***Asbestos: Risk Assessment, Epidemiology, and Health Effects*** provides a cross-disciplinary approach and an authoritative review of asbestos research. The breadth and depth of coverage spans history, pathology, epidemiology, as well as sampling, analysis, and regulatory issues.

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ISBN 0-8493-2829-2
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