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A Clinical Guide to Occupational and Environmental Lung Diseases

Humana Press

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Preface

The air must be pure, habitable, and bright, It should be neither contaminated nor smell of the sewer

(Regimen Sanitatis Salernitanum)

The lungs are the major interface between humans and the environment. We inhale environmental substances in the forms of particles, fibers, and gases every day. While many may be relatively harmless, others have a potential to cause acute or chronic lung diseases. The close and continuous interactions between the lungs and our environment support the observations over centuries that these exposures may participate in the pathogenesis of many diseases. Specifically, exposures can result in most types of lung disease, including those that are currently considered idiopathic. Estimates indicate that up to 15 % or more of adult-onset asthma and COPD cases are due to occupational exposures. The overall burden of all lung disease related to occupational or environmental exposures is unknown but likely represents a significant global burden.

Occupational and environmental lung diseases continue to be a major challenge for physicians. Many clinicians consider occupational and environmental lung diseases complex and time-consuming to diagnose and sometimes "a disease of the past." While certain occupational exposures, such as asbestos, silica, and coal dust, have decreased, lung diseases related to these exposures continue to be observed, with the recognition of a number of new disease manifestations with modified utilization in the workplace. In addition, there has been increased awareness in the past 10 years of other occupational and environmental exposures that can cause lung disease. We now understand more about these diseases and, over the last few years, several evidence-based guidelines were introduced to guide healthcare providers to their appropriate management. It is essential that clinicians are familiar with not only the "old diseases" but also the "emerging conditions" so that they can diagnose these diseases and provide the best clinical and preventive care to their patients.

The aim of this book is thus to deliver a concise clinical guide to the diagnosis and management of occupational and environmental lung diseases, incorporating evidence-based guidelines where available. Each chapter of the book will provide an updated review and a practical approach to occupational and environmental lung diseases. Our target readers are practicing clinicians including internists, pulmonologists, and primary care personnel. Other readers who will find this book of use include industrial hygienists and environmental regulators.

The book starts with a historical perspective from Dr. Blanc that defines the various features that have led to recognition of occupational lung disease. It introduces the readers to important personages in this field and outlines how technological advancements can introduce novel exposure and new risk of diseases. This is followed by a comprehensive discussion of history taking, a key component for effective detection and management of occupational and environmental lung diseases by Dr. Mohr in Chap. 2. Chapters 3 and 4 discuss commonly used laboratory tests, including methacholine challenge test as reviewed by Drs. Malo in Chap. 3. In Chap. 4, Dr. Goodman provides a complete description of the imaging of occupational and environmental pulmonary diseases including the utility of B reading, a standardized assessment used to quantify lung disease associated with particle and fiber exposures.

Chapters 5, 6, 7, 8, 9, 10, 11, 12, 13, and 14 cover traditional and common occupational and environmental lung diseases with a focus on a twenty-first century update. Drs. Riberio and Tarlo review the many environmental and occupational exposures that result in asthma in Chap. 5, while Drs. Ho and Kuschner provide a review of the agents resulting in hypersensitivity pneumonitis, the evaluation of patients suspected of having this disease, including the lack of definitive diagnostic criteria and a comprehensive treatment approach in Chap. 6. In Chap. 7, Drs. Huang and Volker delineate the relationships between air pollution and respiratory disease. The contributions of ozone, particulate matter, nitrogen oxides, carbon monoxide, and sulfur oxides are specified. Dr. Banks answers pivotal questions regarding asbestos exposure in Chap. 8. Included among these and of critical importance to the practicing clinician are the issues of what is a clinically significant exposure to asbestos, does a patient need to have asbestosis prior to diagnosis of an asbestos-related lung cancer, and what chest imaging is recommended for individuals with significant fiber exposure. In Chap. 9, Dr. Ghio reviews the older occupational lung diseases, silicosis, coal workers pneumoconiosis, and asbestosis, reminding us that the diagnosis of these diseases is a clinical one, not requiring pathology, although there are specific criteria for particular compensation programs. In Chap. 10, Drs. Prezant, Smith, and Mohr clarify what the clinician must consider in the diagnosis and treatment of lung disease after exposure to irritant toxic gases and smoke inhalation. Drs. Lam, Kurmi, and Ayres identify the problem of measuring chronic obstructive pulmonary disease in nonsmokers. They further characterize the associations with occupational exposures, burning of biomass, environmental tobacco smoke, and outdoor air pollution. In Chap. 11, Drs. Takada and Moriyama discuss hard metal lung disease, one of the few occupational lung diseases with characteristic pathological findings, giant cell pneumonitis, and the improved method of detect-

ing cobalt, the culprit metal for hard metal lung disease. In Chap. 12, Drs. Ferguson, Mroz, and Maier examine berylliosis, a chronic lung disease mimicking sarcoidosis with a focus on recent advances in understanding of gene–environment interactions contributing to risk of this disease. Drs. Yu, Tse, and Qiu then review lung cancer caused by exposures to occupational and environmental hazards in Chap. 13. This review is most pertinent to nonsmoking patients who develop lung cancer, an entity prevalent in certain parts of the world (e.g., south and pacific northeast Asia). That nonsmokers can also develop chronic lung diseases traditionally associated with cigarette smoking is further highlighted in Chap. 14 by Drs. Lam, Kurmi, and Ayres, who reviewed environmental and occupational risk factors for COPD in nonsmokers. To remind us of the need to consider exposures in the cause of lung diseases, Dr. Huang specifically discusses emerging conditions caused by new agents and new route of exposure to old agents in Chap. 15. Finally, as the diagnosis of an occupational or environmental lung disease may result in the need to assist the patient in the undertaking of compensation and other administrative issues, in Chap. 16 Dr. Cowl discusses the assessment of disability, a topic that is considered most cumbersome to many clinicians. The book ends with a discussion on global burden of occupational and environmental exposure in developing and industrialized countries by Dr. Christiani in Chap. 17.

In summary, exposure to many ambient environmental agents, occupational or nonoccupational, will impact the health of human body, especially the lung. With the rapidly changing technology, new conditions and exposures will undoubtedly emerge. Clinicians need to remain vigilant about assessing the potential link between lung diseases and environmental exposures, and this book provides a practical guide to recognize, diagnose, and prevent occupational and environmental lung diseases.

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Chapter 1
Historical Perspective of Occupational and Environmental Lung Disease

Paul David Blanc

Abstract Occupational and environmental lung disease has a long and complicated history. A more complete grasp of that history, and particularly the technological and social forces that have shaped it, better informs our understanding these issues, past, present, and going forward. Whenever a disease outbreak occurs, whether it is bronchiolitis obliterans from diacetyl use as a flavorant in microwavable popcorn or silicosis from sandblasting denim jeans or asthma from indoor air pollution due to household cleaning product use, putting these events in their historical context is critical. That context includes elements of biography related to important personages in this field, but the history of technology as it has introduced novel exposures and new risks for disease is as important to this story. So too, changing sociopolitical forces have shaped how medicine has viewed diseases in workers as well as the nature of environmental exposures. This chapter will place the story of occupational and environmental lung disease in the context of these three themes: the key historical figures that contributed to the development of the field, the technologic changes that have led to an ever-shifting burden of disease, and the sociopolitical forces that helped set priorities in the field.

Keywords Technology • History of medicine • Pneumoconiosis • Mining • Workers • Industrial Revolution

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Introduction

The goal of this historical overview of occupational and environmental lung disease is to provide structure and orientation to its long and rich legacy. The history of occupational and environmental lung disease is comprised of multiple threads that have been interwoven over time into a single historical cord. One such thread is constituted by the clinicians and researchers who have contributed to the characterization and prevention of these conditions. Most general summaries of occupational and environmental medical history limit their focus to their biographies (often devolving to little more than hagiography). Such bio-historical synopses do include information on lung diseases, but only *inter alia*, along with a range of other conditions. The emphasis in such histories is on the life's work of the individual of interest, not so much the pathogenesis of the disease or specifics of the pathologies with which they were concerned.

Yet, as important as biographical roles are in the historical pageant of occupational and environmental lung disease, other key forces have driven the story of occupational and environmental lung disease every bit as much as the parts played at various times by notable practitioners in the field. First, advances in technology have played a pivotal role in the history of occupational lung disease, as they have in the field of occupational medicine more generally. Moreover, this paramount position for technological innovation is not the case in the evolution of other fields of health. It is inarguably true that advances in diagnostic and therapeutic modalities, from the microscope to the laser, demonstrate the powerful impact that changing technologies can have on medical practice as a whole. But despite the impact of such forces in day-to-day clinical practice, the underlying pathologic processes of concern to practitioners have not changed *because* of new diagnostic or treatment modalities. Simply put, the microscope does not create new respiratory illnesses due to emergent pathogens, nor does improved thoracic imaging cause novel forms of interstitial lung disease, even though well-recognized disease processes may be differently diagnosed or treated because of such innovations. In contradistinction, technologic change continually introduces wholly new or greatly modified occupational and environmental hazards, leading to evolving patterns of established diseases as well as inducing entirely novel conditions never experienced before in human history. This, of course, is true of both pulmonary and non-pulmonary occupational and environmental illness, but it is particularly relevant to diseases of the respiratory tract. Examples range from the emergence of acute inhalation fever from zinc oxide fumes in the nineteenth century following the introduction of new brass-making techniques [1] to markedly increased rates of silicosis following the introduction of pneumatic drilling technology at the turn of the twentieth century [2] to the novel appearance of chemically related bronchiolitis obliterans linked to diacetyl use in microwavable popcorn manufacturing in the twenty-first [3].

Second, both the recognition of occupational and environmental respiratory illnesses and the actions that have been taken (or not taken) in response to such recognition demonstrate the profound impact that larger social movements have had on

the history of these diseases [4]. Of course, the effects of social movements are not limited to the narrow confines of occupational medicine. Especially in regard to medical history, the relative importance of social forces in the practice of occupational and environmental health does not mean that other branches of medicine are wholly immune to such factors. For example, modern medicine as a whole still manifests the after-effects of the French Revolution, transmitted down through the influential work of French medical scientists working at the end of the eighteenth and in the first half of the nineteenth centuries [5, 6]. Nonetheless, the discipline of occupational and environmental medicine, inclusive of lung disease, has tended to wax and wane as a consequence of societal forces in a way that is unparalleled in other areas of medical specialization. The hygienic movement of the nineteenth century (particularly in Great Britain), which was linked in turn to wider social reforms, is a case in point. World War I marked another socialpolitical confluence of forces distinctly impacting the recognition and treatment of occupational and environmental lung disease. More recently, larger historical trends in the late 1960s in the United States coincided with the establishment of OSHA, NIOSH, and the EPA, all of which have profoundly affected the field.

The goal of this chapter is to place the story of occupational and environmental lung disease within the context of these three disparate, yet inter-related themes: the key historical figures that contributed to the development of the field, the technologic changes that have led to an ever-shifting burden of disease, and the sociopolitical forces that helped set priorities in the field.

Occupational and Environmental Lung Diseases in Antiquity

Limited references in the classical period to respiratory conditions that may or may not have been occupational or environmental in origin makes this historical record fragmentary at best [7–9]. The early history of lung disease, work-related or otherwise, is further obscured by the medico-philosophical conceptualization of the lungs and respiration in Western antiquity, as epitomized by the Greeks. In that tradition, *pneuma,* entering the body through respiration, came to be seen as critical to the life force and, at one phase in the evolution of Greek healing, was argued to be the seat of the soul [10]. The lung was not seen as central, however, to respiration, as this function was believed to be equally, if not more importantly, carried out by pores in the skin [11]. Even when respiration did come to be conceptualized as movement of air in and out of the lungs in the Aristotelian period, this was seen as little more than a portal for cooling body heat, not as the mechanism for delivering the pneuma. Thus, although various disease states may be attributed to "bad airs" in classical medical writing, this cannot be extrapolated to mean diseases in which the respiratory tract played a central mediating role.

Despite such limitations, there is information to be gleaned from this period in regard to occupationally related inhalational exposures, particularly among those most heavily exposed. For the most part, the heavily exposed were slave laborers.

As the medical historian Henry Sigerist emphasized many years ago in one of the first overviews of occupational disease in antiquity, the single dominant characteristic of work-associated disease in that period was the central fact of slave labor: "Labor in ancient civilization was primarily slave labor. The pyramids were built by state slaves whose lives had no value whatever, whom every war would replace … We admire the graceful Greek bronze statuettes that fill our museums but we do not think of the copper miners providing material for these works of art, or the coal miners digging for coal to make the bronze, working 10 h in narrow galleries suffocated by heat and smoke" [9].

As noted by Sigerist, and as is clear from every other review of the workers' health in antiquity, the adverse occupational safety and health impacts of slave labor in the ancient world were most dramatic in mining operations. This industry was preindustrial, but nonetheless was marked by technological advancements in mining methods and metallurgy [12] (e.g., pumping systems that allowed mining to delve deeper than ever before). Rosen's *History of Miner's Diseases*, although primarily concerned with later periods, provides a detailed review of this mining in the ancient world [13].

Allusions to various labor hazards by nonmedical writers in antiquity constitute some of the best remaining contemporary documentation of occupational safety and health problems. Many of these are simply terse references in a line or two, such as those that have been noted in the epigrams of Martial or the satires of Juvenal [7, 8]. One of the most notable references is the widely cited Pliny the Elder's description of respiratory protection (Natural History XXXIII, 40) [9]:

> Persons employed in the manufactories in preparing minium (red lead) protect the face with masks of loose bladder-skin, in order to avoid inhaling the dust, which is largely pernicious …

There are other occasional references to working conditions of artisans or laborers beyond the Greco-Roman world. One of the most important is the Egyptian papyrus Sallier II, also known as "The Satire of Trades," which describes the conditions of potters, dyers, weavers, and others with dirty jobs and likely inhalational and non-inhalational exposures [14]. Although fragmentary descriptions of working conditions and their inherent risks may also be preserved from antiquity in the non-Western early written tradition (e.g., Chinese medical or technological texts), such sources have never been systematically reviewed for the light they might shed on the early history of occupational and environmental diseases.

The history of "environmental" respiratory disease in antiquity (in any modern sense of this concept) may be even more obscure. Ancient Roman law codified statutory and other legal remedies for air pollution as early as the first century AD (e.g., a legal opinion by the Roman Aristo that a cheese maker should not emit smoke into the building above it) [15]. As with occupational disease, the richest source of such data from the classical period is not in medical texts, but rather from satires, with one of the most vivid "case reports" being Apuleius' tale of the cuckold discovering his wife's lover through sulfur fume inhalation in an indoor air pollution episode [16]:

> She could find no better hiding-place for her lover than a high wicker cage, with cloths hung over it to bleach in the fumes of the sulfur fire inside. It seemed a safe enough place … But the lover was forced to breathe in the suffocating sulfur fumes, and you know how it is with

> sulfur: the smell is so penetrating that it makes one sneeze and sneeze … . But the noise went on and on, and at last he [the husband] began to take notice and suspect that something was wrong. He pushed the table aside, got up, turned the cage over, and there he found his rival panting for breath, nearly at his last gasp.

It is appropriate to conclude occupational and environmental lung disease in antiquity with Galen, not only because his views were to dominate Western medical thought for the next 1,500 years, but also because he seems to be the first physician who recorded a personal brush with a major occupational-environmental respiratory health hazard. According to one review, "on the Island of Cyprus … he had visited a mine where copper sulfate was recovered. Unaware of the danger, he himself was nearly overcome by the fumes in the mine. He records that the workmen who carried out a vitriolic liquid ran from the mine with all speed with each load to avoid perishing in the midst of the labors" [7].

The Post-Classical Period through the Fifteenth Century

Throughout this long period, Western medicine was firmly tethered to the Galenist tradition, in which the four humors were invoked to explain normal function and pathological dysfunction and to provide the rationale for all treatments. These tendencies were strengthened, rather than weakened, by the reintroduction of classical medical texts preserved through Arabic sources, as well as by access to original medical works by Arab and Jewish writers of this period. Environmental contributions to disease were considered in very general terms of climate and good or bad air, still constrained by the concept that respiration was a function for which the lungs did not play the central role. Oral intake, rather than airborne exposure, was a far greater environmental health concern in this period. Thus, only a single stanza from the medieval *Regimen Sanitatis Salernitanum* concerns air quality, "The air must be pure, habitable, and bright, It should be neither contaminated nor smell of the sewer," while the bulk of the text is devoted to dietary recommendations [17].

Occupation's role in health and disease even in general terms (leaving aside specific attention of lung disease) was an even more marginal concern in the extant medical-scientific writing of the period. Attention was given to metallic poisons, a concern carried down from antiquity. In this regard, old knowledge occasionally was augmented by new observations with relevance to occupational etiologies, most notably Paul of Aegina's seventh century description of lead colic [18]. Certainly, the many dangers inherent in working life did not go unnoticed in the wider social arena, consistent with the medieval Hebrew liturgical poem that notes, "Man earns his bread at the peril of his own life" [19]. But it is important to remember that, throughout the long period in question, there were few, if any, social forces bringing such concerns to the fore. Nor was this a static period in technological terms, with particularly notable advances in the Islamic world and China, but also in Christendom. Ultimately, as the Middle Ages drew to a close, with further technologic innovations vocationally related morbidity and mortality were being introduced, a trend that would become ever more prominent in the following centuries.

The harbinger of these technological trends was the metal-working trade. Novel metals and alloys and new ways of refining were introducing entirely new hazards to metal workers, many of whom were guild members. Moreover, experience taught clearly that there were hazards that entered the body through the portal of the lungs. Entirely consistent with this technological driving force, the first stand-alone publication that was devoted solely to the subject of occupational hazards was written in 1473, at the close of the fifteenth century (although it was not printed until 1524) [20]. Ullrich Ellenbog's seven page pamphlet, *On the Poisonous Wicked Fumes and Smokes of Metals* (*Von den gifftigen besen Tempffen und Reuchen der Metal*), is not a medical manual for physicians, but rather more of a self-help manual, warning his fellow metal workers of the hazards to their health from airborne metal, coal, and acid fumes.

1500–1750

This 250-year period, from the Renaissance through the mid-Enlightenment and up to the cusp of the Industrial Revolution, witnessed the emergence of occupational medicine as a distinct focus of biomedical thought in Europe. Technological innovation, underpinned by an emerging role for scientific enquiry, introduced novel exposures, prime examples being munitions and armaments manufacturing and mining and metal smelting [21–23]. An increasing number of writers began to address the subject of work-related disease, first giving attention to the health of miners and metal workers, then expanding beyond that focus to encompass an ever-widening set of occupations and their attendant hazards. Simultaneously, the chokehold grip of Galenist dogma on medical thought began to weaken and then to let go altogether.

Paracelsus was at the center of this change, both in a new awareness of occupational disease and in rebelling against Galenist orthodoxy. He was uniquely placed for this dual role: by experience, he had first-hand knowledge of exposed workers as a mining physician in central Europe; by inclination, he was an iconoclastic thinker and medical innovator. In 1533 he authored (published posthumously in 1567) the first book-length treatment on occupational medicine: *On the Bergsucht and other Miner's Diseases* (*Von der Bergsucht under anderen Bergkrankheiten*) [24]. Although there is no precise equivalent of bergsucht in modern nosology, it unequivocally describes chronic, slowly progressive disease of the lungs associated with dusty conditions in underground mining, consistent with what came to be known as miner's phthisis and, only much later, pneumoconiosis (with or without concomitant mycobacterial disease) [13]. It is no coincidence that such disease came to be recognized at a time of significant advancements in mining technology and ore smelting, as superbly documented in Agricola's *De Re Metallica* (1556). Agricola, who was also a central European mining physician but would have been unaware of Paracelsus' work on the subject, also addressed occupational health. Even though

De Re Metallica devotes only a few of its many pages to this topic, it does allude to the hazards of dry as opposed to wet mines because "the dust which is stirred and beaten up by digging penetrates into the windpipe and lungs, and produces difficulty in breathing … " Agricola also notes that stagnant air also produces difficulty breathing that can be alleviated by using the ventilation devices he describes [22].

Although his work on the bergsucht is the sole occupational treatise in a much larger corpus by Paracelsus, it does fit in with his broader toxicological interests and his belief that chemical mechanisms, not humoral forces, explained biological functions. This so-called "iatrochemical" approach was further championed in the 1600s by a student of Paracelsus, Jean Baptist van Helmont. Although van Helmont did allude briefly to work-related lung disease in his work, occupational respiratory medicine is most indebted to his rigorous experimentation elucidating the nature of a "gas"—a word which he is credited with coining [25].

Ultimately, the "iatrochemical" challenge to Galenism did not prove to be as potent as a parallel "iatromechanical" construct, whose support gathered strength over the course of the seventeenth century. William Harvey's 1628 publication correctly delineating the circulation of the blood stands as a well-recognized landmark in this regard [26]. The realization that the right-sided circulation flows to the lungs and that the left flows to the rest of the body is inarguably critical to what quickly became the modern concept of cardiac function, but the implications of this insight are no less profound to our understanding of the role of the lungs in health and disease, including in the pathophysiology of occupational lung disease.

By 1700, the innovative streams of iatrochemical and iatromechanical medicine were to flow together in the seminal work on occupational medicine by an Italian physician, Bernadino Ramazzini. His book on the diseases of workers, *De Morbis Artificum Diatriba*, published in that year, was concise yet encyclopedic in scope, covering a far-reaching collection of occupations in its 40 chapters [27]. Not content at leaving it there, 13 years later Ramazzini was to publish a second edition, adding a supplement of 12 more chapters detailing many additional trades [28, 29]. The trades that Ramazzini documents are largely preindustrial. Indeed, during the period in which he was writing, many were unchanged in their fundamentals since Roman times. Technological innovation enters into only a few of the occupations considered, for example: chemists, soldiers, and a relatively new occupation altogether, tobacco workers.

De Morbis Artificum Diatriba reflects the impacts on Ramazzini of the social, cultural, and political forces of the late Italian Renaissance. Ramazzini brought to this work his individual genius, but it was tempered in a time and place (especially in the formative years of his career, in Modena under the patronage of the ducal House of Este, one of the great liberal benefactors of the age) particularly conducive to considering the health of the working person as worthy of serious medical treatise [28].

The impact of this work on the discipline of occupational medicine cannot be overstated. It is interesting to note, however, that despite the breadth and depth of Ramazzini's observations regarding a wide range of hazards, descriptions of respiratory-specific syndromes, nonetheless, are relatively sparse in *De Morbis*

Artificum Diatriba. There are notable exceptions, such as Ramazzini's oft-cited allusion to asthma in flour sifters and grain millers (attributed to a chemical fermentation in the airways leading to a mechanical clogging of the breathing passages, a pertinent example of his integrated mechanistic views). A chapter on flax, hemp, and silk workers emphasizes the respiratory complications of those trades, as does a brief discussion of stone cutters. Of particular note, Ramazzini is a keen and original reporter of irritant inhalation effects, including an early description of persistent cough following an acute irritant gas exposure in a chemist, as well as the irritant attributes of sewer work and sulfur burning. In contrast, even though the lead-off chapter of *De Morbis Artificum Diatriba* addresses the diseases of miners, it is predominantly concerned with the non-respiratory adverse effects of pernicious metals. This shortcoming in regard to that topic is understandable: Ramazzini had no personal experience with mining or mining diseases, basing his text on the work of others. In terms of other respiratory hazards, it should be remembered that cotton weaving, as opposed to working with linen, was not on the occupational map in the Italy of Ramazzini's day and, most saliently, although local petroleum sources were of interest to Ramazzini, fossil coal was neither locally mined nor used as a fuel source occupationally or domestically.

The introduction of fossil coal as fuel (as opposed to wood, peat, or wood-derived charcoal), however, was a key technological change of the age, setting the stage for the Industrial Revolution that was to follow [30]. The new role for coal (centered in Great Britain) began as a limited industrial application, in particular firing lime kilns. Domestic coal use quickly came to dominate demand; the market for coal in Britain, and the expansion of coal mining to feed it, witnessed logarithmic expansion during the sixteenth and seventeenth centuries. The new prominence of coal burning had an inevitable and obvious adverse environmental impact. As a result, nearly contemporaneously to Ramazzini's groundbreaking work on occupational exposures, the first treatise devoted to air pollution was to appear in Britain. John Evelyn's *Fumifugium; or, The Inconveniencie of the Aer and Smoak of London Dissipated* was first published in 1661 [31]. Beyond being the first publication on the subject, Evelyn's colorful tract of 26 pages cannot claim too much rigor. Evelyn was neither a physician nor a scientist; aside from being a polemicist, diarist, and dedicated Royalist, he was, however, a devoted gardener, emphasizing above all the adverse horticultural rather than human effects of coal-fired air pollution.

Although Ramazzini and Evelyn are the two dominant figures in occupational and environmental health in the seventeenth and early eighteenth centuries, their works do not stand in complete isolation. Works on miners' health appeared by writers other than Paracelsus and Agricola [32, 33]. In Italy, there was a particular interest in the inhalation effects of volcanic exhalations [34], on indoor air effects [35], and on ambient air quality as well (Lancisi, a contemporary and correspondent of Ramazzini, suggested reforestation as an intervention to improve the air) [36]. As a telltale sign of other problems to come, a brief (16 page) treatise on asbestos appeared in 1665, although it concerns the technical, not health aspects of what was then a novel material [37].

1750–1900

In 1751, Diderot's encyclopedia (subtitled an *Analytical Dictionary of the Science, Arts, and Trades*) documenting all of the major industrial processes of that time began to be published [38]. Soon enough, much of what had been described was to become obsolete. The pace of mechanical invention was increasing rapidly. The introduction of major technical improvements in textile spinning and weaving, the invention of the steam engine, the introduction of coal-derived coke and other key innovations in iron founding, and innovations in chemical manufacturing all occurred before 1800. These and related technological innovations were introducing fundamental changes in the nature and extent of exposures experienced by workers. This applied not only to those employed in the large manufactories of the new "factory system," but also to all manner of smaller workshops and job sites where the materials that were worked with or the tools to do the job had been transformed. The risk of work-related physical trauma from the moving parts of newly steam-powered equipment was immediate and obvious, while other risks, including for diseases of the lungs, were more insidious, but no less deadly.

Not every one of this latter group of emerging hazards was manifested in respiratory diseases. By the end of the nineteenth century, some of the major extrapulmonary, novel industrial diseases linked directly to new technologies included such diverse problems as: caisson disease (from the new capability of maintaining a hyperbaric working environment); [39] manganese-caused Parkinsonism (from application of manganese in chlorine production); [40] carbon disulfide neurotoxicity (from its use in the new process of cold vulcanization of rubber) [41, 42], osteonecrosis of the jaw (following the introduction of phosphorous-based matches); [43, 44] and, near the end of this period, benzene-related aplastic anemia (from solvent applications) [45] and chloracne (from handling electrolytic rods, also in the chlorine industry) [46]. In addition, various industrial processes markedly increased exposures to other toxins that were already well known in Ramazzini's time, in particular lead and mercury.

Even so, occupationally related lung disease, more than any other group of illnesses, bore the hallmark of the Industrial Revolution and the century that followed it. Silica-caused pulmonary disease represents the most dramatic example, in large part due to the introduction of steam-powered grinding wheels in the metal working and steam-driven pumping that facilitated deep mining in silica-bearing deposits. Such exposures were geographically concentrated: for example, Sheffield, England was infamous for its lethal grinding operations [47, 48].

Coal mining, dominant in Britain but also economically formidable on the Continent, was chiefly of concern in relation to explosion-related fatalities, as opposed to chronic lung disease [49]. The latter only began to be given increased biomedical attention later in the nineteenth century. But the toxicity of inhalants before and after mining conflagrations (specifically methane, carbon dioxide, and carbon monoxide) was a longstanding topic of considerable scientific interest. Indeed, many scientific treatises on the nature of air from the eighteenth century

explicitly discussed the nature of the coal mining atmosphere and its hazards [50, 51]. Davey's highly touted invention of the miner's safety lamp early in the nineteenth century [52], an invention that invoked claims and counter-claims by others for originating the device, underscores how important these questions were seen to be on both scientific and commercial grounds.

Cotton textile manufacturing, central to the technological narrative of the Industrial Revolution, was responsible for widespread cotton dust exposure and resultant lung disease. Here too, the industry was concentrated in Britain, but was not exclusively located there, with large centers in France, the United States, and elsewhere [53].

Although cotton dust, silica, and the coal mining atmosphere together can be seen as the triad of major work-related respiratory exposures dominant in this period, other work-related respiratory diseases were also to emerge between 1750 and 1900, in almost every case related to emerging technologies. Pertinent examples include inhalation fever from disparate causes (brass ague linked to new zinc refining technology and shoddy fever from mechanized waste textile shredding) [54, 55] and irritant gas inhalation injury from the new chlorine bleaching industry [56].

Technological change was critical to evolving patterns of occupational lung disease. At the same time, a series of sociopolitical upheavals were to impact how the basic rights of women and men were seen, including the conditions under which they labored. Importantly, the science and practice of medicine was not insulated from these events. The legacy of the French Revolution in experimental medicine represents a well-recognized example, although the Napoleonic era, which brought the legal systematization of exposure hazards, may be just as relevant specifically to occupational and environmental medicine [57]. Other sociopolitical forces also had important impacts on the discipline. In Britain, the Chartist movement drew on populist antagonism toward the human toll of the factory system, a force counter-balanced by reactionary political applications of theories of population growth, laissez-faire economics, and, somewhat later, the label of "social Darwinism." Nineteenth century British physicians involved in questions of the health of the laboring classes took sides on both ends of this political spectrum [58, 59]. In Germany, the philosophical tradition so influential to the development of the discipline of economics informed the work of Karl Marx, who in turn was specifically interested in occupational injury and illness as a particularly illustrative manifestation of capitalist forces. In *Das Kapital*, for example, Marx cites a key list of publications in occupational health and safety, put together by the Twickenham Safety Museum [60].

This history is well reflected in the rich record of biomedical publications on occupational health that appeared between 1750 and 1900. Early on, Ramazzini's continued influence was marked by three major translations with significant annotations containing material new to the original: in French (1777, preceding the Revolution [61]), in German (1780–1783, nearly doubling the original text with original commentary) [62], and a second French translation and major reworking (1822, during the Bourbon restoration) [63]. As importantly, Ramazzini's work was excerpted wholesale and adapted into important general health texts intended for lay audiences [64, 65]. Moreover, even before 1800, major new treatises appeared on

focused occupational subjects such as maritime health [66], the diseases of armies [67], the hazards of agricultural work [68], and the health of persons of leisure [69] (including sedentary occupations; this latter was as much inspired by Ramazzini's companion treatise on the health of princes, *De Principum Valetudine Tuenda Commentatio* [29], as it was by *De Morbis Artificum Diatriba*).

The most important truly new publication on occupational health in the first half of the nineteenth century, however, was Charles Thackrah's *The Effects of the Principal Arts, Trades, and Professions, and of Civic States and Habits of Living.* First appearing in 1831 [70], by 1832, Thackrah had published a greatly expanded second edition [71] and was working on a third edition when he died in 1833 of tuberculosis (most likely an occupationally acquired pulmonary condition) [72]. Thackrah was based in Leeds, England, writing in a place and at a time well situated to address, for the first time, many of the occupational health risks linked to the new technologies of the Industrial Revolution. He gives particular attention to inhalation exposures in "employments which produce dust, odour, or gaseous emanations," dividing these into work entailing exposures with harmless or at most doubtful effects; potentially beneficial exposures; and, finally, those job-related exposures that were "decidedly injurious." To occupations of the latter group, Thackrah relegates grain millers; persons exposed to malt, tea, coffee, and tobacco dust; dust associated with rag dust, including "shoddy grinders," flax workers (one of his most detailed sections, including a series of individual case summaries); coal miners; metal grinders; those exposed to sulfur fume in bleaching; and brass-founders.

Thackrah's work is notable on several counts. Although his text was clearly inspired by Ramazzini's original opus and the works of his annotators, Thackrah's organization by exposure groupings provides for an important emphasis on respiratory effects. He both summarizes existing knowledge and makes original observations, most notably for respiratory disease in flax workers (which includes measurements of lung volumes by "pulmometer," probably the earliest such application of lung function assessment in a systematic study of an occupational lung disease) and was the first to describe both "shoddy fever" and fever in brass founders (although, not surprisingly, he did not link these to each other). His major oversight was an underappreciation of the respiratory health risks of cotton dust. That industry, based in Lancashire, was not as familiar to him as Yorkshire's woolen industry; thus for cotton, he seems to overly rely on the assessments of others, which may have equivocated on the industry's respiratory hazards [73]. Another curious anomaly is Thackrah's belief that chlorine gas inhalation in its manufacture and use (as opposed to sulfur) was, if anything, beneficial to health; near the end of the book he even describes a series of chlorine inhalations he administered to flax workers, touting the supposed beneficial effects of such treatments. This aspect of Thackrah's work can be squarely placed in the context of work of the British "pneumatic school" of medical science of a generation before. Led by Thomas Beddoes, followers of the pneumatic school had an inherent interest in occupational disease from inhalation exposures [74]. Thackrah's work had an immediate influence on other hygienists of the period, as well as on political reformers for better occupational conditions, in particular those working on the 10 Hours Bill [72].

Although Thackrah's work was to stand alone for several decades as the only new original comprehensive text on occupational diseases in Britain, a number of medical writers there also were concerned with this subject. Their interest was, like Thackrah's, general, but they too emphasized work-related lung disease in particular. The physician most notable for such work was Edward Hadlam Greenhow, who was a close associate of John Simon, the dominant figure in British public health for most of the Victorian era [75]. Greenhow's pivotal work focused on lung disease in a number of different dusty trades involving both inorganic and organic particulates [76–78].

In France and Belgium, the evolution of occupational medicine differed from Britain's in substantial ways. On the Continent, the new science of toxicology dominated the discipline, reflected in the work of Orfila [79], Bernard [80], and the toxicologically oriented journal, *Annales d'Hygiene et de Medicine Legale*. Many of the latter's frequent occupational articles also appeared as separately bound reprints that, although a source of scholarship in the field in general, were typically concerned with non-respiratory syndromes, in particular the systemic manifestations of toxicity. Another key difference between the French–Belgian experience and Britain's was the relative paucity of large manufacturing operations in the latter, as opposed to multiple smaller scale workshops in the former (a pattern particularly characteristic of Paris). The exception to this was textile manufacturing, including cotton spinning and weaving and it was to prove important in the history of occupational lung disease.

Even though Britain was dominant in cotton manufacturing, biomedical attention to the subject of cotton dust-related respiratory disease was relatively sparse there and far from consistent in assessing this as a serious health concern [73, 77, 81]. In contrast, in France and Belgium there was a consistent and well-developed biomedical literature on this subject. As early as 1822, Patissier's update of Ramazzini included a contemporary observation on French cotton spinners, noting cotton cough and chronic lung irritation provoked by the dust in that industry [63]. By 1839, a leading French demographer, Louis Villermé, described chronic progressive lung disease in the textile workers of Lyon as "cotton phthisis" (pathologically distinct from tubercular disease) in a report commissioned by the French Académie des Sciences Morales et Politiques [82]. In 1845, Belgian investigators in the textile center of Ghent carried out a major investigation of disease in this industry, including the astute observation that disease symptoms were most marked early in the week on return to the factory after time off [83]. Finally, an 1877 public health textbook by Dr. Adrien Proust (father of the writer Marcel Proust), in discussing the lung disease of cotton workers, introduced the modern term *byssinosis* (for the Greek "byssos" for fine fiber and correcting an error by a German pathologist who mistakenly suggested *lyssinosis*) [84].

In the latter decades of the nineteenth century, German occupational medicine came into its own, enriched by a particularly strong component of pathological investigation, for which coinage of the term pneumonokoniosis (later altered to pneumoconiosis) is an exemplar [85]. The encyclopedic occupational medicine textbook of Hirt appeared in this period, as did Arnold's text solely devoted to dust inhalation effects [86, 87]. This scientific activity was taking place within a larger public health tradition of "medical police" that has historical links to the later paradigm of "state

medicine." In the occupational arena, the first workers' compensation insurance scheme anywhere, dating to 1884, was introduced in Germany [88]. Nonetheless, occupational public health reforms specifically, and the apparatus of state medicine more generally, by no means marched forward in lock-step across Germany: the pattern of reforms was spotty and often inconsistently manifest [89, 90].

Moreover, the occupational health concerns in Germany of this period largely overlapped with those of Britain, France, and Belgium. They were, however, notable local issues. In terms of occupational lung disease, a newly emerging entity unique to the central European experience proved to be work-related cancer of the lung. Medical descriptions of miners' lung disease in this region go back centuries, dating to the bergsucht of Paracelsus and Agricola, as noted previously. In the late eighteenth century, however, a new pulmonary syndrome was described, geographically specific to the Erzgebirge "ore mountains" region that spans present-day Germany and the Czech Republic. In 1770, Carl Lebrecht Schefflers published *Abhandlung von der Gesundheit der Bergleute*, a treatise on the health of miners that gives particular attention to the health of the cobalt miners of Schneeberg and nearby Annaberg in the Erze region [91]. Although this was a long established region for silver mining, at that time cobalt had only recently begun to be exploited as a lucrative metal for alloying purposes. Because uranium-bearing ores were mineralogically linked to the cobalt in that region, mining the latter also brought exposure to the former. The specific illness that Scheffler described differed from the generic bergsucht, including a very rapid downhill course once manifest: he attributed it to an inhaled gas or emanation, rather than dust per se, noting a higher prevalence of illness in one particular cobalt mine in Schneeberg characterized by long, poorly ventilated galleries through which the miners walked to get to the seam being worked. It took another century before employment in the mines of Schneeberg was linked to neoplasm of the lung, with an initial 1878 notice, followed one year later by a more extensive report [92, 93]. The disease came to be known as the *Schneeberger krankheit* and was reported to be responsible for an astounding 23 % mortality rate among the mining workforce at a time when lung cancer was otherwise a rare entity.

In contrast to the increasing sophistication in the science and practice of occupational medicine from 1750 to 1900, for most of that period the potential health effects of air pollution were addressed only in descriptive and anecdotal, if not polemical terms, although the subject was not forgotten [94]. In 1772, for example, a centenary, second edition of Evelyn's *Fumifugium* appeared, noting in its preface: "Our Author [Evelyn] expresses himself with proper warmth and indignation against the absurd policy of allowing brewers, dyers, soap-boilers, and lime-burners to intermix their noisome works against the dwelling-houses in the city and suburbs; but since his time we have a great increase of glass-houses, foundries, and sugar-bakers, to add to the black catalogue … " [31].

A more systematic approach began to be taken in the last decades of the nineteenth century, as increases in the death rate in London and in other cities were linked to the increasingly dense and pernicious fogs, for example a particularly lethal one that struck in January and February of 1880; these population effects were studied on a new, statistical basis [95]. In parallel, hygienists of the time began to use modern analytic techniques to systematically identify the chemical constituents

of such pollution, including the role of sulfur dioxide leading to acidification of the atmosphere [96, 97].

Against the backdrop of the changes that occurred in the way people went about their work, the air they breathed, and in understanding of the illnesses these exposures could bring, it is also important to call attention to a new recognition of these phenomena in poetry, prose, and the visual arts over this 150-year period. Indeed, in 1752, the first poem addressing the topic of coal mining hazards appeared [98]. Prose fiction took notice of factory conditions in general and of occupational lung disease specifically, for example, the description of cotton dust-caused lung disease in Gaskell's novel *North and South* [99] (notably, ahead of any widespread medical acknowledgement of the problem in Britain). Silicosis was so much a fact of everyday life in the north of England that it even figured into a moralizing children's book of the time [100]. The fine arts lagged behind literature insofar as the industrial milieu was concerned, but took on a far more significant role in terms of ambient air pollution: indeed, it has been argued that Britain's dismal air quality in the later Victorian age served as a major inspiration for the development of the Impressionist urban landscape [101].

The year 1892 marked the appearance of the first new English language occupational medicine textbook since Thackrah's 60 years before [102]. By then, a series of landmark statutes had introduced a number of reforms in Britain, in particular the establishment of a governmental medical factory inspection service that served as the training ground for several generations to come of occupational medicine specialists [103, 104]. Yet ironically, as the century drew to an end, interest in occupational respiratory disease and environmental airborne pollution due to vapors, gas, dust, or fumes and even more dramatically concern over "environmental" illness was waning among the very public health leaders who had once championed these issues. It has been argued cogently that a major contributor to this change was "The New Public Health," a term used to describe the application of germ theory into the population-based preventive medicine of the time. As it became clear that the major epidemic diseases (acute and indolent), especially those attacking the working poor, were infectious in etiology, the priority became controlling contagion and identifying host vulnerability [105, 106]. In that paradigm shift, occupational disease came to be seen through the lens of microbiology (e.g., placing major emphasis on tuberculosis in the workplace, to the near exclusion of concerns over pneumoconiosis or byssinosis as meriting attention in their own right). Even more extreme, the potential for chemical or particulate ambient air pollution causing disease, as opposed to infectious causes, was treated as little more than miasmic superstition [94].

1900 Onwards

Until this point, the United States has been completely left out of this historical narrative. There were scattered examples of medical writers documenting occupational diseases or even environmental air pollution issues prior to this date, including

reviews of the topic in the mid-nineteenth century [107, 108]. In general, such reports were not original but rather addressed the US experience in light of what had already been reported elsewhere, particularly in Britain. In this context, the US textile industry was touted as being notably free of lung disease (and there is little that can be gleaned from other sources, such as the *Lowell Offering*, to provide an alternative picture). There is scant other information specific to occupational lung disease in the United States before 1900 [109].

This was to change quickly in the new century. In January 1900, William Winthrop Betts of Salt Lake City published an extensive report describing a massive outbreak of rapidly fatal dust disease among workers who crushed quartz-bearing rock in a gold-extraction mill [110]. Located in DeLamar, Nevada, the mill began operations in 1894. By the time of Dr. Betts' report, most of the initial workforce was already dead from lung disease consistent with acute silicosis. In a fitting rebuke to the dominance of germ theory, Betts noted, "I believe it is our duty as scientific physicians not only to point out the danger from contagion, and to render innocuous the germs lurking in our food and water-supply, but also to call attention to the causes of disease induced by the industrial occupations, suggest proper sanitary and hygienic measures, and force, by our teachings, a wholesome regard for the comfort, health and life of the employees, thus reducing the dangers to a minimum."

Silica was a long recognized hazard, even if acute silicosis, as reported by Betts, was a novel manifestation of dust-related disease. In the year 1900, on the other side of the Atlantic, an entirely new occupational lung disease appeared. The first known death from asbestos-caused lung scarring occurred in Britain in 1900; details of which were preserved in evidence given to a governmental compensation committee, but were only reported in detail some years later when the disease was first termed "asbestosis" [111, 112].

During the early years of the century, agitation for increased worker protection and compensation for injury in the United States was taking shape within the larger context of the progressive reform movement [113]. There was also greater labor militancy, particularly among mine workers, largely concerned about physical trauma, but also beginning to be concerned with illness [114]. By 1909, the first state workers compensation law had been enacted in the United States [113]. Air pollution was starting to receive some attention in the United States as well, although negative agricultural as opposed to human health effects were emphasized [115].

Even so, there was resistance to change. In addition to the continued dominance of a contagion-control agenda in public health that down-played mechanisms of disease related to vapors, gas, dust, or fumes, progress was further constrained by an emerging corporate influence working against such recognition as well. World War I, however, turned out to be a major factor over-turning the *status quo* in occupational and environmental medicine on both sides of the Atlantic [94]. Armaments production in the munitions and new airplane industry led to chemically related illness outbreaks obviously unrelated to contagion, a subject of particular interest to the leading US occupational medicine figure, Alice Hamilton [116, 117]. The governmental role in investigating and controlling such disease led to new rules and the establishment of the US Public Health Service Bureau of Industrial Hygiene [104].

And most dramatically, mass chemical gas warfare completely negated any dogma holding that germs alone were the sole concern of modern public health [118–121]. Indeed, coming full circle, JS Haldane was recruited to the British war gas effort based on his research experience in the effects of underground mining atmospheres on workers' health [122, 123].

In the decades that followed World War I, a growing politically progressive, left-oriented awareness informed concerns over occupational illness and injury, including lung diseases. In the United States, the physician Alice Hamilton was a leader in this struggle [124, 125]. One of her interests (among many) was silicosis produced by new technological development of air-powered tools being employed in quarries. In Britain, Sir Thomas Legge was another leader in the field whose career was imbued with a commitment to a labor-oriented approach to occupational disease [126]. Further underscoring this trend, key British physicians involved in miners' health also served in the Spanish Civil War or actively supported the Loyalist effort [127–130].

This phenomenon was also manifest in the prose and poetry of this period. In the United States, the infamous outbreak of acute silicosis in the construction of a Union Carbide diversion tunnel came to be widely publicized in the popular press and through Congressional hearings [131]. One of the first allusions to the tragedy in print, however, was a short story that brought early success to Albert Maltz, who went on to become a major Hollywood screenwriter; it tells an eerie tale involving a gaunt hitchhiker, a Gauley Bridge worker dying of acute silicosis [132]. The silicosis epidemic was also the subject of a proletarian novel of the time, as well as a cycle of poems by Muriel Rukeyser and a blues song by Leadbelly [133–135]. In Great Britain A.J. Cronin's novel, *The Citadel*, appeared at nearly the same time, featuring an idealistic mining physician as its protagonist [136].

In central Europe, the history of occupational lung disease was played out in a far different way. The strong biomedical and technical infrastructure in German occupational medicine and industrial hygiene, built up in the late nineteenth century, carried through into the twentieth century despite the disruptions of World War I. For example, accumulating medical reports continued to explore causes of lung cancer among the Schneeberger miners, who by this time were known to be exposed to radioactive substances as well as possibly other toxic materials [137]. The problem certainly had not gone away: by the 1920s the lung cancer death rate was reported to have reached 50% or more among the exposed workforce. Indeed, the *Schneeberger krankheit* was recognized as an occupational disease and compensated as such by the German authorities [138].

The ascendancy of the Nazi regime, in certain limited aspects, intensified governmental interest in occupational disease, often with internally inconsistent policies depending on who was considered to merit protection: for example, the cancer-causing potential of asbestos was given particular attention [138]. The forced exile of physicians and biomedical researchers compromised academic medicine in Germany and Austria in general, having an impact on occupational medicine as well (e.g., Ludwig Teleky, one of the leading figures in German occupational medicine, fled to the United States; he later wrote a major work on the history of occupational

hygiene) [88, 139]. Moreover, occupational physicians who remained were tainted by their involvement with the regime, for example, Ernst Baader, whose occupational medicine textbook went through several editions during this period in Germany [140].

The aftermath of World War II also had impacts on occupational and environmental lung disease, once again reflecting the combined effects of technological change and sociopolitical forces. The post-War growth of petrochemical-based manufacturing, in particular the polymer industry, represented a major technological shift with wide-reaching effects in occupational health [141]. But even less prominent technological changes can be associated with emerging problems. Silo filler's disease is a case in point. This agricultural scenario for nitrogen dioxide over-exposure leading to acute lung injury and bronchiolitis obliterans was unknown as such until the 1950s; temporally, it emerged when the use of newly introduced, nearly airtight, enclosed metal feed silos for corn silage coincided with the application of high nitrogen-content fertilizers [142–144].

New scenarios of ambient inhalation injury were also emerging. In Donora, Pennsylvania in 1948, the United States experienced its first large-scale air pollution disaster [145, 146]. This was soon eclipsed, however, by the so-called "killer-fog" of London in 1952 [147]. The later was almost certainly due in part to the economic policies in post-War Britain that led to preferential export of low-sulfur-content coal and increased domestic consumption of more highly polluting fuel. These air pollution crises drew in occupational hygiene experts to a newly invigorated field of environmental science and refocused governmental concerns: in 1957, the US Public Health Service organized a distinct Air Pollution Division, which began to develop criteria documents to address specific pollutants and their potential control [148].

The Cold War represents the merging together of technological and sociopolitical forces *par excellence*. As a result, the birth of large-scale nuclear weapons manufacturing and the transformation of airplane construction into an aerospace industry brought long-lasting health consequences for a new workforce. Beryllium-related lung disease, although well reported before World War II, became an endemic risk of this new technology [149]. But the health effects of radon gas represent the most striking legacy of this period. Even in the run-up to the arms race, two major US reviews had delved deeply into the question of lung cancer among European radon-exposed miners but came to markedly different conclusions. In the seminal 1942 textbook, *Occupational Tumors and Allied Diseases*, Hueper was unequivocal in his conclusion that, based on epidemiological data, radon was the responsible agent for occupational lung cancer in radon-exposed miners [150]. In contradistinction to this assessment, a 1944 review that appeared in the *National Cancer Institute Journal* discounted radiation exposure as a likely cause, largely because of negative animal studies and mathematical estimations of exposure; the review put forth an alternative explanation of hereditary susceptibility in multigenerational families of miners [151]. The author of this negative review was by that time closely associated with the Manhattan Project [152], but whether or not the needs of the war effort for radioactive materials and the exposures that were to ensue influenced these pivotally

influential conclusions cannot be known. By 1951, a new analysis finally explained the biological potency of radon decay product alpha exposure, making irrefutable the link between uranium mining and lung cancer; these findings, unfortunately, remained a matter for internal governmental consideration only and was not published in the open peer-reviewed literature for decades [153]. In that context it is all the more notable that a 1955 publication by Duncan Holaday, a crusading US Public Health Service scientist, reported that the radon-related radiation dose delivered to US miners was likely to be 100 times higher than that previously calculated, footnoting the unpublished radon decay calculations as a personal communication; [154] he pressed Federal officials for protective actions, but was effectively blocked [155].

By that time, of course, the United States had epidemiological experience with uranium mining-caused lung cancer to compare with that of Schneeberg in central Europe. By 1967, this was being covered in the popular news media, an early example of the new role public awareness and increased scrutiny was to play in late twentieth century in occupational health and even more so in responses to environmental risk [156]. The news reports of lung cancer in uranium miners caught the attention of the then Secretary of the US Department of Labor, a Johnson appointee named Willard Wirtz. He went on to champion far stricter occupational exposure controls for radon, setting a jurisdictional precedent while also laying the political groundwork for the later creation of the Mine Safety and Health Administration and the Occupational Safety and Health Administration [157]. The US National Institute for Occupational Safety and Health and the Federal Environmental Protection Agency followed suit, following a decade of wider cultural change in the United Sates.

The triad of exposures that had dominated the occupational lung disease agenda throughout the nineteenth century continued to present major challenges right through to the end of the twentieth century. Nonetheless, progress was made in addressing longstanding questions, even as new ones were raised. Coal workers' pneumoconiosis, long argued to be attributable to silica while downplaying a specific role for coal dust exposure, was finally well-characterized as a disease process in its own right distinct from silicosis (and separately compensable), albeit with open questions as to the contributions to disease risk related to coal rank and other aspects of the mineral composition of the exploited rock [129, 158, 159]. The biology of silicosis was a matter of sophisticated research progress in the twentieth century, progress that arguably was not paralleled by equally advanced exposure controls. As notable in regard to silica, there were also newly appreciated associations, including the pathological relationship between acute silicosis and pulmonary alveolar proteinosis (an otherwise idiopathic disease first reported in 1958) [160, 161] and the link between silica exposure and cancer of the lung, accepted by IARC at the close of the century [162]. Byssinosis was finally well characterized through systematic British investigations, led early on by Austin Bradford-Hill, who was to become a leader in the general application of epidemiological methods and the interpretation of causality in clinical research [163]. Byssinosis was belatedly recognized as being prevalent in the United States only in the late 1960s [164].

Other new issues in occupational and environmental lung disease were to come to the fore in the twentieth century. Some of these, as other emerging conditions before them, were a direct result of changing industrial processes or novel chemicals,

for example, asthma due to the introduction of proteolytic enzymes into laundry detergent, which became a source of environmental as well as occupational lung disease [165]. Other exposures were not new, but their risks were only appreciable through modern epidemiological or other investigational methods. A case in point can be drawn from the initial independent reports of what would come to be called hypersensitivity pneumonitis (or allergic extrinsic alveolitis). These papers were published in 1932, describing the condition in two disparate groups of workers: one, stripping maple bark to make wooden railway ties and the second, farmers working with dusty hay, moldy after a very wet summer [166, 167]. Neither exposure scenario was driven by the introduction of a new production method or material, rather the availability of radiographic techniques to evaluate these cohorts facilitated the observation of a disease process that presumably had long existed but had gone previously unrecognized. The link to serum precipitins would not occur for another 30 years [168]. Yet, in the final analysis, as significant as any of these historical trends may have been for lung disease related to coal, silica, and cotton dust or to a new appreciation of allergic occupational and environmental lung disease, the preceding hundred years have been, above all, the century of asbestos [169].

Additional Resources

A number of key monographs in the history of occupational and environmental medicine have already been cited in the preceding pages. For general topics, this includes the works of Rosen (including his work on Paracelsus included in a collection edited by Sigerist) [13, 24], Miekeljohn [72],Teleky [88], Sellers [106], Berman [113], and Derickson [114]. Exposure or industry-focused works of note also include Rosner and Markowitz on silica and on the chemical industry [2, 141], Cherniack's history of the Hawk's Nest incident [131], Proctor's study of public health including occupational disease under the Nazi regime [138], Davis' study of the Donora air pollution incident [146], and Brouder's history of the twentieth century asbestos industry [169]. Three key memoirs rich in historical detail are those of Sir Thomas Legge [126], Alice Hamilton (as well as the annotated collection of her letters) [124, 125], and Harriet Hardy [149].

A great deal of additional scholarship is also relevant to the history of occupational and environmental lung disease. The oral history work of McIvor and Johnston has allowed us to learn about occupational lung disease from the workers' perspectives [170, 171]. Other scholarship has addressed byssinosis and coal worker's pneumoconiosis from the US perspective [172, 173] and additional historical investigations of the British experience are noteworthy in occupational health [174, 175] and in air pollution [176]. New scholarship is also going outside the boundaries of a European and North American focus on occupational illness and injury [177]. Finally, the history of technology is central to a deeper understanding of the evolution of occupational respiratory disease and the effects of air pollution. General resources for such history are key; [178] works focused on specific areas can be critical, in particular histories of non-Western technological development [179, 180].

Concluding Comments

In summary, the history of occupational and environmental lung diseases is long and complex. A more complete grasp of that history, and particularly the technological and social forces that have helped shaped it, better informs our understanding these issues, past, present, and going forward. Whenever a disease outbreak occurs, whether it is bronchiolitis obliterans from diacetyl use as a flavorant in microwavable popcorn or silicosis from sandblasting denim jeans or asthma from indoor air pollution due to household cleaning product use, putting these events in their historical context is critical. This is also the case for long established respiratory problems as well. That context includes elements of biography related to important personages in this field, but the history of technology as it has introduced novel exposures and new risks for disease is as important to a full understanding of occupational and environmental lung disease. In addition, changing sociopolitical forces have shaped how medicine has viewed diseases in workers as well as how it conceptualizes environmental exposures and such factors, therefore, should be taken into account from an historical perspective.

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Chapter 2
The Occupational and Environmental History

Lawrence C. Mohr, Jr.

Abstract The occupational and environmental history is fundamentally important to making the correct and timely diagnosis of any illness that may have resulted from a toxic exposure in the workplace, the household, or the general environment. In interviewing the patient with a potential occupational or occupational illness, it is important for the physician to ask questions that efficiently lead the patient into providing useful information about possible associations between the presenting illness and potential toxic exposures. A particularly useful and efficient construct for interviewing a patient about his or her occupational and environmental history is contained in the easy-to-remember mnemonic "WHACOS." The components of the "WHACOS" mnemonic are as follows:

W—*What* do you do? *H*—*How* do you do it? *A*—Are the symptoms *acute or chronic* in nature? *C*—Are any *coworkers, family members, or friends* sick with the same illness? *O*—Do you have any hobbies, pets, or travel *outside* of work? *S*—Are you *satisfied* with your job? These simple questions can efficiently lead the patient into a useful dialog with the physician about occupational and environmental factors that can provide important clues about the etiology of an illness that may be related to a toxic exposure.

Keywords Occupation • Environment • Work • Hobbies • Interview • History

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Introduction

There are a wide variety of respiratory disorders that can result from the inhalation of toxic gases, fumes, particles, and dust. These disorders can occur from toxic inhalational exposures in the workplace, the household, and the general environment. They include asthma, reactive airways dysfunction syndrome, pneumoconioses, hypersensitivity pneumonitis, acute inhalational lung injury, chronic cough, benign pleural disease, mesothelioma, lung cancer, and respiratory infections, such as tuberculosis. In some cases, the root cause of an occupational or environmental respiratory disease is readily apparent. In other cases, the root cause may be elusive and difficult to establish.

The occupational and environmental history is fundamentally important to making the correct and timely diagnosis of any illness that may have resulted from a toxic exposure in the workplace, the household, or the general environment. The aim of the occupational and environmental history is to establish an association between the illness and toxic agents to which an individual may have been exposed, as well as to make an assessment of the extent and time course of the potential toxic exposure. The occupational and environmental history is especially important in the evaluation of the patient with a respiratory disorder that may be related to a toxic inhalation.

Occupational and Environmental Exposure History Forms

A number of standardized forms for compiling a detailed and extensive occupational and environmental exposure history have been published. These forms are readily available in print form and online. These forms allow the patient to provide responses related to the past medical history, drug use, family history, social history, employment history, the workplace environment, the home environment, smoking history, travel history, military service, allergies, and potential toxic exposures. These forms, if properly completed, can provide the physician with valuable background information that becomes an important part of the medical record and can, possibly, provide important clues about possible occupational or environmental causes of the patient's illness. An example of a comprehensive occupational and environmental exposure history form is included in the Appendix to this chapter [1].

Standardized forms, while generally useful, have some limitations. First of all they contain a lot of information that may or may not be useful with respect to the specific problem that the patient presents. Secondly, the responses of the patient may not be entirely accurate or complete. Patients may sometimes misunderstand the nature of some questions on the form and may provide erroneous or irrelevant information. Some patients may also list toxic substances that they think they may have been exposed to when, in fact, they have not been exposed to these toxic substances at all. This can be misleading and potentially confusing to the physician. Thirdly, the patient responses on these forms, while providing a lot of information, do not

make associations between the presenting illness and potential toxic exposures, nor do they make associations between the time course of the presenting illness and the time of potential toxic exposures. Only by the careful interviewing of the patient can the physician begin to make these important associations. Thus, standardized occupational and environmental history forms can best be used to provide background information that can help the physician focus on specific areas during an interview of the patient.

The Patient Interview

In interviewing the patient with a potential occupational or occupational illness, it is important for the physician to ask questions that efficiently lead the patient into providing useful information about possible associations between the presenting illness and potential toxic exposures. This, in turn, can provide the physician with important clues about potential occupational and environmental etiologies of the presenting illness. They can also guide the physician in ordering the most appropriate diagnostic studies for further evaluation of the illness.

A particularly useful and efficient construct for interviewing a patient about his or her occupational and environmental history is contained in the easy-to-remember mnemonic "WHACOS." This construct contains a series of easy-to-understand, open-ended questions that lead the patient into describing and discussing key points about his or her occupational and environmental history [2, 3]. The components of the "WHACOS" mnemonic are as follows:

W: *What* do you do?
H: *How* do you do it?
A: Are the symptoms *acute or chronic* in nature?
C: Are any *coworkers, family members, or friends* sick with the same illness?
O: Do you have any hobbies, pets, or travel *outside* of work?
S: Are you *satisfied* with your job?

These simple questions can efficiently lead the patient into a useful dialog with the physician about occupational and environmental factors that can provide important clues about the etiology of an illness that may be related to a toxic exposure. Each component of the "WHACOS" construct will be discussed in the sections that follow.

What Do You Do?

The job title or the job description oftentimes does not provide an accurate or complete understanding of what the patient actually does at work. In this regard, a job title or job description alone may not facilitate the making of associations that point to an

occupational or environmental etiology of a respiratory illness. Asking a question such as "what is your occupation" or "what is your job" generally has little value. For example, the fact that a patient is a "construction worker" does not tell the physician exactly what the patient does. "I mix and pour cement at construction sites" provides much more useful information. Similarly, a patient who tells you that he is a "foundry worker" provides little information in comparison to a statement such as "I mix and pour green sand into molds then pour molten bronze into the molds to make bronze castings." Thus, by simply asking "what do you do?" the physician can get a very good idea of what the patient may be exposed to in the workplace. Careful follow-up questions can provide more detailed information in this regard.

How Do You Do It?

After the patient tells you exactly what he or she does, it is useful to ask "how do you do it?" This can provide the physician with important information about the processes that the patient uses at work and whether or not the patient uses respiratory protection while engaged in these processes. For example, I was once asked to see a hospitalized patient with alcoholic liver disease who also had significant hypoxemia and diffuse, dense, bilateral fibrotic infiltrates on a CT scan of the chest. At the time of admission no one had taken an occupational and environmental history. Upon asking the patient "what do you do?" he told me that he sandblasted the inside of empty liquid storage tanks in order to clean the inside walls of the tanks. I then asked the patient "how do you do it?" He told me that he was lowered into the tanks with a rope and harness and that he sandblasted the inside walls of the tanks while suspended by the rope. Upon further questioning he told me that he had been doing this for 24 years, that each sandblasting operation inside the tanks took 4–5 h, that it was difficult to see what he was doing because it was dark inside the tanks, and that he never used respiratory protection because it was "too hot" inside the tanks. Upon correlating the patient's responses to "how do you do it?" with the chest CT scan findings, the diagnosis was readily apparent. The patient had progressive massive fibrosis from the inhalation of large quantities of silica dust over a period of 24 years. On further evaluation the patient also had *Mycobacterium avium complex* lung infection, which occurs with increased frequency in individuals with silicosis. This is a good example of how the simple question "how do you do it?" can quickly lead the physician to the correct diagnosis of an occupational or environmental lung disease.

Are the Symptoms Acute or Chronic in Nature?

The rapidity of onset and the time course of a respiratory illness can provide the physician with important clues about the differential diagnosis of the presenting

symptoms, as well as a temporal association between the onset of the illness and potential occupational or environmental exposures.

Illnesses that are acute in onset should guide the physician to consider disorders that can occur shortly after exposures to potentially toxic substances at work, at home, or in the general environment. These include workplace-related asthma, acute inhalational injury, and acute hypersensitivity pneumonitis. Such disorders may result from exposures related to a new job, a change in the workplace environment, the use of a new substance at work or at home, exposures related to new pets or hobbies, or proximity to the acute release of a toxic substance. On the other hand, illnesses that have a chronic or progressive course should suggest disorders that are related to chronic, persistent exposures in the workplace, home, or general environment. These include pneumoconioses, subacute and chronic hypersensitivity pneumonitis, asbestosis, chronic bronchitis, bronchiolitis obliterans, chronic beryllium disease, hard metal lung disease, and tuberculosis. Such disorders may result from the chronic exposure to mineral dusts, organic dusts, molds, microorganisms, asbestos, toxic fumes, or metal dusts. Thus, whether the presenting symptoms are acute or chronic in nature, can be of tremendous help in formulating the differential diagnosis and eventually making the correct diagnosis.

The temporal association between the onset of symptoms and potential occupational or environmental exposures can also be very helpful in making the correct diagnosis. For example, a patient who develops symptoms of asthma during work days, but does not experience these symptoms when away from work, may have occupational asthma. Similarly, a farmer who typically develops dyspnea and a viral-like illness during certain times of the year, such as the time of the year when hay is bailed and stored, may have acute hypersensitivity pneumonitis. Therefore, it is important for the physician to establish any temporal relationship between the onset of symptoms and specific activities at work or home, if an occupational or environmental illness is suspected.

Are Any Coworkers, Family Members, or Friends Sick with the Same Illness?

It is very important for the physician to ask the patient about the occurrence of the same illness among coworkers, family members, or friends if an occupational or environmental illness is suspected. If the patient has coworkers who have similar symptoms, the probability of a workplace-related illness is increased. Similarly, if family members have similar symptoms, an illness related to a toxic exposure in the home environment should be suspected. If the patient has friends with similar symptoms, the physician should ask about activities that the patient and affected friends have engaged in together. Thus, similar symptoms among coworkers, family members, or friends can provide important clues about where a toxic exposure may have occurred. The physician can then initiate an appropriate industrial hygiene

assessment, household exposure assessment, or environmental exposure assessment in order to detect and characterize any toxic substance that could be the root cause of the common illnesses.

Do You Have Any Hobbies, Pets, or Travel Outside of Work?

Activities outside of work may also be the source of toxic exposures that can cause an environmentally related illness. Hobbies may involve the use of potentially toxic substances such as paints, glues, organic solvents, wood dust, metal dust, mineral dust, organic dust, colophony, fertilizers, pesticides, or toxic fumes, all of which have the potential to cause a respiratory illness following acute or chronic exposure. Therefore, it is important for the physician to obtain detailed information about any current or past hobbies of the patient.

Pets can be an especially important source of toxic environmental exposures. The dander of common household pets such as dogs and cats can be a cause of asthma. The urine and feces of household pets can be allergenic, as well as a source of infection. Bird dander is a particularly important cause of hypersensitivity pneumonitis among bird fanciers and pigeon breeders. The physician should specifically ask about exposure to birds when evaluating any patient that is suspected of having acute, subacute, or chronic hypersensitivity pneumonitis. Animal bites and scratches can also be a cause of infections, such as cat-scratch fever, leptospirosis, toxoplasmosis, and rabies. Therefore, asking a patient about pets, as well as any temporal relationship between exposure to pets and the onset of symptoms, is an important part of the occupational and environmental history.

The patient's travel history is also an important part of the occupational and environmental history. Temporal relationships between travel and the onset of symptoms may provide important clues about the etiology of a suspected environmentally related illness. Information about the dates of travel, the travel destination, the length of stay at the destination, activities at the destination, and the means of transportation should be sought by the physician. Known environmental problems at the destination, such as severe air pollution, known water pollution, or toxic releases from industrial plants can then be investigated by the physician. Infections, such as malaria, typhoid fever, yellow fever, coccidioidomycosis, histoplasmosis, giardiasis, and tuberculosis are typically endemic to certain geographical areas. Travel to tropical areas can result in exposure to vegetation, molds, and microorganisms that can trigger asthma or acute hypersensitivity pneumonitis. It is possible that symptoms of a travel-related illness may not occur until after the patient has returned to home and work. This is especially true of travel-related infections. Thus, it is possible for travel-related illnesses to be mistaken for illnesses related to the workplace or home environment. A careful travel history is important in helping to make this distinction.

It is not uncommon for patients to be referred for the evaluation of potential workplace-related illnesses that are, in fact, related to hobbies, pets, or travel. Failure

to ask about activities outside of work may result in an inappropriate, unproductive, time-consuming, frustrating, and expensive medical evaluation that could be avoided by asking the simple question: "Do you have any hobbies, pets, or travel outside of work?"

Are You Satisfied with Your Job?

Occupational stress is an increasing problem in the workplace. Occupational stress can result from a number of workplace situations. Some of the most common causes of occupational stress are a lack of trust in the employer, a difficult and demanding supervisor, interpersonal conflicts with one or more coworkers, inadequate training for difficult tasks, the lack of proper equipment, frequent accidents at the worksite, unpredictable work schedules, failure to meet production quotas, poor communication regarding performance expectations, a poor performance evaluation, fear of job loss, the layoff of coworkers, a reduction in pay or benefits, a dirty or cluttered work environment, improper or inadequate ventilation, inadequate climate control, and boredom from repetitive tasks. Individuals who work with hazardous materials may experience occupational stress from this fact alone. It is also possible for personal or family problems to cause degradation in job performance, which can lead to considerable occupational stress.

It is important for the physician to realize that occupational stress can contribute to the development or exacerbation of medical problems such as hypertension, hypercholesterolemia, diabetes mellitus, metabolic syndrome, coronary artery disease, asthma, chronic obstructive pulmonary disease, depression and anxiety. Dyspnea, hyperventilation, and chest pain are common respiratory complaints of individuals suffering from occupational stress. These symptoms may be related to an underlying respiratory disorder, such as asthma or chronic obstructive pulmonary disease, which is exacerbated by occupational stress. Respiratory symptoms may also be *perceived* as being related to a respiratory illness by a patient suffering from environmental stress, even though no underlying respiratory illness actually exists. This is especially true of individuals who have depression, a generalized anxiety disorder or recurrent panic attacks. In some cases the reported respiratory symptoms may be fictitious, with the patient willfully and knowingly complaining of false symptoms in an attempt to establish a medical reason for being removed from the workplace by the employer, often with the intent of obtaining "secondary gain" through workman's compensation or disability benefits.

In evaluating a patient for symptoms that could be related to a toxic occupational or environmental exposure, it is essential for the physician to consider the possibility that occupational stress may be a contributing factor. Distinguishing between symptoms that are related to an actual occupational or environmental illness, symptoms that are perceived to be related to an occupational or environmental illness that does not exist, or symptoms that are willfully fictitious can be extremely challenging, even for the most astute and experienced physician. The occupational and

environmental history is critical in this regard. A simple and efficient way of assessing the possibility of occupational stress is to ask the simple question, “Are you satisfied with your job?” This is a straightforward and nonthreatening way of leading the patient into a discussion about factors in the workplace that could be a source of environmental stress. If asked with an appropriate sense of empathy and concern, it can oftentimes coax the patient into informing the physician of stressful workplace or home situations that may be related to the presenting symptoms. In most cases it is both necessary and important to obtain objective evidence to establish or exclude the diagnosis of an underlying medical problem, but a strong suspicion of occupational stress or malingering can help the physician plan to most appropriate medical evaluation of the patient. In some cases, this may involve the eventual referral to a mental health professional or a social worker.

Appendix: Occupational and Environmental Exposure History

Patient Name: _____ Medical Record Number: _____
Date of Form Completion: _____ Date of Birth: _____

A. Current Occupational History

Are you currently employed?
Yes _____ No _____
If yes, what was your approximate date of hire? _____
Please fill out the following regarding your current job:

Name of Employer	Job Title	Job Description

Describe your typical work shifts in a week (e.g. Monday 8AM-5PM, Tuesday 12noon-8PM etc.):
Monday _____
Tuesday _____
Wednesday _____
Thursday _____
Friday _____
Saturday _____
Sunday _____
Can you smell the chemicals or materials that you work with?
Yes _____ No _____
Have you ever worked in a dusty environment?
Yes _____ No _____
Have you ever worked in a moldy or musty environment?
Yes _____ No _____
Do you ever get material from work on your clothes or skin?
Yes _____ No _____
Do you wash your hands with solvents in the workplace?
Yes _____ No _____
Do your work clothes get laundered at home?
Yes _____ No _____
Do you shower regularly at work?
Yes _____ No _____
Do you use protective equipment such as gloves, masks, respirators or hearing protectors at work?
Yes _____ No _____
Have you ever been advised to use protective equipment?
Yes _____ No _____
Have you been instructed in the use of protective equipment?
Yes _____ No _____
Is there smoke at the workplace?

Yes _____ No _____
Do you smoke in the workplace?
Yes _____ No _____
Do you eat at the work place?
Yes _____ No _____
Have you ever been off work for more than 1 day because of an illness related to work?
Yes _____ No _____
Have you ever changed jobs or work assignments because of health problems or injuries?
Yes _____ No _____
Has your work routine changed recently?
Yes _____ No _____
Is the ventilation system at your workplace adequate and working properly?
Yes _____ No _____

B. Hazardous Exposures at Work or Home (circle all that apply)

Animals	Extreme Heat/Cold	Nickel
Arsenic	Fertilizers	Paints/Varnishes
Asbestos	Fumes	Pesticides
Benzene	Glues/Adhesives	Petroleum Products/Gasoline
Beryllium	Grain Dust	Phosphates
Biological Hazards	Isocyanates	Power Tools
Cadmium	Latex	Sand/Stone Dust
Chromates	Lead	Silica
Cigarette Smoke	Lifting	Smoke
Coal Dust	Loud Noise	Solvents
Cobalt	Mercury	Vanadium
Cutting Oils	Metal-Grinding Dust	Vibration
Dust	Metal-Working Fluid	Wood Dust/Saw Dust

Other:_____

Are any co-workers exposed to any of the hazardous exposures listed above?
Yes _____ No _____
Are there any co-workers with symptoms similar to those that you are experiencing?
Yes _____ No _____
Is anyone in your home exposed to any of the hazardous exposures listed above?
Yes _____ No _____
Are there any family members with symptoms similar to those that you are experiencing?
Yes _____ No _____

C. Previous Occupational History

Please fill out the following table regarding past jobs, including temporary, seasonal, part-time and military employment

Employer	Date Started/Ended	Job Title/Description	Known Hazards

D. Environmental History

Community Environment:

Do you live close to any of the following? Check all that apply.

Heavy Traffic	Industrial Plant	Power Plant
Waste Dump	Superfund Site	Construction Site

Home Environment:

In approximately what year was your house built? _____

Circle all that apply to your home.

Septic system	Central heating	Fireplace/Wood Stove
Air humidifier	Central air conditioner	Gas stove
Well water	Window air conditioner	Water leaks
City water	Gas space heater	Other:_____

Do you have a basement?
Yes _____ No _____
If yes, please answer the following questions:
Does your basement have a musty or moldy odor?
Yes _____ No _____
Does your basement have a water problem?
Yes _____ No _____
Has your basement ever flooded?
Yes _____ No _____
Is your kitchen stove exhausted to the outside from a range hood?
Yes _____ No _____
Is air from your bathroom(s) exhausted to the outside?
Yes _____ No _____
Is there mold growth on any of your bathroom walls?
Yes _____ No _____
Is there mold growth on any of your shower curtains?
Yes _____ No _____

Hobbies:
Circle all that apply.

Auto Body Repair/Restoration	Hunting	Photography
Auto Mechanics	Leather Working	Sculpture
Ceramics/Pottery	Masonry	Stone Work
Electronics	Metal Working	Taxidermy
Fishing	Model Making	Woodworking
Gardening	Painting	Other:

Do you use any solvents in any of your hobbies?
Yes _____ No _____
Do you do any soldering in any of your hobbies?
Yes _____ No _____
Do you have any pets?
Yes _____ No _____ If yes, what kind of pets? _____
Have you ever kept birds as pets?
Yes _____ No _____If yes, what kind of bird(s)? _____

Personal Exposures:
Do you currently smoke?
Yes _____ No _____
If yes, _____ packs/day for _____ years
Is there someone else in your household that smokes?
Yes _____ No _____
If yes, _____ packs/day for _____ years
Approximately how many drinks of alcohol do you have per week? _____
Do you take any prescription drugs?
Yes _____ No _____
If yes, please list each drug that you take, the dose of each drug and how often you take each drug.

_____
_____
_____
_____
_____

Do you take any herbal or vitamin supplements?
Yes _____ No _____
If yes, what do you take and how often do you take it?

_____
_____
_____
_____
_____

Do you use recreational drugs?
Yes _____ No _____

If yes, what do you use and how often do you use it?

_____
_____
_____
_____
_____

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Chapter 3
Use of Laboratory Tests in Occupational and Environmental Lung Diseases

Jean-Luc Malo

Abstract This article reviews and comments various laboratory tests that are commonly used in the investigation and assessment of environmental and occupational lung diseases affecting both the lung parenchyma per se as well as the airways and caused by exposure to various organic and inorganic materials. These conditions include asbestosis and silicosis, asthma, and hypersensitivity pneumonitis. The tests that are reviewed are (1) general lung function tests: lung volumes, CO diffusion, exercise testing; (2) specialized lung function tests: assessment of nonspecific bronchial responsiveness with methacholine and other agents, serial assessments of airway caliber with peak expiratory flows; specific inhalation tests; (3) assessment of airway inflammation by induced sputum and exhaled NO. The clinical indications and methodology of these tests are presented and discussed.

Keywords Occupational asthma • Asbestosis • Silicosis • Hypersensitivity pneumonitis

Introduction

Exposure through inhalation to environmental and occupational agents in either organic or inorganic forms can cause pathological alterations of the airways and lung parenchyma. Laboratory testing that will be covered in this chapter is therefore designed to assess the functional, inflammatory, and structural status of the airways and lung parenchyma. These may be present in a broad spectrum of diseases.

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Parenchymal Lung Diseases

Fibrosis of the lung can be caused not only by inhalation of inorganic materials, such as asbestos and silica dusts, but also by inhalation of organic materials (molds and various proteins) present in general and occupational environments, all agents that can induce hypersensitivity pneumonitis. The latter condition is a type III immunological disease in which increased levels of specific IgG causing precipitins are demonstrated [1]. There has been great concern about berylliosis in recent years, although the frequency of this condition remains very low, with sensitization to beryllium very rarely turning into berylliosis. This has also been found in farmers' lung, in which the increase in specific IgGs is not predictive of possible later development of farmers' lung.

Airway Diseases

Exposure to various ubiquitous inhaled substances (house dust and mites; animal-derived allergens; molds and pollens) as well as to a wide spectrum of high-(protein-derived) and low-molecular-weight (chemical) occupational agents, of which there are currently more than 300 (see www.asthme.csst.qc.ca), can cause asthma and occupational asthma (OA) [2]. OA is defined as a type of asthma that is specifically caused by an agent present in the workplace [3]. Two types of OA can be differentiated by whether they occur after a latency period necessary for the acquisition of sensitization (generally of the IgE type) or acutely, after inhalation of substances with irritating properties. The latter condition is called reactive airways dysfunction syndrome (acronym: RADS) or irritant-induced asthma. Besides OA, exposure at work can lead to the aggravation of asthma (work-aggravated asthma), a condition that often carries as serious socioeconomic consequences as OA [2, 4].

It has lately been discovered that not only tobacco smoke but also exposure to various environmental and occupational irritants can lead to chronic obstructive lung diseases (COPD). Based on data since 2000, Blanc and Toren estimated the median population-attributable risk value of exposure at work for both chronic bronchitis and COPD at 15% [5].

Table 3.1 presents a summary of information on the relevance of laboratory testing for various airway and lung diseases due to environmental and occupational agents, as detailed and discussed below.

General Lung Function Tests

These usually include the assessment of lung volumes through body plethysmography, spirometry that includes forced expiratory volume in one second (FEV1) and the Tiffeneau index (ratio of FEV1/forced vital capacity), carbon monoxide diffusion, and arterial gases.

Table 3.1 Laboratory testing for various airway and lung diseases due to environmental and occupational agents

Diseases	Relevant laboratory tests
Affecting lung parenchyma	
Asbestosis	General lung function tests + assessment of mechanical properties
	Exercise testing
Silicosis	General lung function tests (spirometry after bronchodilator) + assessment of mechanical properties
	Exercise testing
Hypersensitivity pneumonitis	General lung function tests and exercise testing
Affecting the airways	
Asthma	General lung function tests + assessment of bronchial responsiveness to methacholine
	Monitoring of PEF
	Analysis of induced sputum and/or exhaled NO
	Specific inhalation challenges
COPD	General lung function tests
	Assessment of mechanical properties
	Exercise testing

Lung Volumes

Reduction Pattern

It is essential to assess lung volumes in occupational lung diseases due to inhalation of inorganic materials, such as asbestos and silica dusts, that cause lung fibrosis, and in the chronic form of hypersensitivity pneumonitis due to a type III sensitizing process to occupational allergens, such as moldy hay and various chemicals (viz. diisocyanates). Some environmental allergens (birds such as pigeons and budgerigars, molds in humidifiers) can also cause hypersensitivity pneumonitis. Reduction in lung volumes (vital capacity, total lung capacity) to 80% predicted or lower values is not a sensitive test, as such alterations will usually only occur in moderate to severe diseases.

Hyperinflation Pattern

In conditions with airway obstruction (asthma, nonspecific chronic obstructive airway disease, COPD, silicosis) (see below), there is often an associated hyperinflation that can be documented by an increase in residual volume, functional residual capacity, and total lung capacity. However, the presence of hyperinflation is not a *sine qua non* of obstructive lung diseases, particularly if the condition is also associated with a restrictive pattern.

Spirometry and Response to Bronchodilator

The FEV1 and the Tiffeneau index (FEV1/FVC), proposed by this researcher and several physiologists half a century ago, are still the keystones for assessing airway caliber. FEV1 is highly reproducible and reflects both central and peripheral airway caliber. Although various indices derived from the end part of FVC were proposed in the 1970s, such as mid-expiratory flow rates (MMF) and flows at the lower end of forced expiration (FEF50% and FEF25%), they are rarely used now, due to poor reproducibility and too large standard deviations for reference values, which makes interpretation awkward. When there is evidence of airway obstruction, the response of flows after administering an inhaled short-acting beta-2 adrenergic agent is very useful, especially in confirming asthma. According to the American Thoracic Society standardization document, a significant bronchodilator response is shown by at least a 12% improvement and 0.2 L increase in either FEV1 or FVC [6]. Conditions directly affecting the airways (asthma and COPD) can cause airway obstruction, but there is often also a pattern of airway obstruction in silicosis (in which condition the response to bronchodilator is surprisingly often significant) and peripheral airway involvement in hypersensitivity pneumonitis (which is referred to by some as bronchiolo-alveolitis).

Diffusion Capacity

The carbon monoxide diffusion capacity reflects an alteration of the lung parenchyma (either emphysema or fibrosis). In asbestosis, it is much more sensitive than changes in lung volumes (documentation of a restrictive pattern, see above). It is also a reasonable reflection of emphysema, although corroboration with CT scans is valuable and relevant.

Arterial Blood Gases

The status of arterial oxygen pressure (paO_2) and carbon dioxide ($paCO_2$) is useful in severe restrictive and obstructive lung diseases. These can be assessed both at rest and on exercise, either on a cycle ergometer or by monitoring oxygen saturation during the frequently used 6-min walk test. These tests are particularly useful in end-stage diseases, to document the need for oxygen treatment.

Specialized Lung Function Tests

Mechanical Properties of the Lung

Lung fibrosis is characterized by increased rigidity of the lung parenchyma, which can be assessed by measuring lung compliance and maximum elastic pressure derived from pressure–volume curves. These tests, together with CT scans, are sensitive indices of early lung fibrosis.

Airway Hyperresponsiveness

In the majority of asthmatic patients, airway caliber assessed by FEV1 and FEV1/FVC is normal. This is often due to the fact that asthma is a fluctuating condition and patients are not seen at a time when they are symptomatic. Fluctuations in airway caliber can be demonstrated by asking subjects to serially record their airway caliber through self-assessment of peak expiratory flows (PEF) with portable instruments (see below). Since these fluctuations in airway caliber reflect airway hyperresponsiveness (AHR) [7], the assessment of nonspecific bronchial provocation testing is reliable.

History and Justification

Although injections of cholinergic agents have been known since the beginning of the twentieth century to cause asthma, it was only in the 1940s and 1950s that tests by inhalation of pharmacologic agents (histamine, acetylcholine and its derivatives) were developed in Europe [8, 9] and the United States [10]. However, it was not until the 1970s that standardizations were proposed using two different methodologies, the deep inspiration method [11] and the tidal volume breathing method [12], which led to consensus and clinical guideline documents [6].

The currently accepted definitions of asthma (see www.ginasthma.org) [13] include clinical features (recurrent episodes of respiratory symptoms, including wheezing), inflammatory characteristics (including eosinophilic inflammation), and functional abnormalities: (1) fluctuation in airway caliber, both spontaneously and as a result of treatment (bronchodilators anti-inflammatory preparations) and (2) AHR. It is often difficult to make a correct diagnosis of asthma based only on clinical features [14], which justifies the use of functional tests (AHR) or assessment of airway inflammation (see below). Often, there is a discrepancy between the importance of symptoms reported by patients and their functional status, even assessed at a time when the patients are symptomatic, frequently because hyperventilation may

mimic asthma and is a common accompanying condition to asthma [15]. It is therefore relevant in these circumstances to get information on the status of airway responsiveness, which is an indirect reflection of airway inflammation.

Testing

Besides the pharmacologic agents (histamine acetylcholine derivatives, especially methacholine) that were initially proposed, many other physical and pharmacological agents may induce AHR. Among physical agents, exercise, especially if carried out by breathing unconditioned (cold, dry) air, has been used, as reviewed [16]. Extensive studies on the mechanism of exercise-induced asthma were indeed carried out in the late 1970s by teams in Boston [17] and Australia [18] and clinical guidelines for testing were proposed, as with methacholine [6]. However, even when it involves breathing cold dry air, exercise is a test that is less sensitive than testing with pharmacologic agents [19]. The same comment applies to challenge tests that use other chemical agents, such as mannitol and adenosine, which are more specific than sensitive for the diagnosis of asthma [20].

Methacholine is for sure and by far the most common agent used to test AHR. When carried out by using proposed well-standardized methodologies, it is a very safe test that does not cause side effects, even when using concentrations of methacholine up to 128 mg/mL. It can be used not only in a hospital laboratory but also in epidemiological field studies, and the occurrence of major bronchoconstrictive events (although these are easily reversible by administering a short-acting beta-2 adrenergic agent) is rare [21]. Response to methacholine inhalation is assessed by the provocative concentration that causes a 20% change in FEV1, called the PC20. The threshold of a "positive" response that indicates significant AHR has been set at PC20 at 4.0 or 16 mg/ml [6], a value of 12 mg/mL being the value with the best specificity/sensitivity ratio [22]. The interpretation of methacholine testing is interesting not only in referring to the PC20 value but also in examining the nature of symptoms that occur during the test, because the test often also reproduces symptoms experienced by patients in daily life, especially in the case of a positive challenge [23]. This information is therefore also relevant to interpreting the test.

It is known that natural exposure to environmental allergens, such as what happens in pollen seasons, leads to enhancement of airway responsiveness to methacholine [24]. The same phenomenon occurs after exposure to occupational agents, either in the workplace [25] or in a hospital laboratory after the occurrence of asthmatic reactions to such agents [26, 27]. Moreover, changes in responsiveness to methacholine have been found to precede the occurrence of specific reactions to occupational agents and are therefore an early and sensitive indicator of specific reactivity to an allergen [28]. In the investigation of OA, the absence of significant AHR in subjects still exposed to the causal agent at work and at a time when the subject is symptomatic virtually rules out asthma and OA. This being said, AHR may on occasion recover rapidly to normal values after a positive specific inhalation challenge [29].

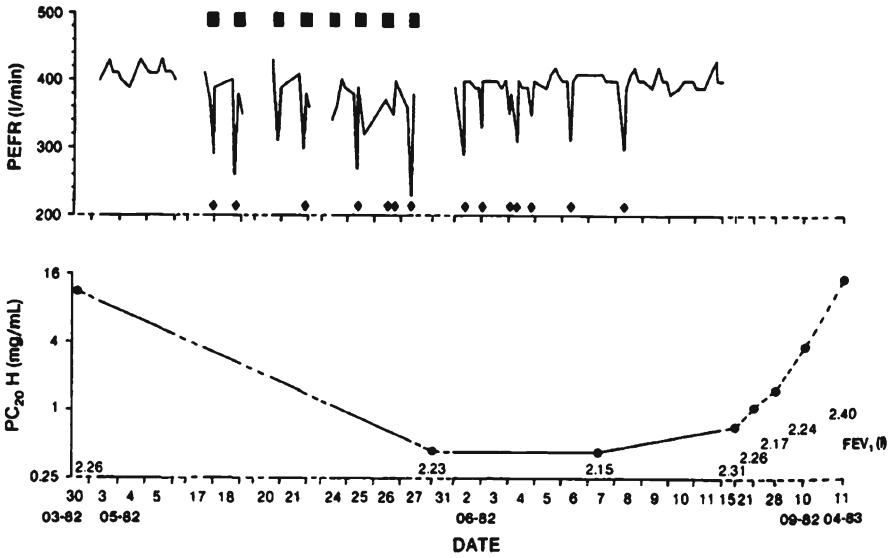

Fig. 3.1 Serial changes in peak expiratory flow rate (PEFR) (*upper*) and airway responsiveness to methacholine measured as PC20 (*bottom*) in a patient. The *solid squares* indicate periods at work. Note that the airway hyperresponsiveness took almost 1 year to recover

The level of AHR and the magnitude of IgE-mediated sensitization to allergens both play a role in conditioning the magnitude of specific reactivity to allergens, as initially proposed by Tiffeneau [30]. This has been confirmed in the case of ubiquitous allergens [31, 32] and occupational agents [33, 34]. Therefore, by examining results of skin prick tests (weal diameter) or specific IgE levels, both reflecting immunological reactivity, and the degree of AHR, the magnitude of the immediate specific reaction to an agent can be predicted, which makes specific testing safer because the dose of allergen that can be administered to cause a 20% fall in FEV1 can be predicted.

Although the relationship is far from being perfect, the level of AHR is significantly associated with the severity of asthma and the need for treatment [12]. It is also significantly related to various features of airway inflammation (especially eosinophils) [35] and structural changes (thickening of the subepithelial space) [36]. It is inversely related to response to the bronchodilator.

AHR is not only present in asthma. It can be documented in subjects with rhinitis [12], though the degree of hyperresponsiveness is generally low, and in chronic bronchitis, also generally at a low level and especially in the presence of airway obstruction [37].

In subjects with OA, who are removed from the workplace, medicolegal agencies may request that disability/impairment be ascertained. Combined with clinical information (nature and doses of inhaled steroids used to control asthma) and spirometric values, the level of AHR can be used for this purpose as suggested [38, 39]. Figure 3.1 shows the serial changes in AHR after a relatively short period of exposure to a sensitizing occupational agent. AHR took almost 1 year to recover.

Serial Assessments of Peak Flow Rates

Since asthma is a fluctuating condition, airway caliber may warrant being followed serially by patients, particularly at a time when they are symptomatic. Monitoring of PEF was proposed more than 40 years ago in the UK [40]. PEF is satisfactorily correlated with FEV1, the gold standard, in the assessment of airway caliber, although the former is less sensitive to changes in airway caliber than the latter. This assessment has been found to be particularly useful in identifying asthmatics who are at risk of dying due to brittle nocturnal asthma [41, 42]. Portable low-cost devices are available. Moreover, the expiratory maneuver is easy to perform, without supervision by a technician, which is not the case for FEV1. Usually, three forced expiratory maneuvers are required and the better of two values within 20 L/min is kept for analysis. Action plans based on this recording are proposed for patients who can increase their medication in case of an asthmatic flare-up. The main problem with this recording is the generally poor compliance, especially over long periods; it seems more fruitful to persuade diabetic patients to monitor their blood sugar than to have asthmatic subjects assess their PEF at least once daily [43].

Serial PEF monitoring has been advocated in the diagnostic investigation of subjects suspected of suffering from OA [44, 45]. Several patterns of changes in PEF have been identified in workers who are asked to monitor their PEF at least four times a day or even every 2 h while at work and away from work [46]. A computerized interpretation system is available online [47]. It is, however, difficult at times to distinguish patterns found in OA from what can occur in asthma aggravated at work through exposure to various irritating conditions. Also, falsification of self-recorded data may occur [48]. Therefore, for some this methodology does not sufficiently correspond with the results of specific inhalation challenges (see below), which are still regarded as the gold standard, to make it useful in the diagnosis of OA. Figure 3.2 shows the results of combined monitoring of PEF and AHR in the investigation of OA.

Specific Inhalation Challenges

It is reported that Charles Blackley was the first researcher who, in the late nineteenth century, carried out inhalation challenges on himself to reproduce symptoms of seasonal rhinitis [49]. Inhalation challenges with ubiquitous allergens were often performed in the early twentieth century to elicit causes of asthma [50]. Inhalation challenges with occupational agents were proposed in the 1970s by Jack Pepys [51], who not only elicited new causal agents for OA but also thoroughly described the temporal patterns of reactions and the blocking effect of sodium cromoglycate and inhaled steroids.

Bronchial challenges with ubiquitous allergens are currently primarily performed for research purposes, while specific challenges with occupational agents are used

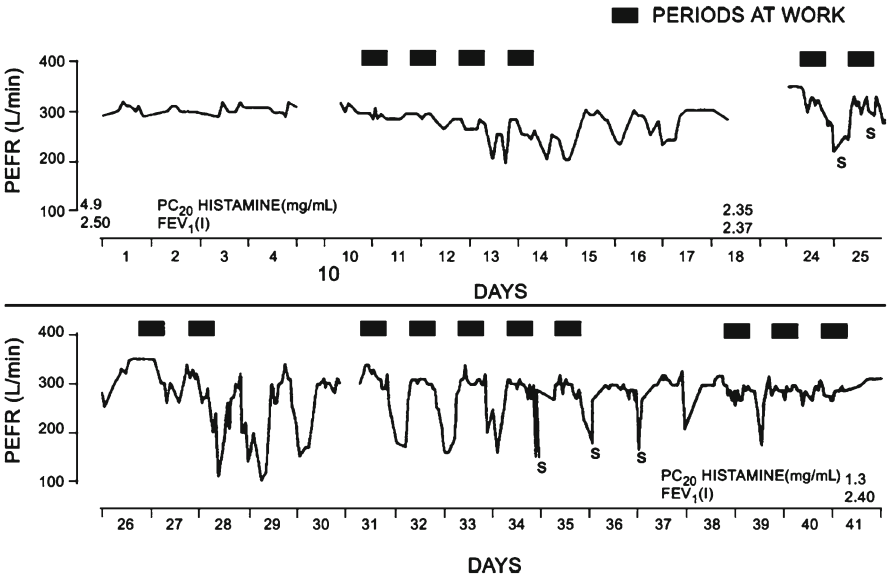

Fig. 3.2 Example of the use of peak expiratory flow rate (PEFR) (*upper*) and airway responsiveness (*lower*) in the investigation of occupational asthma. Solid squares indicate days at work and "s" indicates where inhaled bronchodilator is taken. PC20 histamine went down from a baseline value of 4.9 mg/mL while away from work to 2.35 mg/mL after 1 week at work and 1.3 mg/mL on the fourth week of work

for clinical purposes in the diagnosis of OA. They are considered the gold standard for confirming the diagnosis of OA [52]. The methodology of testing has been described in detail [53, 54]. Briefly, workers are first exposed to a control agent (in powder, aerosol, or vapor form, depending on the physical nature of the causal agent). Spirometry is assessed before exposure and then serially, immediately after stopping exposure, every 10 min for 1 h, every 30 min for 2 h, and hourly up to 7 or 8 h after stopping exposure. At the end of the day, airway responsiveness to methacholine is assessed and an induced sample is obtained. The next day, workers are exposed to possible causal agents in a progressive manner. In the case of high-molecular-weight agents (proteinaceous material) that cause immediate reactions (sometimes followed by late reactions), progressive exposure is carried out on a single day for a total of 2 h in fragmented periods. For low-molecular-weight agents (chemicals), progressive exposure is carried out over 3–4 days because isolated late reactions that exposure to these agents can cause cannot be predicted and administering too large a "dose" can lead to severe asthmatic reactions. At the end of the days of exposure, airway responsiveness to methacholine is assessed and an induced sample is obtained, as for the control day. A positive reaction is defined as a ≥20% fall in FEV1 in the case of immediate reactions and 15–20% fall in FEV1 for late reactions. Figure 3.3 shows examples of the most frequent temporal reactions: immediate, late, and combined immediate and late. Late reactions and also immediate

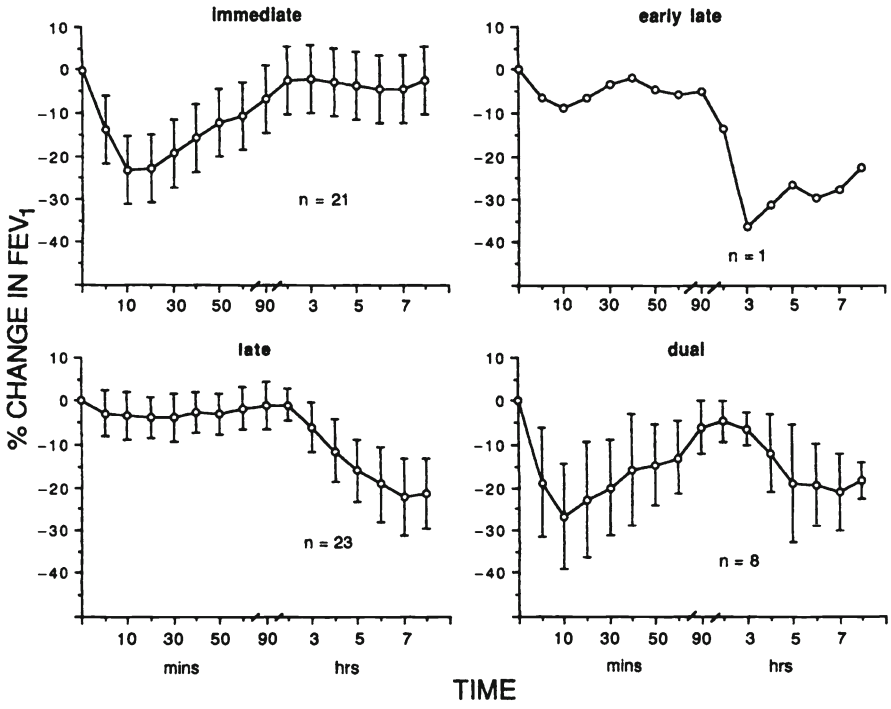

Fig. 3.3 Patterns of asthmatic reactions after exposure to an occupational agent. The values are mean ± SD of percentage falls in FEV1, except for early late reaction. N indicates number of subjects. The asthmatic reactions after exposure to an occupational agent can be isolated immediate, late, dual, or early late

reactions, although less frequently, are often accompanied by significant changes in AHR and enhanced inflammation in induced sputum. Exposure to the control and occupational agents can be carried out in a realistic way in small well-ventilated cubicles or by using apparatuses that allow the generation of low and stable concentrations of dusts, vapors, and aerosols [55].

Assessment of Airway and Lung Inflammation

Bronchoscopy, Bronchoalveolar Lavage, and Transbronchial Biopsies

In cases of lung infiltrates of unknown etiology, it may be indicated to perform a bronchoscopy with transbronchial biopsies and bronchoalveolar lavage. In subjects with acute hypersensitivity pneumonitis, bronchoalveolar lavage will show increased

lymphocytosis and a CD4/CD8 ratio of less than one. Lung biopsies document granulomas with giant cells and a lymphoplasmacytic interstitial infiltrate. In subjects exposed to beryllium, bronchoalveolar lavage (in the same way as peripheral blood) can be useful in documenting specific lymphocytic transformation. In subjects with coughs of unknown etiology, if induced sputum cannot be obtained, bronchoscopy with bronchial biopsies and bronchoalveolar lavage can reveal eosinophilic bronchitis, a condition identified 20 years ago [56], which can be of occupational origin [57] and rarely turns into asthma [58]. Besides examining the cellular component of bronchoalveolar lavage, it is possible to assess various markers of inflammation (interleukins, prostaglandins, matrix metalloproteases) [59].

Induced Sputum

Current definitions of asthma include features of inflammation [13]. Since so-called late asthmatic reactions were first described [60, 61], much interest has focused on the mechanism of such reactions that leads to the discovery of the so-called slow reactive substance of anaphylaxis (SRS-A) [62] and the description of the leukotriene cascade [63]. It was later proposed that chronic inflammation, which is closely related to the late phase of the asthmatic reaction, leads to structural changes and airway remodeling [36, 64].

Although sputum of asthmatic subjects had been examined before [65], it was only with the development of methodologies that made it possible to obtain satisfactory sputum samples [66, 67] in the majority of subjects tested that clinical applications were proposed. First, in the assessment of subjects who present with respiratory symptoms, whether typical of asthma or not, it is often useful to have a methacholine test followed by assessment of induced sputum. In the presence of AHR and 2 or 3% eosinophils in induced sputum, the diagnosis is highly probable. Second, it has been proposed that the control of asthma that parallels the control of inflammation can be tackled by serial assessments of induced sputum by modifying anti-inflammatory treatment [68, 69]. It is therefore possible to follow the status of inflammation after exposure to environmental and occupational allergens. This has been carried out fruitfully in the field of investigation of OA. Information on induced sputum can be added to PEF monitoring, which improves the sensitivity and specificity of diagnosis [70]. Induced sputum can be examined in the same way as airway responsiveness to methacholine before and after specific inhalation challenges (see below) [34]. The interpretation of significant changes in the percentage of eosinophils is questionable, however. If on the baseline day the percentage of eosinophils is normal (<1%) and increases to abnormal levels (2–3% or more), interpretation is straightforward. However, if there is significant eosinophilic inflammation on the baseline day, it is difficult to determine when the threshold of a significant increase in the level of inflammation is reached. The same comment applies in the case of serial monitoring of the inflammatory status of asthma. Whereas significant changes are represented by a 2–3.2-fold reduction in PC20 [71],

the threshold is not known in the case of sputum eosinophils. In the same way, for sputum neutrophils, which also play a significant role in asthma, especially severe asthma [72] and in OA caused by diisocyanates [73], it remains unknown what represents an abnormal level and enhanced changes.

Besides examining the cellular portion of induced sputum, it is also possible, as for bronchoalveolar lavage, to assess markers of inflammation that can be detected in the liquid [74–76]. However, a research tool designed to quantify these is still under development.

Exhaled Breath Condensate

It is possible to analyze exhaled breath condensate with the purpose of monitoring inflammation and oxidative stress in the airways, and other pathophysiological (including carcinogenic) processes in the lung. Exhaled breath condensate is a sample of airway lining fluid that is collected by cooling exhaled air during spontaneous breathing. This liquid contains various compounds, mediators of inflammation and markers of oxidative stress (nitrites). For the time being, because proper standardization has not been carried out and normal values are not well known, this procedure remains a research tool [77].

Exhaled NO

In recent years, measurement of fractional nitric oxide (NO) concentration in exhaled breath has been proposed as a useful noninvasive test in the diagnosis and monitoring of asthma, with recently published recommendations for clinical use [78, 79]. Although the mechanisms of action remain imprecise, NO is implicated in the pathophysiology of asthma, particularly eosinophilic inflammation. Exhaled air assessment of NO has developed rapidly due to the use of chemiluminescence analyzers. Asthmatic subjects have high levels of NO that can be brought down by the use of inhaled corticosteroids, especially if eosinophilic inflammation is present. Although significant relationships between exhaled NO and the presence of eosinophils in bronchial biopsies, bronchoalveolar lavage, and induced sputum have been quite consistently reported as reviewed [79], the correlation coefficients are not generally high. A low value of expired NO is of greater value in determining the absence of eosinophilic inflammation than the reverse [79]. Smoking and atopy affect the levels of expired NO. Exposure to environmental [80] and occupational [81] allergens increases the level of exhaled NO. However, increases in induced sputum seem better correlated to the likelihood of a positive specific inhalation challenge with an occupational agent than increases in exhaled NO [81]. Exhaled NO can be used in the monitoring of anti-inflammatory treatment for asthma [82], but is not generally recommended, as this additional method has no beneficial effect on asthma outcomes [79].

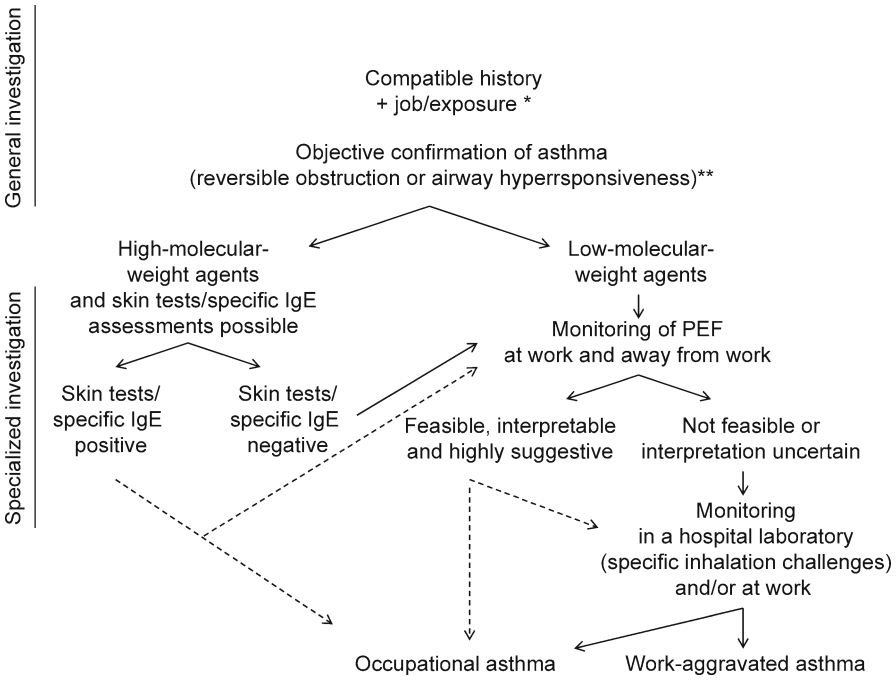

Fig. 3.4 Proposed decision tree for the investigation of occupational asthma (OA), using the type of investigation (nonspecialized followed by specialized) and the nature of the occupational agent (high- vs. low-molecular-weight agent). Nonspecialized investigations can be carried out by general practitioners or internists, while specialized investigations refer to tests that should be performed at medical centers. *Single asterisk*: either the job or the exposure can result in increased risk. *Double asterisk*: airway responsiveness can be assessed ideally at a time when the worker is at work and has been symptomatic recently; even if a worker is no longer at work, airway responsiveness can persist in 75% of workers with OA. The dashed lines indicate that there are two possibilities. For example, even if interpretation of PEF is suggestive of OA, some would prefer to carry on monitoring of airway function and inflammation

Other Tests

In some circumstances, it may be useful to assess exposure to environmental and occupational agents. This can be done by collecting urine with assessment of metabolites, as is the case for diisocyanates [83].

Figure 3.4 shows a suggested decision tree for the investigation of OA, with distinctions between types of investigation centers (nonspecialized and specialized) and the nature of agents (high- vs. low-molecular-weight agents).

Conclusion

Assessment of environmental and occupational diseases that affect the lung parenchyma should include both various radiological tests (including the standard chest radiograph as well as CT scan) and a combination of lung function tests, the former examining the extent of the disease, the latter exploring its functional consequences and the disability it may cause. Airways are examined by a combination of lung function tests with assessment of inflammatory involvement.

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Chapter 4
Radiography and CT of Occupational and Environmental Lung Diseases

Philip C. Goodman

Abstract This chapter addresses the imaging of the more common pneumoconioses and hypersensitivity pneumonitis and offers a brief description of the International Labour Office (ILO) International Classification of Radiographs of Pneumonoconioses. The imaging abnormalities of this group of diseases vary depending on the nature of the lung insult, but generally include homogeneous, hazy, ground-glass opacities as well as heterogeneous opacities including small irregular linear and nodular opacities. End-stage fibrosis may be manifested by volume loss, traction bronchiectasis, and honeycomb lung. Asbestosis usually involves the lower lobes and produces small irregular opacities that are frequently seen in conjunction with pleura plaques. Silicosis usually involves the upper lobes and is characterized by small nodules which may eventually grow and coalesce into large opacities or progressive massive fibrosis with distorted lung and emphysema. Talcosis may resemble either asbestosis or silicosis. Berylliosis tends to mimic the appearance of sarcoidosis which in turn, at times, resembles silicosis. Coal worker's pneumoconiosis similarly mimics silicosis. Hard metal exposure produces images with ground-glass and irregular linear opacities as well as centrilobular nodules and emphysema. Hypersensitivity pneumonitis appears as scattered ground-glass and centrilobular opacities, air trapping, and, in late stages, pulmonary fibrosis with predominant upper lobe involvement. A description of the ILO classification of pneumoconioses and a brief description of the B-reading process including history, object, uses, and future direction are also included in this chapter.

Keywords Imaging • Chest radiography • Chest CT • Asbestosis • Silicosis • Coal worker's pneumoconiosis • Berylliosis • Talcosis • Hard metal lung disease • Hypersensitivity pneumonitis • International Labour Office • B-reading

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This chapter is devoted to the chest film and computed tomography (CT) imaging characteristics of occupational and environmental diseases. Various diseases are discussed in greater or lesser detail determined by their incidence and significance. Also, while much of the chapter is directed at diseases caused by the inhalation of inorganic dust, i.e., pneumoconioses, a portion of the chapter is set aside for the description of abnormalities seen in patients who develop hypersensitivity pneumonitis (aka extrinsic allergic alveolitis) to inhaled organic allergens, pathogens, and/or gases. Finally the last portion of the chapter traces the development of scoring techniques regarding the quantity and quality of abnormalities seen on chest films and CT scanning, most notably the International Labour Office (ILO) Classification of Radiographs of the Pneumoconioses or B-reading classification (see section on this topic near the end of the chapter.).

Inorganic Inhalational Diseases, Pneumoconioses

Asbestos-Related Pleura and Lung Disease

Thoracic imaging of asbestos-related abnormalities of the pleura and lungs has been a topic of concern of numerous articles at least since the coining of the term asbestosis in 1927 [1]. While initial imaging investigations of this disease centered about the chest radiograph, it has since been recognized that CT scanning is a more sensitive and at times more specific tool for elucidating the presence of disease caused by exposure to a variety of fibrous silicates.

Pleura Effusion

One of the earliest radiographic abnormalities seen following asbestos exposure is pleura effusion. This was observed in 3.1% of asbestos-exposed individuals and was noted as early as 3 years after initial exposure in some patients, and in two-thirds of patients within a 20 year latency period [2]. The fluid collection is usually small, only 88.6% had effusions less than 500 mL; unilateral, 91.4% of the cohort; and sometimes evanescent, 28.6% of people demonstrated spontaneous resolution and reoccurrence. In 91.4% of patients a residual blunted costophrenic angle was observed, and in 54% of the group diffuse pleura thickening was noted on follow-up chest film. Associated findings included pleura plaques in 20%, extremely rare calcification, and asbestosis in less than 10% of individuals. Other investigators have observed similar findings [3]. Since the amounts of fluid are small, they may be difficult to appreciate on PA upright films, and in some instances lateral decubitus views of the chest may be helpful. CT scanning of the chest can also detect the presence of small amounts of pleura effusion but would be an unusual imaging technique to use as a screening exam for this purpose. The left pleura space may be more likely involved than the right [4].

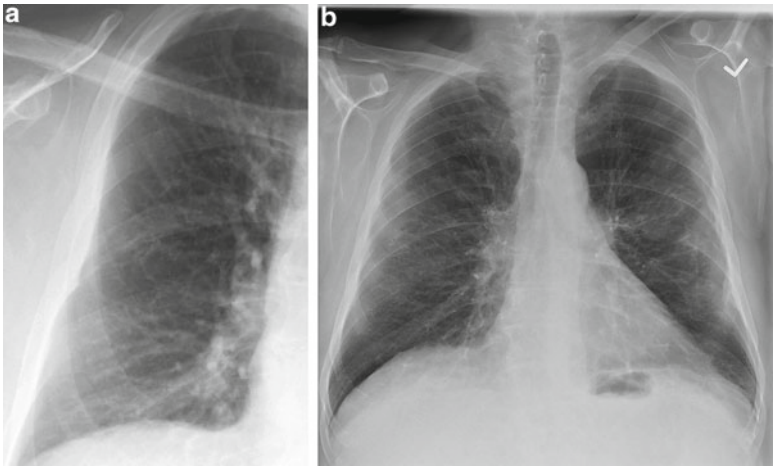

Fig. 4.1 Asbestos-related pleural plaques: (**a**) close-up of PA chest film demonstrates a noncalcified pleural plaque in profile on the *right* in the mid-pleural space. These lateral pleural plaques are typically seen adjacent to the 5th–8th ribs. (**b**) PA chest film demonstrates increased hazy opacities in the lateral aspects of both hemithoraces in typical distribution and appearance of noncalcified pleural plaques en face. In both cases as is usual, the apices and costophrenic angle regions are not involved

Pleura Plaques

Pleura plaques are identified radiographically as circumscribed or focal areas of calcified or noncalcified pleura thickening. On chest film they may be observed in profile or en face (Fig. 4.1). By CT they are seen in profile except when calcified over the diaphragm. These plaques are typically seen in the mid portion of the thorax between the fifth and eighth ribs laterally. The chest apices and costophrenic angles are generally spared [5–7]. Other sites of pleura plaque formation that are common include the medial pleura space adjacent to the vertebral bodies and over the mid portion of the diaphragm, but plaques here are more difficult to detect if not calcified (Fig. 4.2). Over the diaphragm, noncalcified plaques may be confused with eventration, elevation, or undulation of this structure. As opposed to these conditions of the diaphragm, plaques tend to be less rounded and more plateau like and this may help with differentiation (Fig. 4.3). Pleura plaques associated with asbestos exposure are seen bilaterally in 87% of patients. Bilateral pleura thickening itself predicts a background of asbestos exposure in 67% of patients, and if other etiologies for pleura disease can be excluded, asbestos exposure is predicted in 81% of patients [8]. When seen in profile, plaques appear as raised, sharply marginated, relatively long, focal regions of increased opacity against the lateral ribs on frontal view and posterior ribs on lateral view. When seen en face, pleura plaques on PA and lateral chest films may be difficult to distinguish from overlying chest wall soft tissue opacity. On frontal projection one should look for focal areas of increased

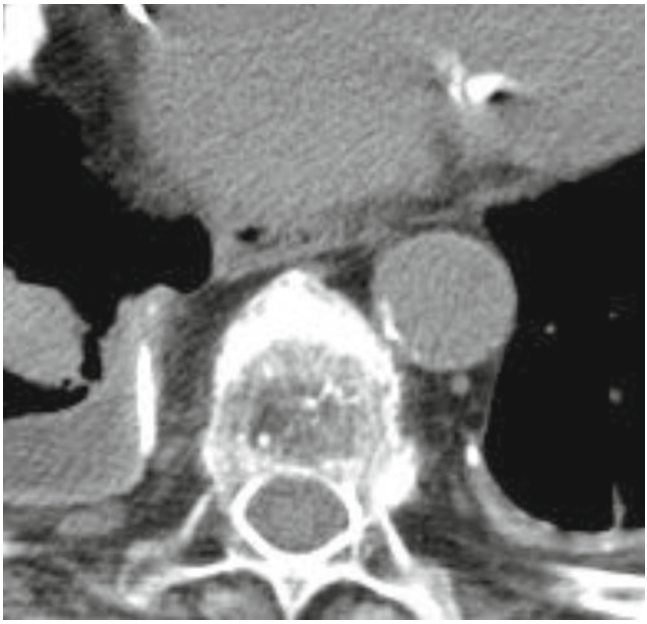

Fig. 4.2 Asbestos-related pleural plaques. Close-up of CT scan demonstrates *right* greater than *left* calcified pleural plaques along vertebral body. In this location the presence of plaques is difficult to detect on chest films

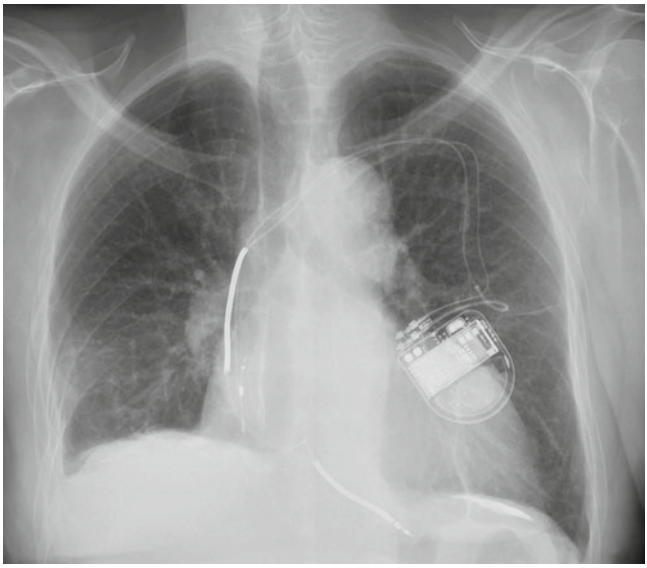

Fig. 4.3 Asbestos-related pleural plaques. PA chest film demonstrates arcuate appearance of calcified left diaphragmatic pleural plaque. Also note blunting of right costophrenic angle and slight pleural thickening in the lower lateral right pleural space representing diffuse pleural plaque, as well as hazy opacity over the right lower lateral hemithorax representing diffuse pleural plaque en face. The left-sided abnormality is virtually pathognomonic of asbestos-related pleural disease whereas the right-sided abnormality is less specific

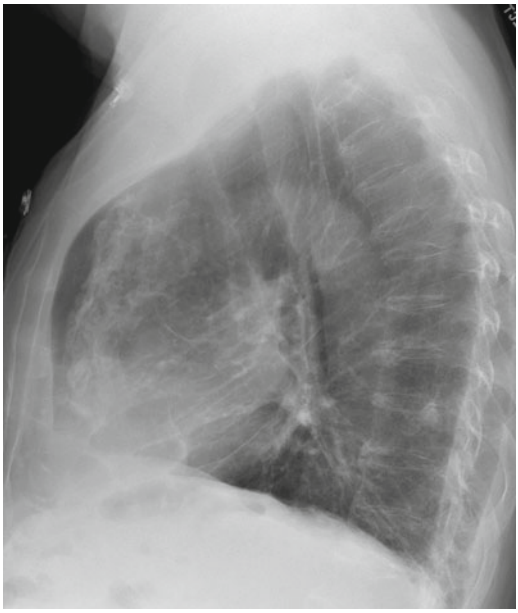

Fig. 4.4 Asbestos-related pleural plaques. Same patient as in Fig. 4.5. Lateral chest film demonstrates that most of the plaques are located anteriorly in this case

hazy opacity in the periphery of the lateral mid-hemithoraces. Plaques, en face, usually have indistinct margins, but occasionally a partial well-defined interface is noted. On lateral projection, en face plaques may be identified posterior in the thorax and anterior-superior to the heart (Fig. 4.4). Unlike lung nodules, the area of increased opacity may appear denser in its periphery [7]. When calcium is present in pleura plaques in profile, it will be recognized as a coarse or thick linear band of high attenuation over the hemidiaphragm or laterally in the expected position of pleura plaques [9]. In most patients calcification takes some years to develop, but in some cases calcified diaphragmatic pleura plaques have been seen after a relatively short exposure, under 1 year [10]. If seen en face, calcified pleura plaques may have sharply marginated angular and irregular edges leading some to compare their appearance to that of a holly leaf or melted candle wax (Fig. 4.5). Calcified pleura plaques are occasionally recognized along the pericardium, but it is difficult and unusual to identify pleura plaques along the vertebral bodies on plain films, even if calcified. As with pleura effusions, there has been a report suggesting an increased occurrence of left-sided pleura plaques when unilateral plaques were present [11]. However this was not borne out in a more recent CT investigation where no significant right- or left-sided incidence was observed [12].

With CT scanning even small areas of calcified or noncalcified pleura plaques are easier to discern throughout the thorax and particularly in areas not appreciated well on chest films, for example, paravertebral region. Localization of en face pleura plaques suspected on chest film, either anterior or posterior, is much easier on CT scanning.

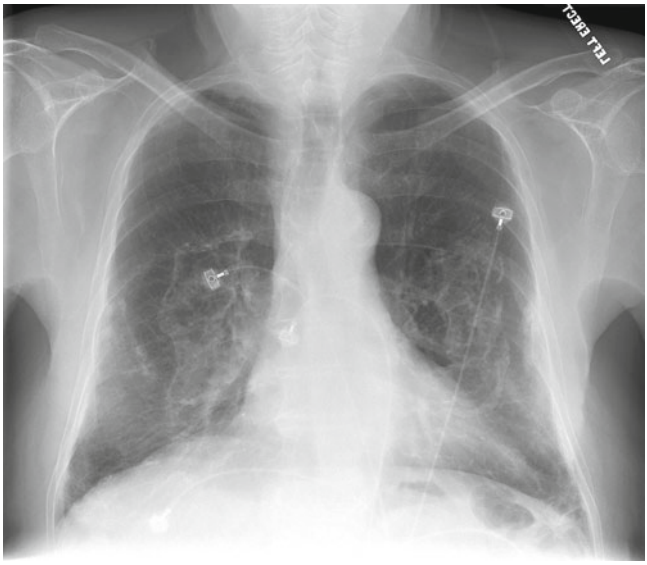

Fig. 4.5 Asbestos-related pleural plaques. PA chest film demonstrates some calcified and noncalcified plaques in profile, but also the "melted candlewax" appearance of calcified pleural plaques seen en face with more opacity at the periphery of the en face plaques

In general, localized pleura plaques involve the parietal pleura, but occasionally they occur in the visceral pleura and may be noted as pleura thickening in the interlobar fissures [13–15]. When this occurs, minor fissure plaques are best seen on frontal view, whereas major fissure plaques are more easily detected on lateral projection, as in both conditions they would be seen in tangent. Isolated fissural plaques could be confused with a lung nodule on CT scan [16].

One of the problems in identifying pleura plaques is that they may be confused with normal anatomic structures and/or extrapleura fat. Both the serratus anterior and exterior oblique muscle insertions frequently cause symmetric opacities along the lateral chest wall and may be mistaken for pleura plaques (Fig. 4.6). These confounding shadows may be seen in as many as 75% of normal PA chest radiographs. Distinguishing between pleura plaques and these normal anatomic opacities may be difficult. The serratus muscle insertions are triangular, generally fairly symmetric, and tend to run vertically or gently concave medially through the lower anterior ribs at a different angle than plaques. These muscles are very similar in appearance from one level to the other, whereas plaques vary in shape, may appear more convex or undulate medially, and are generally longer than the muscles [5, 17]. CT scanning may be beneficial in distinguishing between muscle insertions and pleura plaques, as the muscle insertions frequently are seen between ribs whereas pleura plaques are generally adjacent to ribs [18]. Another common mimic of pleura plaques is extrapleura fat. Extrapleura fat tends to occur more frequently, but not always, in obese individuals. The margin of extrapleura fat occasionally is noted to be undulat-

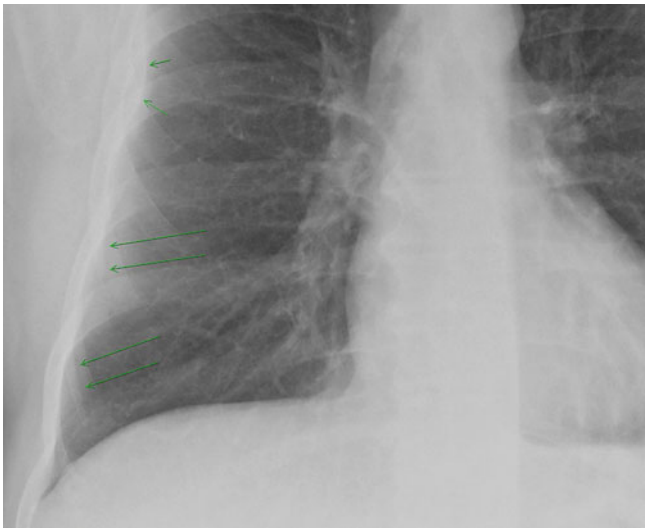

Fig. 4.6 Serratus anterior muscle insertion. Close-up of PA chest film demonstrates the typical appearance of the serratus anterior muscle insertion on rib. The larger arrows point to the gently concave medial shape of the muscle as it is projected through an anterior rib. The shorter arrows point to the typical convex medial shape of a lateral pleural plaque

ing and seen against the ribs on oblique views [19]. Bilateral rib companion shadows made up of extrapleura fat and connective tissue are seen frequently adjacent to the posterior aspect of the second rib on PA chest films, and may also be seen extending down the lateral chest wall to the level of the sixth rib. These opacities generally have a concave or vertical appearance medially, and because of their position, shape, and symmetry, they may be suspected to be normal as opposed to representing pleura plaques. CT scanning can help differentiate between extrapleura fat and pleura plaques by density (measured as Hounsfield units); pleura plaques measure positive whereas extrapleura fat measures negative [20] (Fig. 4.7).

The value of oblique chest radiographs in evaluating patients with asbestos exposure has been debated over the years, but the use of these projections has decreased with the advent of CT scanning. In the past it was thought that oblique projections of the chest could increase the recognition of pleura plaques whereas others found the value to be less important [9]. According to some authors, oblique radiographs of the chest might be able to help distinguish between serratus anterior muscle and pleura plaques [5, 21–23].

In an attempt to decrease the misinterpretation of normal structures as representing pleura plaques, more attention has been directed to the threshold criteria for pleura thickening. However the trade-off for using strict minimum thickness requirements before suggesting pleura disease is a loss of sensitivity for a gain in specificity; that is, some pleura abnormalities will be overlooked, but there will be a reduction in false positive readings [24]. The most recent adaptation of the ILO standards for

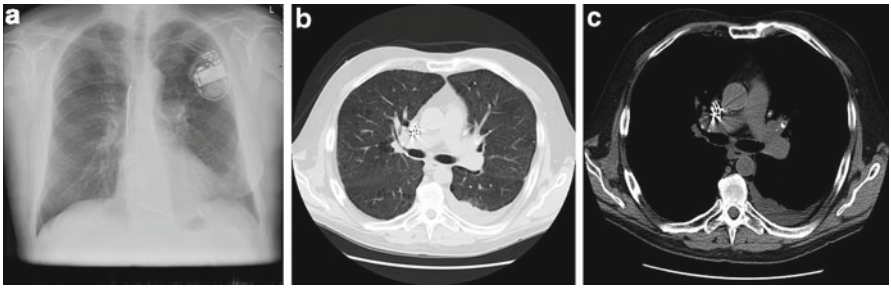

Fig. 4.7 Extrapleural fat. (**a**) PA chest film demonstrates what appears to be a long pleural plaque in the right lateral hemithorax. (**b**) Single slice of a CT scan in lung windows demonstrates increased soft tissue opacity along the right lateral hemithorax. (**c**) The same CT slice as in (**b**) is now imaged with mediastinal windows and the soft tissue opacity disappears revealing that it is extrapleural fat, not a plaque

interpreting chest films for the purposes of occupational exposure has adopted a minimum thickness of 3 mm before identifying and coding the presence of pleura abnormality [25].

Diffuse Pleura Thickening

Diffuse pleura thickening may be seen on chest radiograph or CT scan. It is frequently associated with costophrenic angle blunting unlike the more focal pleura thickening of pleura plaques (Fig. 4.3). This type of diffuse pleura thickening is considerably less frequent than pleura plaques, and in approximately 30% of individuals, it is associated with a known prior history of benign asbestos pleurisy or benign asbestos-related pleura effusion [26]. By definition, on CT scanning some authors regard diffuse pleura thickening as being more than 5 cm wide, 8 cm or more in craniocaudal dimension, and greater than 3 mm thick. On CT scans, diffuse pleura thickening is typically in the lower, posterior, and posteromedial aspects of the thorax [27]. The diffuse pleura thickening must be associated and continuous with costophrenic angle blunting to be recognized according to the latest ILO classification of PA chest films.

Round Atelectasis

Round atelectasis is an unusual form of lung collapse which may simulate a lung mass or neoplasm. This abnormality generally appears as a large, 2–7 cm in diameter round or oval opacity adjacent to and caused by pleura fluid and/or thickening, thus its frequency and association with asbestos-related pleura disease [28, 29]. One

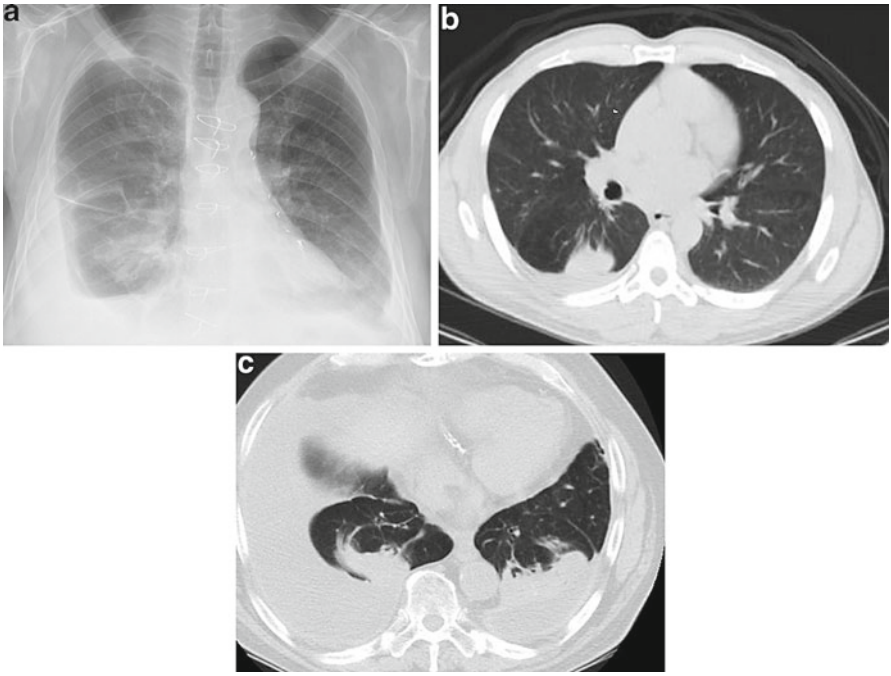

Fig. 4.8 Round atelectasis. (**a**) PA chest film demonstrates a poorly marginated right lower lobe mass on frontal view as well as right pleural fluid. (**b**) CT scan of same patient demonstrates a moderate right pleural effusion with round mass anterior to it. (**c**) A different slice demonstrates curved vessels entering the mass; some have called this the "comet tail" sign which is fairly reliable in discerning round atelectasis

of the distinctive features of round atelectasis that may help distinguish it from a neoplasm is the curvilinear nature of vessels and bronchi coursing from a hilar direction into the mass. This may be seen on both plain films and CT scans of the chest and has been called the "comet tail" sign (Fig. 4.8). [30] Occasionally, air bronchograms are seen near the center of the mass and there may be increased density in the periphery of the mass unlike most neoplasms. Round atelectasis is typically (approximately 80% of instances) located in the periphery of the posterior lung adjacent to pleura thickening; however, it may be seen in any portion of the lung where pleura thickening is present. The margins of the mass are generally discreet but not sharply etched, the mass is not completely surrounded by air, and an acute angle is usually formed with the pleura. Volume loss may be detected. More than one area of both round atelectasis and bilateral lesions have been reported [31–35].

In smaller lesions of round atelectasis the curvilinear bronchovascular bundle extending into the mass may not be identified; however, round atelectasis may still be suspected by its close association with a persistent area of pleura thickening.

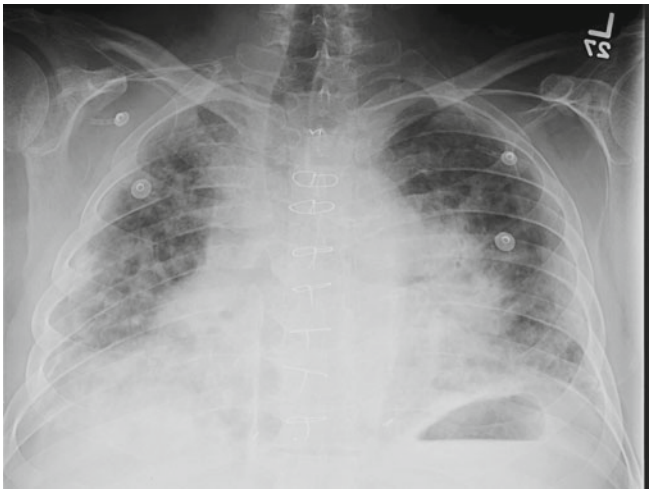

Fig. 4.9 Asbestosis. PA chest film demonstrates bilateral irregular opacities predominantly involving the lower lobes with indistinctness of the heart borders and diaphragm

In cases without the more telling feature of curvilinear opacity associated with a mass, further evaluation could include follow-up chest films or CT scanning. 2-[18F]fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (FDG-PET) scanning may help to distinguish between round atelectasis and neoplasm in confusing cases as the atelectatic lung should not be hypermetabolic [36].

Asbestosis

Fibrosis of the lung parenchyma caused by asbestos has been termed asbestosis. The primary imaging modality of this disease is the chest radiograph. However the chest film may be normal in up to 18% of patients [37–39]. It was also discovered that a great majority of patients with proven asbestosis had pathologic disease which was greater than the disease suggested by their B-reading classification [37]. Furthermore not all chest-film suspected lung disease can firmly be ascribed to asbestos exposure as other etiologies may contribute to an abnormal appearance including radiographic technique, obesity, smoking, emphysema, and other causes of lung fibrosis [40].

Small irregular opacities including fine, medium, and/or coarse linear and/or reticular opacities primarily in the lung bases are typically seen on abnormal chest films. The various patterns of abnormality include interlobular septal lines including Kerley B lines, honeycomb lung, traction bronchiectasis, indistinct heart border or "shaggy heart," and indistinct diaphragm—all evidence of fibrosis in the lungs (Figs. 4.9 and 4.10) [41]. The lung abnormalities are frequently identified in

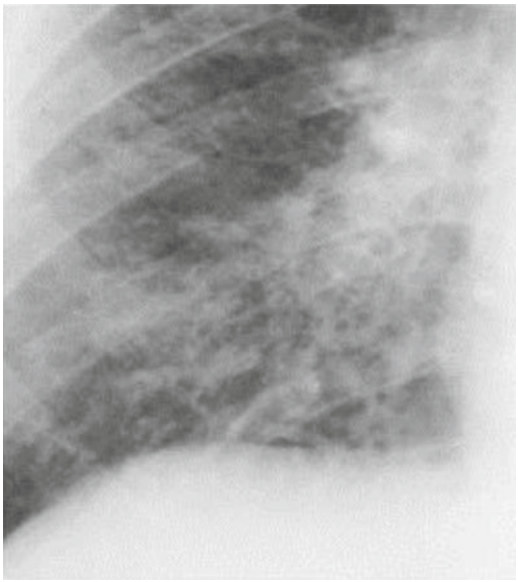

Fig. 4.10 Asbestosis. Close-up of a PA chest film in a patient with asbestosis demonstrates small irregular opacities, some may call reticular or linear, which cause indistinctness of the vessels in the lower lobe

conjunction with the benign and/or malignant changes of asbestos-related exposure (Fig. 4.11). Thus asbestos-related parenchymal fibrosis without pleura thickening is unusual, seen in approximately 10% of individuals in one series [42]. In addition, concomitant round atelectasis or lung cancers may also be noted. With increasing time or greater exposure, mid-lungs and upper lobes may become involved; in some cases, this may rarely (1–2% of cases) become advanced [43]. Mediastinal or hilar lymphadenopathy is not generally observed on chest films unless metastatic disease to these nodes caused by a lung cancer or mesothelioma has occurred. Usually, overall lung volumes are reduced by the extensive fibrosis, but occasionally increased lung volume may be noted and is presumed to be secondary to cigarette smoking, which is noted in a large percentage of patients with asbestos exposure. The lung fibrosis identified on chest film may progress over time even after withdrawal from exposure to asbestos in the workplace [44]. While the progression of fibrosis is usually prolonged, in one study 14–31% of patients demonstrated rapid (3–4 years) radiographic progression of fibrosis on chest films [45].

CT scanning for the diagnosis of asbestosis is a more sensitive imaging tool [46, 47]. On CT scanning the earliest findings of asbestosis have been identified as subpleura dots or branching structures that link to the most peripheral branch of pulmonary artery. Since these very early abnormalities may be confused with dependent vascular engorgement, one must recognize that vessels show tapering as they approach the visceral pleura [48]. Also the early pleura dots are seen in the mid-lungs as well as the dependent portions of lungs where small vessel engorgement might otherwise be identified. Other features of asbestosis include intra- and interlobular septal lines, curvilinear subpleura lines, parenchymal bands, honeycombing, and less frequently ground-glass opacities (Fig. 4.12) [46, 47].

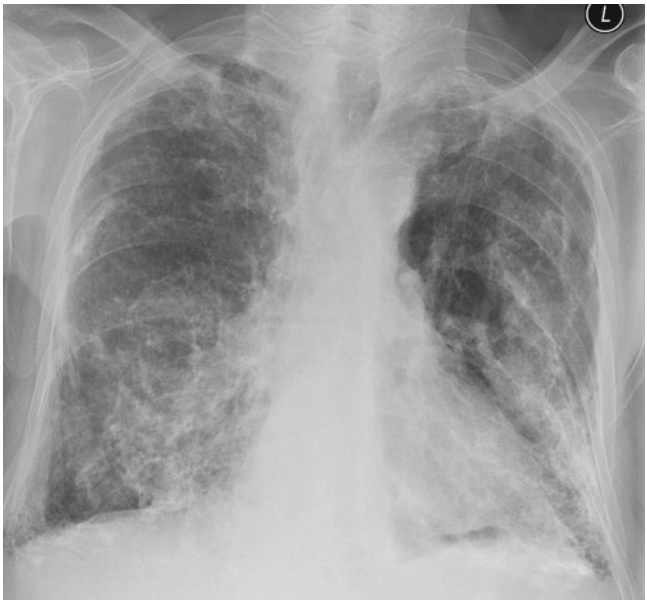

Fig. 4.11 Asbestosis and asbestos-related pleural plaques. PA chest film demonstrates bibasilar heterogeneous irregular lung opacities (look at lung overlying both costophrenic angles) as well as calcified bilateral pleural plaques, many seen en face, which makes assessment of underlying lung disease difficult

While mediastinal lymphadenopathy has not been commonly reported on chest films in patients with asbestos exposure, on CT scanning in a group of patients with asbestosis, 14 of 14 patients had at least one enlarged lymph node in some portion of the mediastinum [49]. The authors suggest that the CT presence of mediastinal lymphadenopathy should not necessarily be taken as evidence of metastatic disease in patients with asbestos exposure who develop lung cancer. They propose that further investigation should be performed to make this determination.

The parenchymal abnormalities seen with asbestosis are certainly not specific for the diagnosis. In an attempt to semiquantitatively evaluate the number and distribution of high-resolution CT findings in patients with proven diagnoses of asbestosis, some authors found that if three different types of CT abnormalities were seen on HRCT, the proportion of patients with asbestosis was 100%. However this dropped to 80% if two CT findings were observed and to only 60% if one CT finding was present. They also discovered that, as with chest films, high-resolution CT scanning could be normal or limited even in the presence of histopathologically demonstrated asbestosis (9 of 25 cases), and that, as with chest films, a very large number (85%) of patients who demonstrated CT findings of asbestosis also had evidence of pleura plaques [50].

Prone CT imaging may be necessary to distinguish between dependent atelectasis and lung fibrosis, and in many institutions, it is an integral part of their interstitial

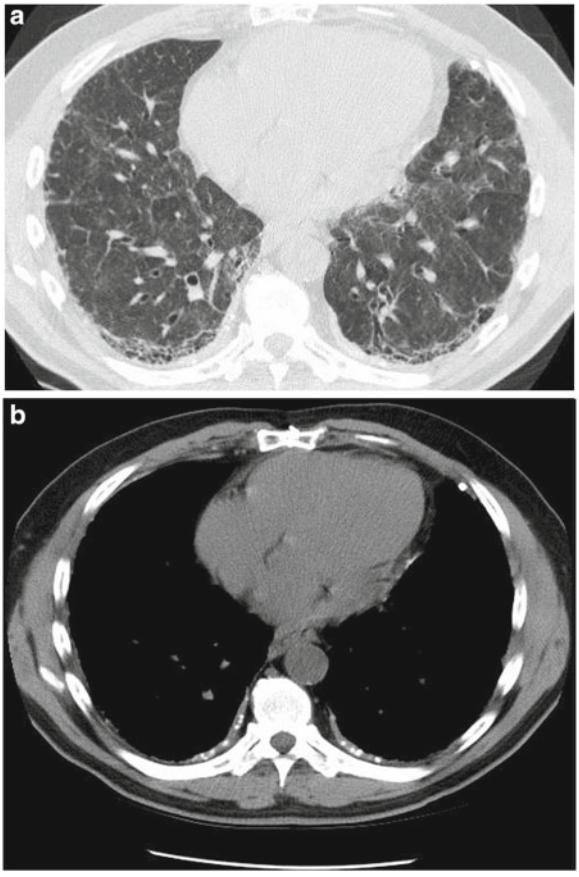

Fig. 4.12 Asbestosis. (**a**) Single slice from a CT scan in lung windows demonstrates honeycomb lung posteriorly in the *right* and *left* lower lobes. Interlobular opacities are seen anteriorly and laterally on the *right*. Traction bronchiectasis is seen in the *left* dorsal lung. (**b**) Note that calcified pleural plaques over *left* and *right* anterior and posterior pleural space are better seen on the same slice imaged with mediastinal windows

lung disease CT protocol. Distinguishing between idiopathic pulmonary fibrosis (IPF) and asbestosis is best determined by the presence of concomitant pleura disease commonly seen with asbestos-related disease, However other criteria have been proposed. Some have noted that ground-glass opacities were more common with IPF whereas parenchymal bands and subpleura curvilinear lines were more common with asbestosis [50]. Others have found that the fibrosis seen in IPF was more frequently basal and subpleura than that seen with asbestosis [51]. In another investigation, differences between asbestosis and IPF included more subpleura dots, subpleura curvilinear lines, and parenchymal bands with early asbestosis, a combination rare in patients with IPF [52]. Some authors, conceding that there may be a close resemblance between IPF and asbestosis, suggest that there are more significant differences between asbestosis and nonspecific interstitial pneumonitis (NSIP); the latter disease having greater amounts of ground-glass opacification and less coarse irregular opacities [51].

And yet while there may be some discriminating CT features of asbestosis vs. IPF, CT itself is not necessarily specific for asbestosis. One study suggests

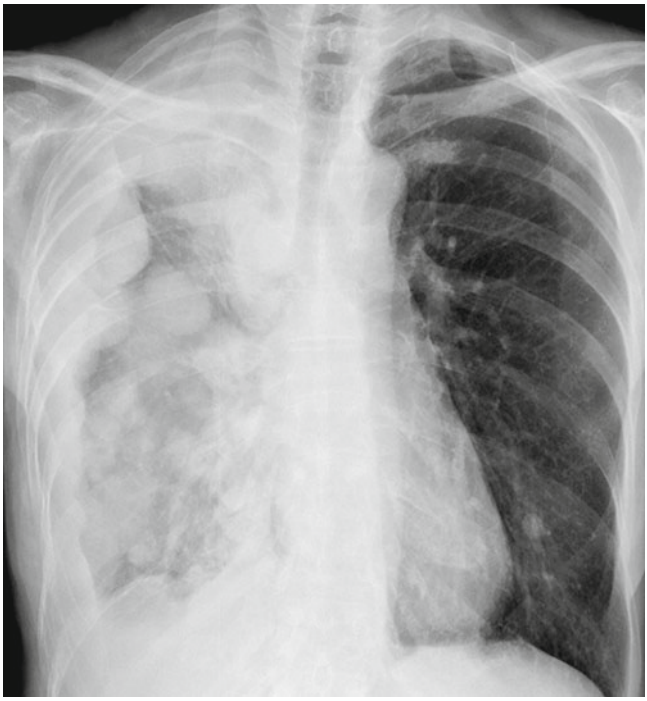

Fig. 4.13 Mesothelioma. PA chest film demonstrates bulky pleural thickening encasing the right hemithorax including the mediastinal region. This appearance should suggest malignant mesothelioma or metastatic disease of the pleura

that even though high-resolution CT findings might suggest asbestosis, this set of abnormalities may be seen in individuals without a history of asbestos exposure [53].

Mesothelioma

This aggressive and frequently fatal neoplasm of the pleura space might be suspected in an individual with asbestos exposure and unilateral pleura effusion as pleura fluid on chest films is seen in nearly 50% of patients with this diagnosis [54]. More suggestive of the diagnosis of mesothelioma is encasement of an entire unilateral pleura space associated with volume loss as noted on either chest film or chest CT. As opposed to benign asbestos pleura disease, mesothelioma is more frequently nodular, frequently thicker, greater than 1 cm, and more likely to involve the mediastinal pleura (Fig. 4.13) [55]. CT scanning with reformatted

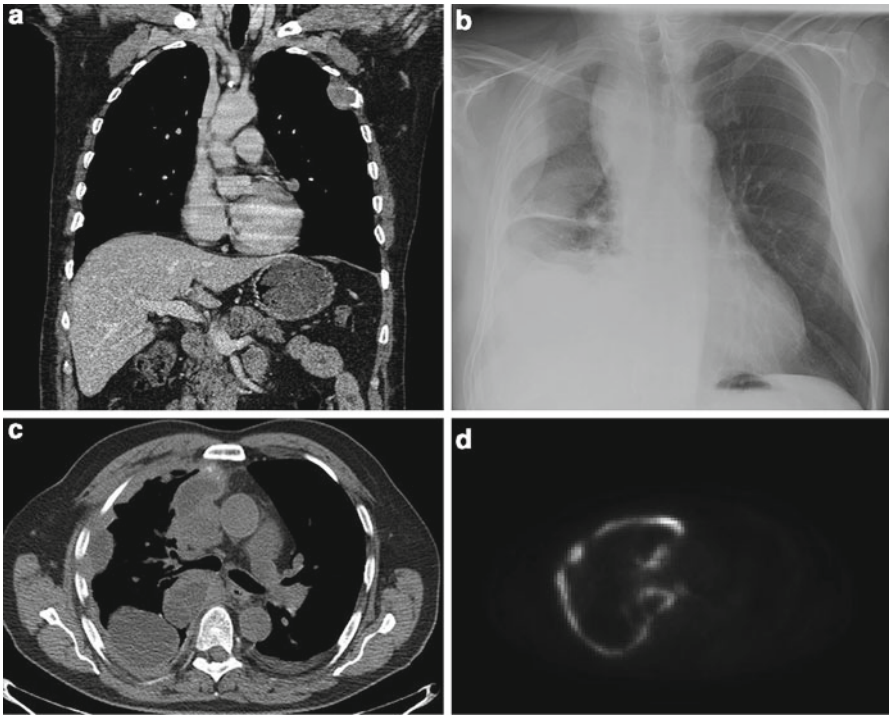

Fig. 4.14 Mesothelioma. (**a**) Coronal reformatted image of a CT scan demonstrates a left upper lateral mesothelioma with contiguous involvement of the adjacent rib. (**b**) PA chest film demonstrates lobular pleural thickening surrounding the right pleural space; (**c**) Single slice from a CT scan demonstrates soft tissue masses throughout the pleura; (**d**) Single slice from a PET scan reveals hypermetabolic activity in the pleura suggesting malignancy

coronal and sagittal images as well as magnetic resonance imaging of the thorax are both used to identify the extent of spread of mesothelioma, which tends to involve contiguous structures below the diaphragm, in the mediastinum, and throughout the chest wall (Fig. 4.14) [56]. However neither of these cross-sectional imaging modalities may be useful in predicting the likely success of surgical resection of mesothelioma [57].

Pulmonary Talcosis

At least four forms of talc involvement in the lung have been reported including talcosilicosis, talcoasbestosis, talcosis, and intravenous administration of talc [58]. The first two forms have similar or identical radiographic features as silicosis and

asbestosis, respectively (see those sections in this chapter.). Talc injection may occur when drug abusers mix oral medications containing talc for intravenous use. Chest films in this situation may reveal lower lobe emphysema and small pulmonary nodules which may coalesce to form larger opacities [59]. The CT abnormalities of inhalational and intravenous talcosis may be similar, but lower lobe emphysema is only seen with the injected variety of disease, particularly in individuals who inject methylphenidate (Ritalin). With pure talcosis, chest radiographic findings include small irregular, reticular opacities in the lungs. CT scan findings in patients with inhaled talc disease include centrilobular nodules and/or diffuse ground-glass opacities, which may coalesce to form areas of progressive massive fibrosis (PMF). Unlike the PMF seen with silicosis (upper lobe distribution and internal high attenuation punctuate opacities), the PMF with talcosis is more widespread in the lungs and contains more diffuse high attenuation regions presumably from the talc itself. Hilar and mediastinal lymph nodes may be seen with talcosis, but calcification in these lymph nodes is uncommon as compared to silicosis [60]. Subpleural nodules, septal lines, subpleural lines, and ground-glass opacities have also been described in talcosis [61].

Berylliosis

Berylliosis is a pneumoconiosis with the disease caused by a chronic hypersensitivity reaction. Acute cases are rare since recognition of the effects of exposure have led to workplace improvements. However the chronic form is still seen. The chest film and CT in patients with berylliosis may be normal. When abnormal, the most common findings were small diffuse nodules, measuring approximately 1–4 mm in diameter, or irregular opacities. In later stages the chest film may reveal lymphadenopathy, spontaneous pneumothorax, coarse linear and nodular opacities, distorted upper lobe lung architecture, emphysema, and calcification of the parenchymal opacities [62]. These chest film radiographic findings have corresponding abnormalities on CT [63, 64]. A variety of CT scan abnormalities seen with berylliosis mimic the findings seen with sarcoidosis and include hilar and mediastinal adenopathy in 25–32% of patients, parenchymal nodules and septal lines in 50–57% of patients, and scattered areas of ground-glass attenuation in nearly one-third of patients. The small parenchymal nodules were generally seen along bronchovascular bundles or interlobular septa, and pseudoplaques presumed to be the result of coalescence of subpleural nodules were observed. Also chronic disease led to honeycomb lung and coarse distorted end-stage lung, although conglomerate masses and honeycomb lung were seen in a considerably smaller percentage of individuals. Airway disease, depicted by bronchial wall thickening, was evident in 46% of patients [64, 65]. As with most other diseases, CT scanning was much more sensitive than chest radiography in detecting abnormalities in patients with chronic berylliosis.

Silicosis

Acute Silicosis

The radiographic effects of exposure to silica may be divided into acute silicosis, simple silicosis, complicated silicosis, and secondary effects of silicosis. With acute silicosis, or as sometimes termed, acute silicoproteinosis, findings may mimic pulmonary alveolar proteinosis. Plain films of the chest demonstrate homogeneous opacification of both lungs, frequently with air bronchograms, which may progress rapidly to involve more predominantly the upper lobes. As with other predominantly alveolar processes, the margins of the homogeneous opacities seen in patients with acute silicosis are indistinct. Reticulonodular opacities are also identified in patients with acute silicosis, and evidence of volume loss may be noted by upward retraction of the hila. Spontaneous pneumothorax was noted in two of four patients reported in one series, and mediastinal adenopathy may also be identified [66]. With acute silicosis CT scans demonstrate bilateral ground-glass centrilobular nodules, homogeneous opacities, and "crazy-paving" where ground-glass opacities, through which interstitial irregular opacities, are observed [67].

Simple Silicosis

In simple silicosis the classic radiograph demonstrates multiple round nodules measuring approximately 1–8 mm in diameter, uniform in size, fairly well marginated, and predominantly in the upper lungs (Fig. 4.15). Lymph node enlargement is common and calcification of the lymph nodes may be seen, occasionally as an eggshell type of calcification (Fig. 4.16) [55, 68]. As with other pneumoconioses, the sensitivity of CT scanning for the detection of abnormalities in the lungs in patients with early silicosis is significantly better than that of plain radiography. In one study, 13 of 49 patients had nodular opacities, which were seen on CT scans but not on chest films. On CT scans, small nodules were distributed equally on right and left sides and were seen in upper and lower lungs (Fig. 4.17). Different reader variability in interpreting CT scans, in this series of patients with minimal disease, was significantly diminished compared to the plain film interpretations [69].

Complicated Silicosis

Complicated silicosis occurs when the small nodules of simple silicosis begin to coalesce and form large opacities ranging in size from one centimeter to several centimeters occupying great portions of lung. They are associated with volume loss frequently noted by elevated hila on chest film (Fig. 4.18). The large opacities are

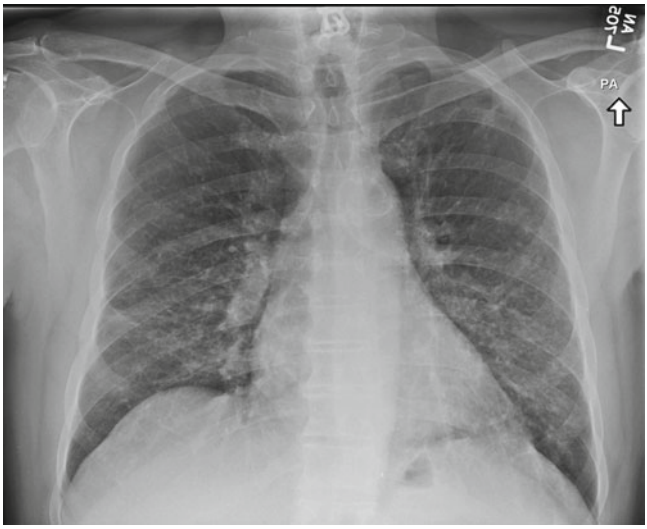

Fig. 4.15 Silicosis. PA chest film demonstrates bilateral small nodules seen best over the lingua

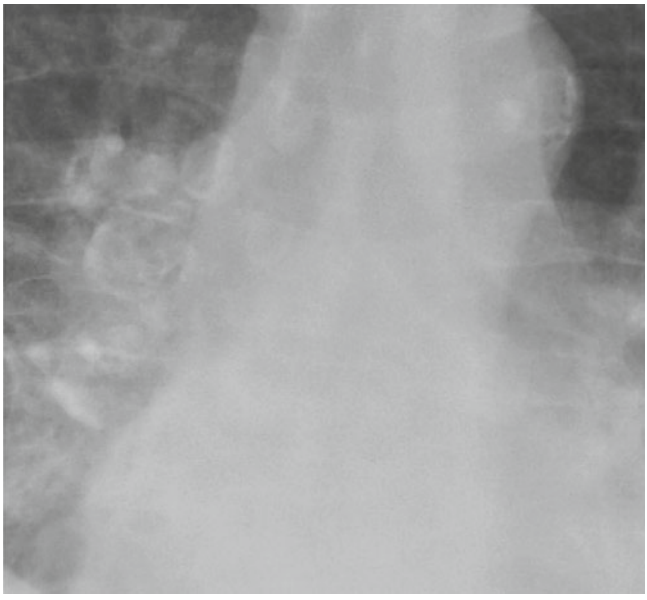

Fig. 4.16 Silicosis. Close-up of a PA chest film demonstrates calcified right hilar lymph nodes, some with a peripheral margin of increased opacity termed eggshell calcification

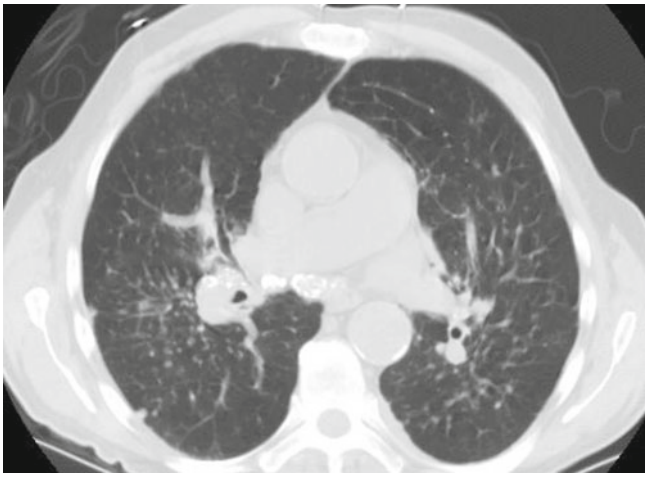

Fig. 4.17 Silicosis. Single slice from a CT scan demonstrates small clustered well-defined nodules in *right* greater than *left* upper lobes as well as subpleural nodules in the right upper lobe. Also note calcified mediastinal lymph nodes including "eggshell" calcification in one of the subcarinal nodes. These findings are good indicators of exposure to silica, although other etiologies, in particular sarcoidosis, could have a similar appearance

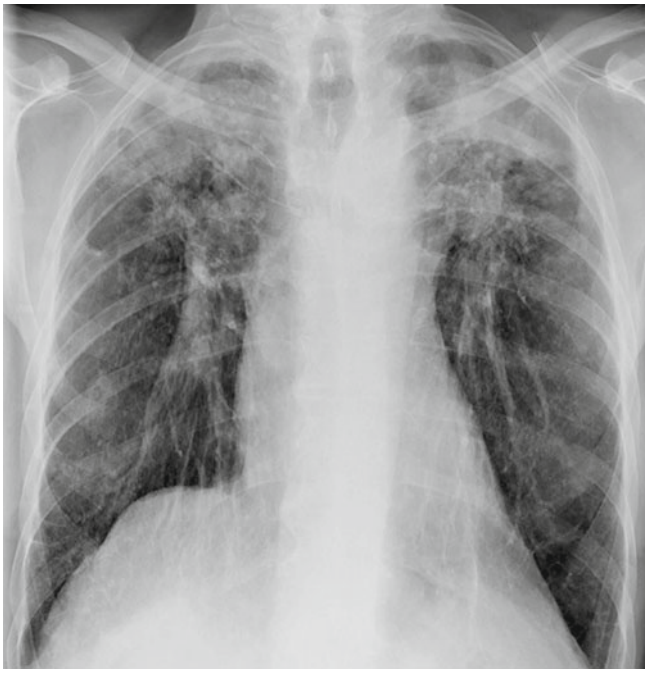

Fig. 4.18 Silicosis. PA chest film demonstrates bilateral upper lobe progressive massive fibrosis in the lung apices and small irregular nodules in the less-involved areas. Also some of the nodules within the conglomerate opacities are calcified. A right hilar calcified lymph node is also present

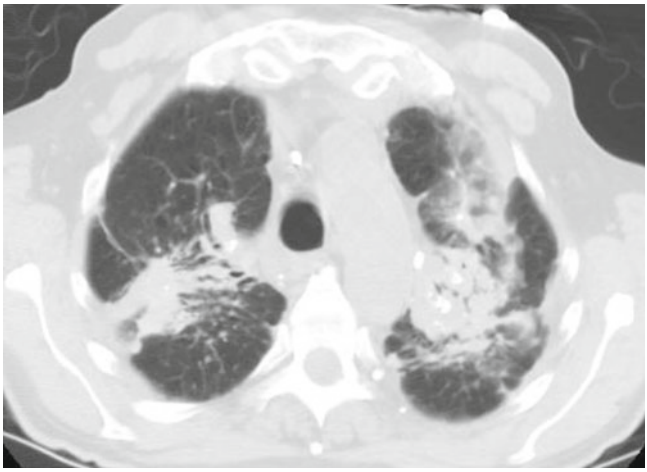

Fig. 4.19 Silicosis. Single slice from a CT scan in lung windows demonstrates the typical upper posterior location of conglomerate opacities or progressive massive fibrosis in a patient with silicosis. Note the small clustered nodules posterior to the right-sided PMF as well as the bilateral hilar and mediastinal calcified lymph nodes. Also note that some calcified parenchymal nodules are incorporated in the PMF

generally symmetric, irregular, and not well marginated, but are very distinct and usually seen in the posterior portion of the upper lobes bilaterally in a supra-perihilar distribution (Fig. 4.19). Occasionally, cavitation caused by ischemia is noted within these masses and uncommonly calcification may be identified [55]. Peripheral emphysema lateral to the large opacities is also noted, especially as the areas of PMF seemingly move toward the hila [68]. CT scans are better than plain films not only in the detection of early disease but also in the detection of early conglomerate opacities, thus indicating complicated silicosis. In a series of 49 patients, the authors found six individuals with early conglomerate opacities on CT scan, not detectable on plain film [69]. In a different group of 58 patients who had early and late ILO B-reading classified silicosis, additional information in the form of complicated silicosis or conglomerate opacities was noted in 33% of patients on CT scanning as opposed to plain films of the chest [70]. The progression of radiographic abnormalities in 141 patients with silicosis was followed with serial chest films over a period of 2–17 years, and it was discovered that 37% of patients had some type of disease worsening. Thirty-one percent had an increase in profusion when starting with category 1; 37% had an increase in profusion when starting with category 2; and 52% of patients with complicated silicosis demonstrated increasing size of large opacities or profusion [71].

Complications of Silicosis

Emphysema has been seen in up to 81% of patients with complicated silicosis, that is, those patients with conglomerate opacities. In particular the paracicatricial type of emphysema was identified although other types were seen. In addition some patients with simple silicosis also have had emphysema noted on CT scan and this was highly represented as compared to a control group. Some of these patients, however, were former heavy smokers. Air-trapping has also been revealed on inspiratory–expiratory CT imaging [72–74].

In simple silicosis what appears to be pleura thickening is most likely pseudoplaque formation caused by a coalescence of subpleural nodules. However in a recent paper, a large number of patients with actual pleura thickening was reported. These authors demonstrated that 47.3% of their patients had pleura thickening on chest films and 58.2% had thickening on CT scans, but acknowledge that most radiology literature does not support their findings [75].

Coal Workers' Pneumoconiosis

The chest film and CT scan abnormalities of patients with coal workers' pneumoconiosis (CWP) are similar to those seen in patients with silicosis. Small nodules ranging in size from 1 to 10 mm in diameter are initially observed in the simple form of disease. Some state that the nodules in CWP are less well defined than those seen with silicosis, but this would be difficult to appreciate in an individual case [76]. In one series, parenchymal calcification was reported in up to 19% of patients, emphysema was noted in 12%, PMF in 4%, enlarged hilar nodes in 4%, and eggshell calcification of mediastinal and hilar nodes in 1%—all values less than those seen with silicosis [77]. In the complicated form of CWP there is coalescence of nodules to form large opacities, that is, PMF (Fig. 4.20).

The results of CT scanning for CWP have also been reported [78]. In this study CT was found to be more sensitive than plain film radiography demonstrating CWP in 23% of patients whose chest radiograph was without evidence of disease by ILO B-reading standards. The authors found an upper lobe predominance of small lung nodules in a subpleural and perilymphatic distribution. Calcification was noted in 28–38% of the subpleural nodules and in 4% of the other parenchymal nodules. With progression of disease the nodules increased in size and PMF was observed in 29% of cases (Fig. 4.21). In a small number of patients, honeycomb lung was observed generally in the lower lungs. A high percentage of patients demonstrated some emphysema, and enlarged lymph nodes (85% calcified) were also identified in a large number of patients. Coalescence of subpleural nodules seen in patients with CWP may form pseudoplaques as observed in silicosis. Other investigators have noted discreet areas of centrilobular emphysema on high resolution CT scanning [79].

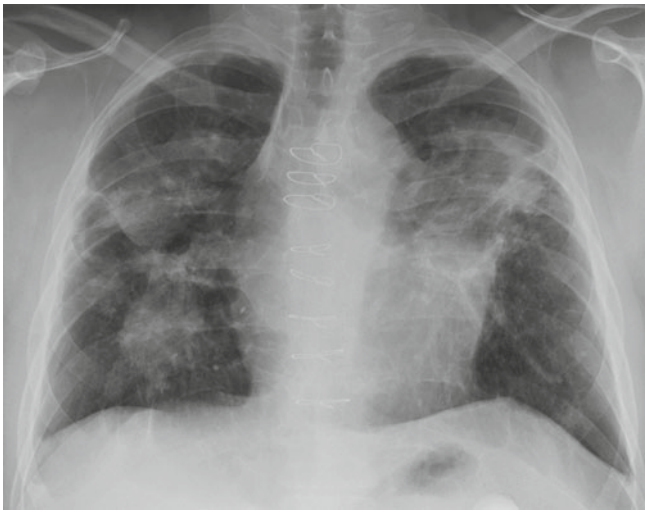

Fig. 4.20 Coal worker's pneumoconiosis. PA chest film: This study demonstrates progressive massive fibrosis, which is usually seen in the upper lobes and posterior to midline on lateral view. Peripheral to the masses is lucency, also very characteristic as the masses "migrate" toward the hila

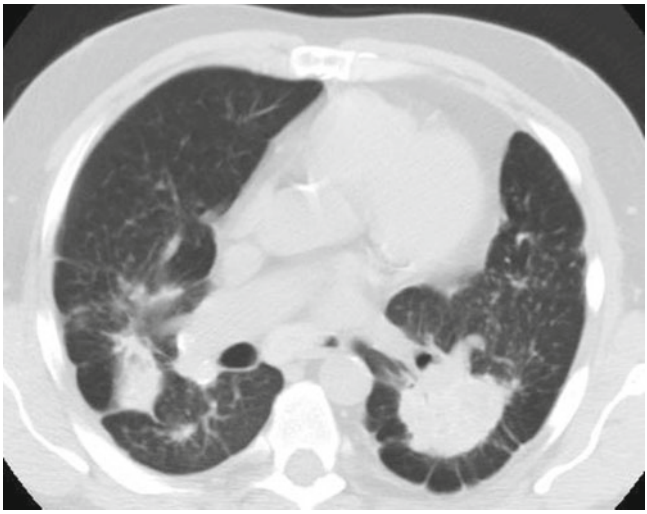

Fig. 4.21 Coal worker's pneumoconiosis (same patient as in Fig. 4.20). Single slice of a CT scan demonstrates progressive massive fibrosis as represented by the larger opacities posterior to midline in the upper lobes. Just adjacent to the masses are very small nodular opacities which represent the earlier changes of coal worker's pneumoconiosis. As these small nodules coalesce, the large opacities are formed. As the masses migrate centrally, areas of emphysema are formed in the lung periphery as seen here bilaterally

Areas of PMF can become necrotic and cavitate with or without concurrent infection; however, the possibility of mycobacterial disease should be considered in this situation [80]. Progressive massive fibrosis can lead to distorted lung disease with peripheral emphysema similar to that seen with silicosis. Eggshell calcification of lymph nodes is thought to occur less commonly with coal worker's pneumoconiosis [76].

Hard Metal Lung Disease

The radiographic effects of exposure to hard metal (i.e., a combination of cobalt and tungsten carbide associated with other elements such as titanium, nickel, chromium, and others) have been described in several articles [81–83]. The chest films have demonstrated bilateral hazy and homogeneous opacities simulating pulmonary edema as well as small irregular opacities. In general the lower lobes have been favored. On CT scanning, bilateral ground-glass opacities, irregular linear opacities, nodules, emphysema, homogeneous opacities, and honeycomb lung have been noted. The distribution on CT scan was most predominantly in the lower lobes particularly in patients with heterogeneous opacities. Honeycomb lung, small centrilobular nodules, and emphysema were less common than the other findings. Some investigators report traction bronchiectasis as opposed to honeycomb lung [83]. Overall the abnormalities resembled IPF and NSIP [81]. Some investigators have found more of a mid and upper lung distribution of abnormal findings similar to those reported by others [84].

Hypersensitivity Pneumonitis

This process, caused by a number of organic and inorganic substances, carries the titles of many expressive diseases such as farmer's lung, bird fanciers lung, mushroom worker's disease, maple bark disease, and others. The clinical presentation of hypersensitivity pneumonitis (HP) is similar across the etiologies and has been divided into acute, subacute, and chronic forms. With acute hypersensitivity pneumonitis, chest films demonstrate bilateral homogeneous opacities which are usually poorly marginated and frequently symmetric. In other words the pattern of acute HP on chest film and chest CT resembles pulmonary edema [85]. As with many other pulmonary diseases, CT scanning is more sensitive than plain chest films in illustrating the abnormalities in patients with HP [86].

In patients with subacute hypersensitivity pneumonitis, bilateral scattered ground-glass opacities and poorly marginated centrilobular nodules are typically identified (Fig. 4.22). Air trapping may be seen on expiratory CT studies [87, 88]. Other investigators have reported similar findings with some mosaic vascular distribution observed on high-resolution CT and air trapping noted on expiratory views. Air-filled lung cysts, generally less than 2.5 cm in diameter and associated with

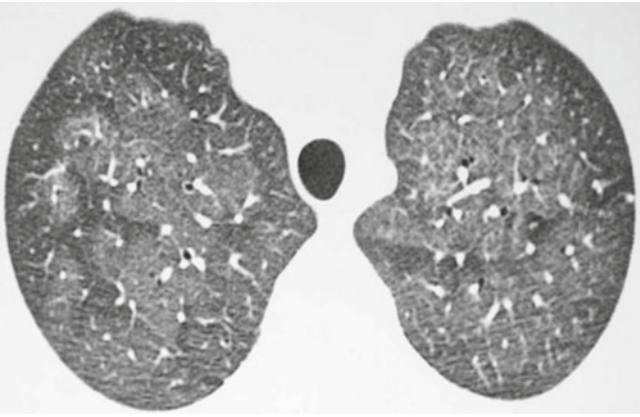

Fig. 4.22 Hypersensitivity pneumonitis. Bird-fancier's lung. Single slice of a CT scan demonstrates diffuse upper lobe ground-glass opacities which are seen characteristically in acute hypersensitivity pneumonitis

ground-glass opacities, were reported in 13% of patients with subacute hypersensitivity pneumonitis [89].

With chronic hypersensitivity pneumonitis, the chest radiograph demonstrates linear opacities with lung distortion, and high-resolution CT scans reveal reticular opacities with traction bronchiectasis distributed randomly in the lungs or occasionally in subpleural and peribronchovascular distribution. In general the upper and mid lungs are involved with some sparing of the lung bases [86–88]. Serial HRCT scanning of patients with hypersensitivity pneumonitis reveals that, with time, ground-glass and centrilobular opacities decrease whereas honeycomb lung increases [90]. Other observations regarding HP include pulmonary hypertension, mediastinal lymph node enlargement in 30% of patients with farmer's lung, and in 8% of patients with proven HP, normal lungs on HRCT [91–93].

Several studies have looked at distinguishing the high-resolution CT findings of hypersensitivity pneumonitis from those of IPF. Differences include a predominance of lower lung disease with IPF, lobular areas of decreased attenuation, and centrilobular nodules with HP [92, 94, 95].

International Classification of Radiographs of Pneumoconioses

After World War I, in 1919, the International Labour Organization was founded with a goal of promoting peace and social justice throughout the world. Since that time the organization has provided assistance to numerous countries regarding labor practices, and through their ILO, a research and publishing division, has published a small booklet entitled "Guidelines for the Use of the ILO International Classification

of Radiographs of Pneumoconioses." The first version of the classification was published in 1930 as part of the proceedings of an international meeting on silicosis [96]. A more modern precursor to the current edition originated in Sydney, Australia in 1950 and through an intermittent series of meetings and experiments, it has evolved through several revisions until the most recent 2000 edition was published in 2002 [25]. Through the 1958 classification, the scheme was only designed to code abnormalities of silicosis and CWP. However the success of this revision was the springboard to enlarge the scope of the classification to include asbestosis in the 1971 revision. Over the years, in addition to the published guidelines, a set of standard radiographs illustrating abnormalities seen in patients with occupational exposure was made available (Fig. 4.23). The films in this set are used with the published definitions of abnormality to aid in classifying the chest films of individual patients (Fig. 4.24). The booklet elucidates the scope, object, uses, and specific instructions for using the classification. Of particular note: "The classification neither defines pathological entities nor takes into account working capacity. It does not imply legal definitions of pneumoconioses for compensation purposes and does not set or imply a level at which compensation is payable." The classification was designed primarily to be used for "epidemiological research, for screening and surveillance of those in dusty occupations, and for clinical purposes" [25].

The value of the classification depends upon a technically adequate chest radiograph, the quality of which should be of great importance to the interpreting physician and radiology technologist. If the chest film is deemed adequate for evaluation, then the film is scored on a standard form for parenchymal and pleura abnormalities consistent with pneumonconiosis, and other radiographic findings thought to be of importance and, on the form, either represented by symbols or communicated by checked boxes and/or free text (Fig. 4.25). Chest film quality may have profound implications on interpretation as it has been shown that underpenetrated films may produce readings of worse disease than actually present while overpenetrated films can have the opposite effect [97].

Within the parenchymal abnormality section of the standard form, the chest film findings that are classified include small opacities, coded for shape (round or irregular) and size according to the written and film-based instructions or illustrations. The letters p, q, and r are used to denote round opacities of increasingly larger size; letters s, t, and u are used to denote irregular opacities of increasing size. The locations of the abnormalities are indicated by checking boxes labeled right and left, upper, middle, or lower. The degree of intensity of the nodules is recorded on a 12-point scale of profusion with major categories 0, 1, 2, 3, indicating normal and then increasingly greater involvement, and minor categories denoted by numerator and denominator, for example, 2/3, suggesting that based on comparison with the standard films, the interpreter gauged the abnormality to be most likely of profusion type 2; however, profusion type 3 was also entertained as a possibility.

Large opacities are denoted by absence with a check in the O box or as being present with increasing size and indicated by check marks in boxes A, B, or C.

Pleura abnormalities are coded as to whether they represent pleura plaques seen in profile or en face, where they are located in the thorax, as to the presence of

pleura calcification, and as to size by nature of vertical extent and width of the disease. The evaluator can mark a box to indicate the presence of costophrenic angle blunting and also the presence of diffuse pleura thickening. A minimum width of 3 mm is required before coding either pleura plaques or diffuse pleura thickening.

Some of the obligatory symbols recognized in another section of the classification indicate the possibility of atherosclerotic disease of the aorta, bullae, lung cancer, enlarged noncalcified hilar or mediastinal lymph nodes, and a variety of many other diseases or findings.

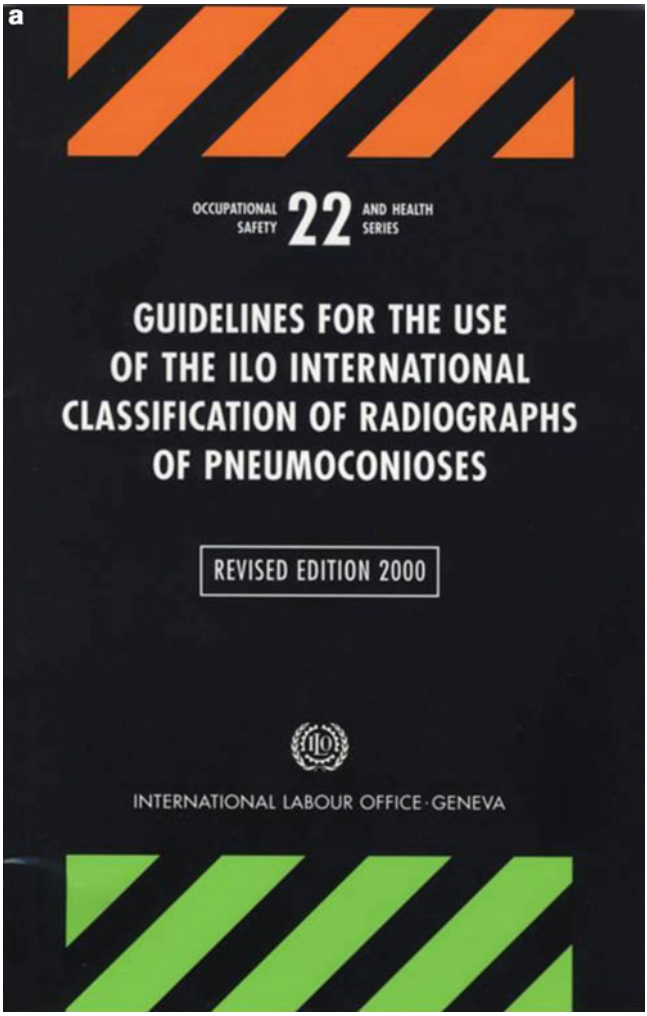

Fig. 4.23 ILO material. Photographs of the covers of the latest guidelines (**a**) and box of standard films (**b**) for B-reading

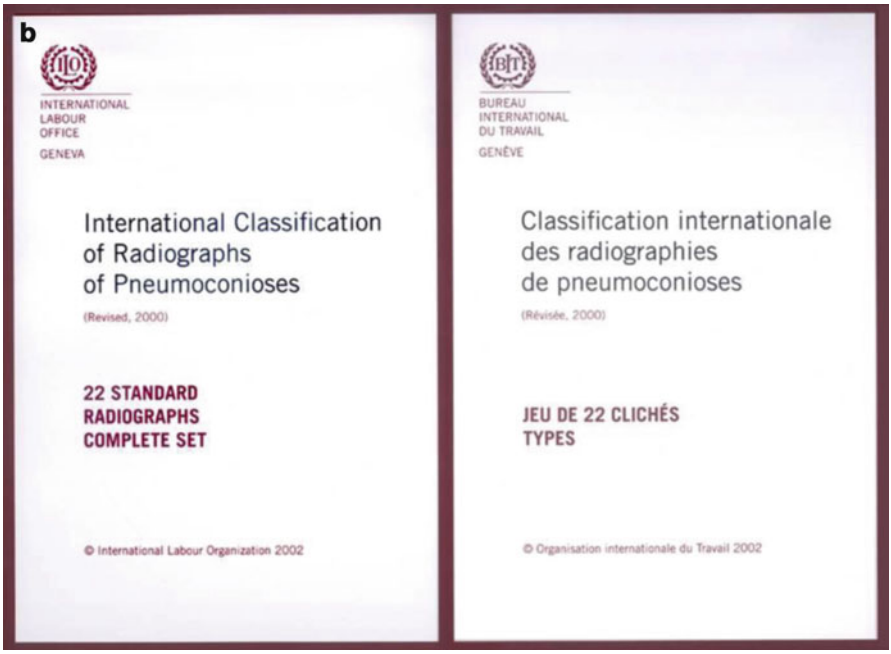

Fig. 4.23 (continued)

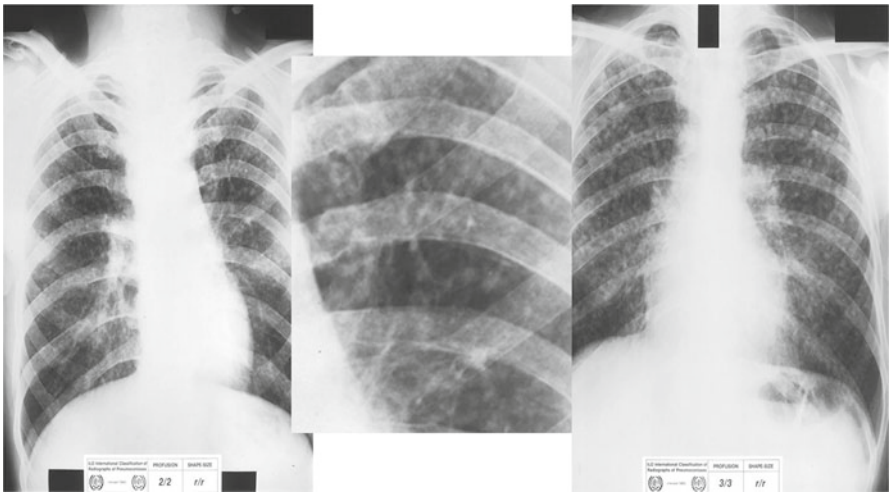

Fig. 4.24 B-reader comparison: In the center is a close-up of the film being assessed. On the sides are the standard films which the B-reader thought were closest in type and size to the patient film; on the *left* is the 2/2, r/r standard and on the *right* is the 3/3, r/r standard. In this instance the B-reader observed that the target film was very much like the 3/3, r/r standard, and assigned this score

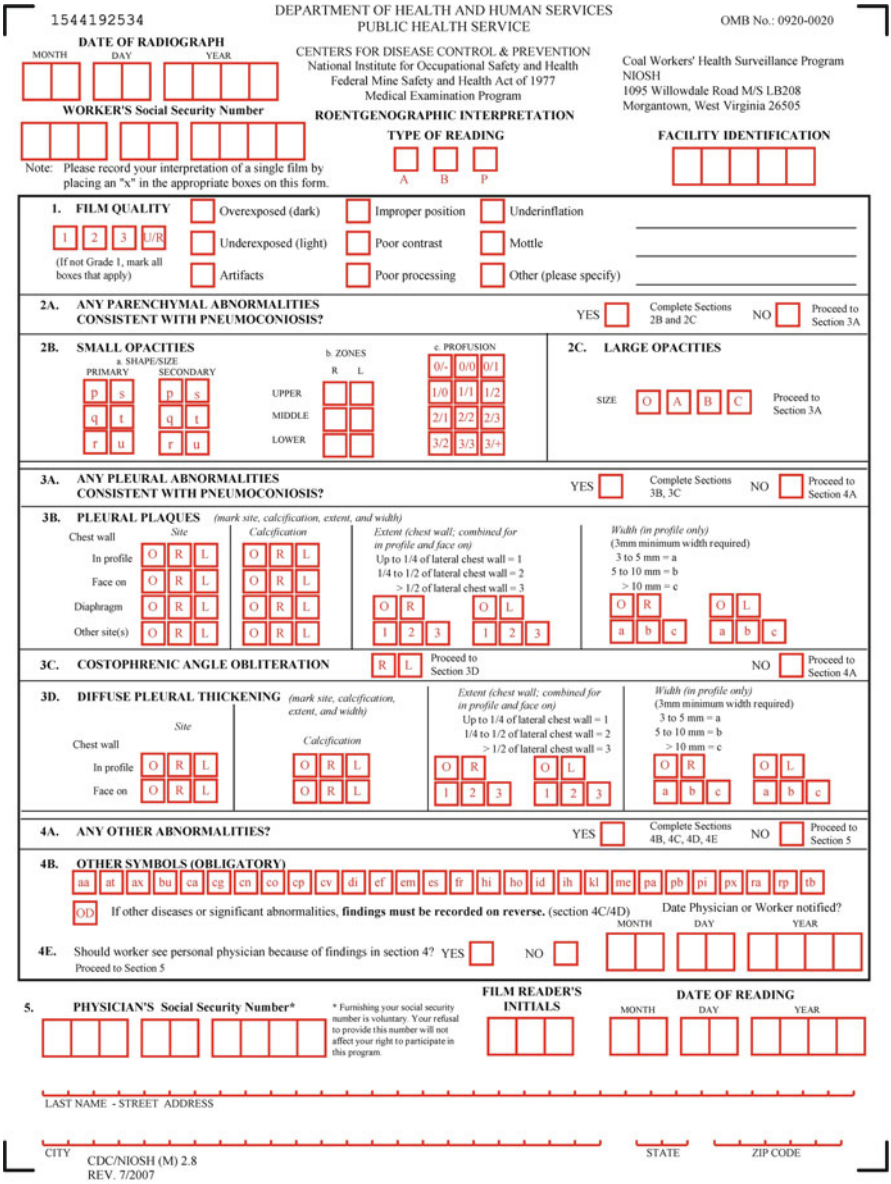

Fig. 4.25 B-reader score sheet. This typical form is the one used by the National Institute for Occupational Safety and Health. The major sections assign scores for film quality, parenchymal abnormalities consistent with pneumoconiosis, pleural abnormalities consistent with pneumoconiosis, and other abnormalities

Despite the use of the ILO classification scheme and standard scoring form, there were still significant discrepancies in interpretations of chest films. Thus in 1974, the National Institute for Occupational Safety and Health (NIOSH) in Morgantown, West Virginia developed a proficiency certification program to qualify readers for this purpose. The NIOSH B-reader program was widely administered by 1978 [98]. Physicians of any specialty can sit for a qualifying examination to become certified as a B-reader. A preparatory seminar regarding the ILO classification of pneumoconioses on chest film is periodically given by the American College of Radiology. Otherwise individuals may prepare for the examination using a self-study syllabus. If the examination is passed, the qualifying physician is certified as a NIOSH B-reader for 4 years at which point recertification is required.

The proficiency examination consists of 125 films of individuals who have been predominantly exposed not only to coal and silica but also to other inorganic dusts including asbestos, beryllium, and iron. The examination is 6 h long and the films are scored on a standard report form using the ILO classification. The types of abnormalities that are present on the test films include all of those incorporated in the classification [99]. Results of an individual candidate's readings are compared to those of an expert panel and a candidate is scored using a variety of end points including overreading and underreading, false-negative and false-positive errors, detection of clinical disease other than pneumoconiosis, and corrected standard reading error. When it was first used, the examination was tested for intra-reader reliability and was shown to be reasonably consistent upon repetition [99]. Candidates with formal radiology training or internal medicine training have produced higher test scores on the exam than physicians without expertise in these fields [99]. It is well known that significant inter-observer variability in the interpretation of chest radiographs using the ILO classification occurs [100]. Also, the ILO classification has been applied to a population without known occupational exposure and revealed that 18% of 200 patients had small opacities with a profusion level greater than 1/0, thus considered "positive." The authors concluded that this represents a confounding factor when assessing the presence of occupational lung disease as some "normal" individuals may test positive [101].

Nevertheless the ILO classification has been accepted internationally and has demonstrated some value in epidemiologic studies exploring the appearance of pneumoconiosis as it relates to the amount and type of dust exposure which individuals experience [102]. Government laws, including the Federal Coal Mine Health and Safety Act (1969) and the Asbestos Medical Surveillance program administered by the Navy Environmental Health Center both require interpretation of chest films of their patients using ILO classification by B-readers. The chest films used in the federally mandated programs are generally obtained using a specific radiographic technique. To date, no allowance for the rapid and overwhelming use of digital radiography has been accounted for in ILO classification. However there is clearly an understanding that an update to the current system incorporating digital radiography is necessary [103]. A number of articles have been written comparing the use of digital chest imaging to traditional chest films and the comparison has been favorable in regard to recognizing pneumoconiosis

[104, 105]. A moderate to good inter-modality agreement has been recognized. However, image interpreters had a slight tendency to classify more small irregular opacities using computed radiography as opposed to traditional technique. The authors found that as with traditional film interpretations, there was an inherent variability in classification of radiographs using computed radiography. The authors also noted that computed radiography appeared to result in a greater number of opacities coded as small and reticular as compared to traditional radiography and suggest that a selection of standard images for incorporation in the ILO classification system will need to pay attention to this. The implication is that a new standard set of images will need to be produced and used when classifying digital images for purposes of classifying pneumoconioses [103]. Investigations into the use of digital chest imaging for classifying the pneumonconioses are ongoing. A new classification document has been posted online and a standard set of digital images is expected to be released in early 2012 [106, 107].

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Chapter 5
Environmental and Occupational Causes of Asthma

Marcos Ribeiro and Susan M. Tarlo

Abstract Airborne allergens are one of the major causes of asthma. People living in urban areas more frequently experience allergic respiratory symptoms than those living in rural areas. Seasonal exposure to outdoor allergens, (pollens, and molds) is an important cause. Identification and reduction of exposure to allergens is a very important part of the management of respiratory allergic diseases. Indoor humidity and water damage are important factors in the production of mite and mold allergens, and discarded human food items are important sources of proliferation of cockroaches and mice.

The particular plants or molds and the amount of exposure to these allergens are determined by the local climate, and published local pollen and mold counts are available to determine the time and amount of exposure. One of several causes of the rise in morbidity associated with allergic respiratory diseases is the increased presence of outdoor air pollutants resulting from more intense energy consumption and exhaust emissions from cars and other vehicles. Urban air pollution is now a serious public health hazard. The most abundant components of urban air pollution in urban areas with high levels of vehicle traffic are airborne particulate matter, nitrogen dioxide, and ozone. In addition, the earth's temperature is increasing, mainly as a result of factors like fossil fuel combustion and greenhouse gas emissions from energy supply, transport, industry, and agriculture, and climate change alters the concentration and distribution of air pollutants and interferes with the seasonal presence of allergenic pollens.

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Occupational asthma is the most common occupational respiratory disorder in industrialized countries and more than 250 agents have been reported to cause occupational asthma. The most frequent are diisocyanates, flour and grain dust, airborne particles from other foods (especially fish), colophony and fluxes, latex, animals (especially laboratory animals), aldehydes, and wood dust. For physicians caring for adult patients with asthma, an understanding of the contribution of occupational exposure to the pathogenesis of the disease is important. Prevention of new cases is the best approach to reducing the burden of asthma attributable to occupational exposures.

Keywords Air pollution • Allergy • Asthma • Environmental diseases • Occupational asthma • Climate change

Asthma is a chronic disease characterized by variable airflow obstruction, airway hyper-responsiveness (AHR) and airway inflammation, and risk of long-term airway remodeling and fixed airflow obstruction [1]; furthermore, asthma patients are hyperresponsive to triggers. However, asthma is heterogeneous in terms of its clinical presentation, natural history, and pathophysiology. Although the pathogenesis of asthma is not completely understood, it is evident that this clinical condition has a multifactorial etiology.

Because so much evidence points to environmental and occupational factors as triggers of the exuberant immune response, there has been much attention to identifying specific environmental and occupational factors that are most responsible for provoking asthma and developing strategies to minimize relevant exposures. Indeed, avoidance of environmental and occupational factors that provoke asthma, where feasible, is a logical way to improve asthma-related health and to minimize the need for long-term use of asthma medications [2].

Management of asthma requires attention to relevant environmental exposures that originate from both the outdoor and indoor environments, but those originating indoors may be more important for some patients with asthma. In some cases the risk of encountering certain environmental factors known to exacerbate asthma (e.g., dust mite) is only relevant in the indoor environment, whereas in other cases the indoor environment accounts for most of the individuals' exposure time, although the inciting factor could be found outdoors (e.g., particulate matter) [3].

Also, in contrast to the outdoors, people may have a greater ability to modify indoor environmental exposures. For example, most individuals do not have direct control over outdoor pollutant concentrations, but they may be able to decrease concentrations of specific pollutants in their homes [4].

Asthma can be provoked by a wide range of stimuli that include infectious, allergic, occupational, and environmental agents. Ambient or outdoor environmental exposure to ozone, particulate matter, sulphur dioxide, and nitrogen oxides (NO_x) has been well documented to exacerbate asthma. It is important to note that an individual's response to air pollution depends on the source and components of the pollution, as well

as on climatic agents and individual factors. Some air pollution-related episodes of asthma exacerbation are due to climatic factors that favor the accumulation of air pollutants at ground level [5] and some cities are perennially affected by black smog caused by motor vehicles.

It appears there is a link between the increase in the prevalence of allergic airway diseases and the increase in air pollution. Studies have shown the adverse effects of ambient air pollution on respiratory health [6], and exposure to components of air pollution enhances the airway response to inhaled allergens in susceptible subjects. In most industrialized countries, people who live in urban areas tend to be more affected by allergic respiratory diseases than those of rural areas [7].

Ambient or outdoor environmental exposures to ozone (O_3), particulate matter (PM), sulphur dioxide (SO_2), and NO_x are well known to exacerbate asthma [8]. Generally, investigators have examined the effect of small particles with different mass mean aerodynamic diameters (fine—PM2.5 <2.5 μm, and coarse—PM10 <10 μm, PM10—2.5), and the gases SO_2, CO, NO_x, and O_3 on the development of asthma. These pollutants can be ranked from strongest to weakest according to their effects on asthma as follows: PM2.5 > PM10 > SO_2 > O_3 > NO_x [9].

Controlled exposure studies have shown wide variability in response to the same level of exposure to a given air pollutant, even among healthy persons [10]. Similar to that of other triggers, the significance of air pollutants in asthma exacerbations varies widely from person to person. The observed increases in morbidity and mortality associated with acute and long-term increases in PM may disproportionately affect older adults and persons with preexisting heart disease [11]. Many epidemiologic and controlled exposure studies also have shown that anyone may experience symptoms and compromised lung function from exposure to ozone and PM [12].

Although the nature and concentration of outdoor pollutants vary from one area to another, the most abundant pollutants in the atmosphere of urban areas are NO_x, O_3, and respirable PM. Sulphur dioxide is an additional concern in industrial areas. The Air Quality Index for "criteria" pollutants (see Chap. 7 for more details) can be found on a number of publicly available media sources, including the Web site for the US Environmental Protection Agency, as well as Web sites maintained by many state governmental agencies, that are generally updated on a daily basis.

Specific Outdoor Environmental Exposures

Ozone

Ozone is of particular concern for patients with lung disease. This strong oxidizing compound injures lung tissue and promotes airway inflammation. Ultraviolet light from the sun drives the photochemical reactions that produce ozone from NO_x and volatile organic compounds (VOCs). Therefore, ozone levels tend to be highest in

the summer, with a broad peak from late morning to early evening. Ozone is usually generated in urban areas that have high concentrations of NO_x and VOCs, but it can be transported hundreds of miles downwind where levels may peak later in the evening or at night [13]. Approximately 40–60% of inhaled O_3 is absorbed in the nasal airways, the remainder reaching the lower airways.

There is little debate that increased ambient air ozone levels induce exacerbations of asthma, as measured by hospitalizations, rescue medication use, and symptoms [14]. These events typically occur 24–48 h after exposure to increased ozone levels. Even very low levels of ozone have been linked to increased exacerbations of asthma [15].

Exposure to increased atmospheric levels of O_3 causes decrements in lung function, increased airway reactivity to nonspecific and specific bronchoconstrictor agents and is related to an increased risk of asthma exacerbation in susceptible asthmatic patients [16].

One approach that subjects can take to decrease exposure to pollutants is to avoid or minimize outdoor activities during times when ambient air pollutants will be increased. Although outdoor air pollutants infiltrate homes and other buildings, indoor levels are generally lower than outdoor levels. The difference between indoor and outdoor levels varies with the type of pollutant and other factors, such as ventilation rates.

Particulate Matter

Airborne PM, which is a major component of urban air pollution, is a mixture of solid and liquid particles of different origin, size, and composition, among which pollen grains and other vegetable particles carrying allergens and mould spores are included. Inhalable PM that can reach the lower airways is measured as PM10 and PM2.5 [17]. Human lung parenchyma retains PM2.5, while particles >5 and <10 μm only reach the proximal airways, where they are eliminated by mucociliary clearance if the airway mucosa is intact [18].

PM is the most serious air pollution problem in many cities and towns and it appears to be the component of air pollution associated most consistently with adverse health effects. Particulate air pollution is significantly associated with enhanced mortality from respiratory and cardiovascular diseases, exacerbation of allergies, asthma, chronic bronchitis, respiratory tract infections, and hospital admissions in many geographical areas [19].

Increased exposure to respirable particulate matter (<10 μm in size) has been associated with exacerbation of asthma across the world [20, 21]. The effects of air pollutants on lung function depend largely on the type of pollutant and its environmental concentration, the duration of pollutant exposure and the total ventilation of exposed persons. Aeroallergens, such as those derived from pollen grains and fungal spores, lead to bronchial obstruction in predisposed allergic subjects and pollen is

widely used to study the interrelationship between air pollution and respiratory atopic diseases [22].

The relationship of proximity to a roadway, and presumably vehicular traffic, is correlated with increased asthma. In fact, road traffic with its gaseous and particulate emissions is currently, and is likely to remain, the main contributor to air pollution in most urban settings.

Sulphur Dioxide

SO_2 is generated primarily from the burning of sulphur-containing fossil fuel and is released into the atmosphere primarily as a result of industrial combustion of high sulphur-containing coal and oil. SO_2 has clearly been shown to induce acute bronchoconstriction in asthmatic subjects at concentrations well below those required to induce this response in healthy subjects [23].

SO_2 has a rapid effect on the lung function of asthmatic subjects, and significant responses are observed within 2 min; maximal response is seen within 5–10 min. There can also be spontaneous recovery (30 min after challenge) and a refractory period of up to 4 h, whereas repeated exposure to low levels of SO_2 results in tolerance to subsequent exposure [24].

Total emergency department visits for respiratory problems and increased hospital admission rates have been linked with increased ambient exposure to SO_2. However, in many studies, it is difficult to separate the effects of SO_2 from those of particulate air pollutants [25].

Nitrogen Oxides

Nitrogen oxides are precursors of photochemical smog; they are found in outdoor air in urban and industrial regions and, in conjunction with sunlight and hydrocarbons, result in the production of ozone (O_3). Automobile exhaust is the most significant source of outdoor NO_x, although power plants and other sources that burn fossil fuels also release NO_x into the environment. Indoors, the most significant exposure to NO_2 occurs in conjunction with the use of gas cooking stoves and kerosene space heaters. Most ambient NO_x is generated by the burning of fossil-derived fuels.

There is a strong relationship between ambient air NO_x levels and changes in lung function. NO_2 challenge enhances airway inflammation, primarily with an influx of airway polymorphonuclear cells (PMNs). These effects are most notable at higher levels of NO_2 and might affect the airway function of asthmatic subjects [26]. SO_2 also has an effect on the response to airway allergen in allergic asthmatic subjects [27].

Outdoor Allergens

Pollen and mold allergens are the predominant outdoor allergens. Tree, grass, and weed pollen are present in all regions of the United States and Canada and cause seasonal asthma exacerbations. Tree pollen is produced primarily in the spring, though the levels peak at slightly different times, depending on the regional climate. Grass pollen peaks in the summer, and weed pollen peaks in the fall. Levels are higher on dry, windy days. The seasonal peaks vary by region, so understanding the timing of pollen seasons in one's region is helpful when evaluating a patient with seasonal asthma exacerbations. Pollen grains are relatively large with a diameter ~10 μm, so would not be expected to reach the smaller airways, but following thunderstorms there may be disruption of pollen grains into smaller particles that can be inhaled into smaller airways. Outdoor fungi mainly grow in association with vegetation and the allergens are associated with smaller particles ~3 μm in diameter (from spores and hyphae). Counts are highest during hot and humid months of the year and in agricultural areas. Indoor exposures to pollen and fungal allergens from outdoors can be reduced by use of air conditioning while keeping the doors and windows closed.

Indoor Environmental Exposures

Exposure to ambient air pollutants has been shown to cause increased airway reactivity, asthma exacerbations, and respiratory symptoms, decreased lung function, and altered host defence [28]. However, because indoor air pollution concentrations can greatly exceed outdoor air pollution concentrations [29], indoor pollutants may have a greater influence on asthma. Therefore, indoor environmental exposures must be considered when evaluating patients who either have asthma or are at risk for developing asthma.

Mouse Allergen

Mice excrete urinary allergens that are carried on particles that readily become airborne. Several studies have demonstrated that almost all inner-city homes and more than three-quarters of suburban homes have detectable mouse allergen levels [30]. It is estimated that 18–50% of inner-city youth are sensitized to mouse allergen [31]. Sensitization to mouse allergen is less common in rural and suburban areas [32]. Sensitization to mouse has been causally related to early wheeze in one cohort, suggesting that mouse allergy could increase the risk of developing asthma [33].

Cockroach Allergen

The two most common cockroaches found in United States homes are the German cockroach (*Blatella germanica*) and the American cockroach (*Periplaneta americana*). Cockroach allergen is a common allergen in the inner city, where most homes contain detectable levels. At least half of inner-city homes have clinically relevant levels of cockroach allergen. As many as 30% of suburban, middle class homes also have detectable levels of cockroach allergen, but the levels in suburban homes are generally much lower than in inner-city homes [34]. Cockroach allergen can be found in high concentrations on floors, carpets, counters, and other flat surfaces, especially in rooms that contain discarded or stored food. Cockroach allergens have also been reported in bedding, although this might be from passive transport of allergens from floor dust to the bed by persons living in cockroach-infested locations.

In inner-city populations, 60–80% of children with asthma are sensitized to cockroach [35]. Sensitization to cockroach allergen has been linked to the development of wheeze in young children [33]. Cockroach allergen has also been directly linked to poorer asthma outcomes in inner-city children with asthma, including increased asthma-related healthcare utilization [36].

Pet Allergens

Pet allergens can be found in virtually all homes, but the concentrations are 10–1,000 times lower in homes without pets than in homes with pets [37]. Cat and dog allergens can also be found in a wide distribution of places, including public buildings such as schools [38]. Allergic sensitization to cat and dog is quite common, and pet allergen exposure has been linked to poorer asthma outcomes in animal-sensitized patients with asthma [39].

The combination of widespread exposure to pet allergens and high prevalence of allergic sensitization to these allergens suggests that a substantial proportion of patients with asthma are at risk for cat or dog allergen-induced asthma symptoms. In fact, several studies have directly linked animal allergen exposure to poorer asthma outcomes among animal-sensitized patients with asthma [39].

Assessing pet allergen exposure in patients is fairly straightforward and can be accomplished by taking a history focused on pet ownership, recent relocation into a home where pets had been living, and for children in particular, pet exposure at daycare. Most, but not all, relevant sources of exposure can be identified with this approach. Because furred pet allergens are airborne and adhere to clothing, it is impossible to eliminate exposure entirely. Pet removal is the only method of substantially reducing the animal allergen level, but it will not decline significantly for 4–6 months [40], so clinical benefit may be slow to realize.

Dust Mite Allergens

The two primary species of house dust mite associated with asthma are *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. The prevalence of immunoglobulin E (IgE) sensitization to mites varies with the local environment; arid environments are associated with low-level sensitization (5%), whereas up to 60% of the population can be sensitized in humid locales [41]. Dust mites are arachnids that infest bedding, carpet, upholstered furniture, and fabric. Their main food source is human skin scales, and they grow best in warm, humid environments, so they are rarely found in arid regions, such as the desert Southwestern United States, but are common in more humid regions such as the Northwestern and Southeastern United States. The allergens are predominantly found on larger particles, in the range of 10–20 μm, which rapidly settle on dependent surfaces after disturbance.

There are two major groups of mite allergens, with group 1 being derived from proteins found in the mite gut and group two being primarily male reproductive glycoproteins. A major source of mite allergens is mite fecal pellets. These allergens are found on particles that range from 10 to 20 mm in size, which means they tend to settle on surfaces and are not suspended in ambient air [42].

The prevalence of allergic sensitization to dust mites varies regionally and depends on the local prevalence of dust mites which, in turn, is highly dependent on the humidity of the climate. Like many other allergens, exposure to dust mite allergen in sensitized patients is associated with poorer lung function, greater medication requirements, and more asthma symptoms. Dust mite allergen exposure has been causally linked with the development of asthma in susceptible children [43] and with causing asthma exacerbations in sensitized individuals [44].

There is evidence that dust mite allergen leads to the development of asthma, in addition to exacerbating preexisting asthma in dust mite-sensitized patients. A prospective cohort study found that infants exposed to high levels of dust mite allergen were significantly more likely to have asthma later in childhood than were infants who were not exposed to high levels [43]. Thus, reducing dust mite allergen exposure by controlling indoor humidity, by vigorous cleaning and removing allergen reservoirs, including accumulated dust by removing, carpeting, and encasing bedding with impermeable mattress and pillow encasings would be expected to both improve asthma control in sensitized patients and prevent the development of asthma in children. However, intervention studies to reduce dust mites have shown variable results on asthma outcomes for reasons that are unclear.

Molds

Mold is a term that encompasses hundreds of species of saprophytic fungi that can be found in the indoor and outdoor environment. Molds usually require high humidity and moisture, adequate temperature, and nutrients. It is clear that IgE-mediated sensitization can occur to molds, and there is great interest in the role these allergens

play in asthma exacerbation and pathogenesis. Assessing the effects of mold exposure on asthma is complex because of the sheer number of molds, the variety of methods through which they are quantified, and the fact that molds can cause adverse health effects through multiple mechanisms. Despite these challenges, there is growing evidence that allergic responses to inhaled mold allergens are associated with increased asthma symptoms. *Alternaria*, found both indoors and outdoors, is the best studied mold in asthma. Exposure to *Alternaria* has been associated with increases in asthma symptoms, bronchial hyper-responsiveness, and severe asthma in sensitized individuals [45].

Other Rodent Allergens

In addition to mice, rats and other rodents excrete urinary allergens that are carried on small particles that readily become airborne, similar to allergens from other furred animals such as cats and dogs [46]. The allergens are pheromone-binding proteins that are thought to have a role in mating practices and are excreted in very large quantities in the urine. Although these allergens have long been known to cause occupational asthma, their role in nonoccupational asthma was only recently described [31].

Indoor Combustion (Nitrogen Dioxide)

Nitrogen dioxide is a common air pollutant, and there are many potential indoor sources of NO_2, including gas stoves, space heaters, furnaces, and fireplaces. It has been postulated that NO_2 may cause respiratory symptoms through its oxidizing potential. NO_2 has been shown to produce extracellular reactive oxygen species that can induce airway symptoms through interaction with antioxidants in the epithelial layer of the lung [47]. This may represent one mechanism through which NO_2 may cause increased respiratory symptoms in patients with allergic asthma.

In a study of inner-city children with asthma, there was a strong and significant association between higher indoor NO_2 and respiratory morbidity, including wheeze, chest tightness, breathlessness, and daytime and night-time asthma attacks [48]. NO_2 exposure has also been found to impair host resistance to respiratory viruses and bacteria, by reducing bacterial clearance and impairing innate immunity [49]. Higher personal NO_2 exposure increased the severity of virus-induced asthma exacerbations, as measured by symptom severity and peak-flow reduction [50].

Secondhand Smoke

Secondhand smoke is involuntarily inhaled tobacco smoke that contains particles and gases generated by the combustion of the tobacco, paper, and additives of

cigarettes. Secondhand smoke exposure is very common in the USA, and the causal relationship between SHS (second-hand smoking) exposure and asthma incidence and morbidity in children is well established [51]. SHS (second-hand smoking) exposure in utero through maternal smoking is linked to decreased lung function, recurrent wheeze, and increased incidence of asthma in infants [52].

Furthermore, one study [53] demonstrated an association between in utero smoke exposure and increased risk of corticosteroid resistance among adolescents with asthma, highlighting the potential long-term effects of in utero SHS exposure.

Exposure to secondhand smoke is convincingly linked to greater disease severity among children and adults with asthma [54]. Secondhand smoke is associated with worse lung function and greater airway inflammation, daytime and nocturnal symptoms, exacerbations, health care utilization, and intubation [51].

Ozone

The indoor ozone (O_3) level tends to be high only in warmer months of the year, because the level can be influenced by ozone penetration from outdoors [29]. Indoor ozone sources are uncommon, but include ionizers and ozone generators, which are sold as air-freshening or air-cleaning devices, and xerographic copy machines, found in offices and schools. Epidemiologic studies of ambient ozone and experimental studies show a significant association with asthma-related morbidity, including symptoms, health care utilization, airway inflammation, and decreases in lung function [55].

Particulate Matter

Particulate matter generated from indoor sources (such as cooking exhaust, wood-burning stoves and fireplaces, and cleaning activities that resuspend particles) may be more potent in decreasing lung function than particulate matter generated from outdoor sources [56]. Previous studies and a recent meta-analysis have concluded that exposure to high indoor particulate matter concentrations is associated with decreased lung function and respiratory symptoms in children [57].

High-efficiency particulate air (HEPA) filters have been shown to be effective in lowering the concentration of indoor particulate matter, and this may have a modest effect on reducing asthma symptoms [58].

Occupational Asthma

Work exposures are significant contributors to the burden of asthma. Work-related asthma can be broadly defined as occupational asthma (i.e., asthma caused by specific agents in the workplace), and work-exacerbated asthma (coincidental asthma that is worsened but not caused by work) [59]. There are two major forms of

occupational asthma: sensitizer-induced occupational asthma characterized by a latency period; and irritant-induced asthma characterized by rapid onset of asthma following single or multiple exposures to high concentrations of irritant compounds.

Occupational asthma is the most common chronic occupational respiratory disorder in industrialized countries, estimated to account for 5–15% of asthma cases in adults of working age, especially those with newly developed asthma [60], and a study in 13 European countries reported an OA prevalence of 10–25% among new-onset adult asthmatics [61]. It has also been reported that occupation contributes to approximately one in seven cases of severe exacerbation of asthma in a working population [62].

More than 250 agents have been reported to cause occupational asthma and the number is increasing due to the introduction of new chemicals. Although the majority of cases of work-related asthma probably represent work-exacerbated asthma, in a relevant proportion of cases asthma is actually caused by one or more agents present in the workplace [63].

Occupational sensitizers may be classified as high- or low-molecular-weight compounds. High-molecular-weight allergens have molecular weight greater than 10 kDa and are similar in many respects to common environmental allergens, such as dust mites, pollen, molds, and animal dander allergens. Low-molecular-weight agents are small organic or inorganic compounds. Low-molecular-weight chemicals can act as haptens that must be conjugated to a carrier protein to form complete antigens. However, the majority of low-molecular-weight chemicals that cause occupational asthma do so by unknown mechanisms.

The most frequent sensitizers are isocyanates, flour and grain dust, airborne particles from other foods (especially fish), colophony and fluxes, latex, animals (especially laboratory animals), aldehydes, and wood dust [64]. Development of asthma is often preceded by allergic rhinitis. Dust or low-molecular-weight compounds released into the outdoor air from the workplace can also cause asthma in the nearby communities.

High-Molecular-Weight Agents

High-molecular-weight agents are usually protein-derived antigens that cause sensitization through an IgE-mediated mechanism. Virtually all inhaled proteins of animal or plant origin are capable of causing IgE-dependent sensitization, rhinoconjunctivitis, and asthma.

Cereals and Flours

Cereals and flour are the oldest causes reported and remain, with isocyanates, the most common causes of OA. Dockworkers are exposed to various cereals and other food allergens that can cause, apart from OA, different syndromes as a result of exposure to

organic dust, including allergen-induced airway obstruction and hypersensitivity pneumonitis. Wheat is the most commonly incriminated cereal, probably because it is the most frequently encountered, but soya is highly allergenic, responsible for cases of allergy and asthma in population living in the vicinity of harbors [65]. There also is significant cross-reactivity between wheat, rye, barley, and oat flour as shown by radioallergosorbent test (RAST) inhibition studies [66].

Bakers are at risk of developing sensitization not only to various cereal flours they handle at work but also to storage mites, various other added protein products, and enzymes (α-amylase is the most common) that are added to offer better control of processing.

Laboratory Animals and Shellfish Allergy

Small animals represent a frequent cause of OA in laboratory technicians and veterinarians. Of all proteins present in the workplace, whatever their nature, proteins excreted in urine are among the most potent source of sensitization, especially proteins produced by male rats. An incidence of 8.9 per 100 person-years has been found in approximately 400 apprentices examined before and after starting exposure [67], with this figure dropping to 1.3 per 100 person-years in those employed and seen on average 8 years afterward [68], showing that onset of sensitization and symptoms is more common soon after exposure starts, with the latency period here relatively short.

Atopy is a risk factor of relatively low impact. The main personal risk factor is baseline sensitization to pet dogs and cats [67]. As for antigens in bakeries, quantification of airborne antigens is feasible with reasonable precision. Animal facilities represent a workplace where control of exposure should represent a priority because this is feasible using individually ventilated cages. Animal handlers are exposed not only to animal-derived allergens but also to endotoxin (which may play a role in the allergic response and/or directly contribute to airway inflammation).

Urinary and salivary allergens have been identified and extracted from pelts of guinea pigs, rabbits, dogs, and cats. Pelt allergens not derived from urine or saliva also have been demonstrated in these animals [69]. Rats are a common cause of laboratory animal allergy. A major source of the allergen is rat urine, and it has been identified as a 17-kDa protein of the α2μ-globulin class [70]. This protein is produced in a higher concentration in male rats, and its concentration in urine increases with age. Feeding and cleaning of cages increase exposure to rat allergen; exposure also is influenced by the type of cage and litter used. Exposure to larger animals such as cows is also a common cause of OA and is the leading cause of OA in Finland [71].

Various fishes [72] and shellfish can cause OA, especially crab, for unknown reasons, more often than lobster. Both species are intensively harvested in waters off most parts of the northeastern coast of North America [73]. Allergic sensitization and occupational asthma have been reported in the seafood processing industry in oyster, prawn, and fish workers [74].

Natural Rubber Latex (Latex)

Latex allergy caused a real epidemic of allergies and OA in the 1980s. Allergic sensitization causing life-threatening anaphylactic reactions has been documented in patients as well as workers. Health professionals are affected by skin and anaphylactic reactions as well as asthma. The prevalence of OA was 2.5% in 1 study [75]. Diagnosis was initially hampered by the lack of approved satisfactory and safe extracts for skin testing. Adequate reduction of this allergen in workplaces provided proof that environmental control (e.g., use of low-latex content gloves, low-powdered gloves, or no latex gloves) can considerably reduce the number of cases. This has been the case in health care workers who are nowadays much less frequently affected.

Natural rubber latex contains at least ten important allergens and several other minor allergens. Ten latex proteins have the designation of allergens (Hev b 1, 2, 3, 4, 5, 6.01, 6.02, 6.03, 7, and 8). Prohevein (hev b 6.01) and hevein (hev b 6.02) are major latex allergens important in latex allergy in health care workers. Hevein is the major latex protein responsible for the association between latex allergy and hypersensitivity to foods, especially avocado, banana, chestnut, fig, and kiwi [76].

Enzymes

Before latex allergy became a major cause of OA in the 1980s, enzymes presented a major threat of allergic sensitization, especially in the detergent industry, in the 1970s. The prevalence of sensitization to enzymes derived from *Bacillus subtilis*, alcalase and maxatase, reached levels of 20–60% at the time. Although adequate control of the environment through encapsulation has greatly reduced the risk of sensitization, cases continue to be reported. Enzymes were the first occupational sensitizer for which control of the environment was convincingly shown to reduce the risk greatly. A multitude of plant-derived and microbe-derived enzymes are used in the workplace, and many have been reported to cause sensitization and asthma.

Agriculture and Horticulture

Various occupational allergens of plant and flower origins, beans and gums, can cause OA. Greenhouse workers, who represent a high-risk group, have been the focus of epidemiologic surveys because they represent a large population and the environment can be characterized well [77].

Farmers are at risk for occupational asthma from several high-molecular-weight allergen sources. Workers involved in the poultry industry may develop occupational asthma from exposure to airborne contaminants present in confined areas. Such contaminants include skin and feather debris, insect parts, aerosolized feed, and poultry excreta [78].

Low-Molecular-Weight Agents

Low-molecular-weight chemicals can be incomplete antigens (i.e., haptens) that must bind to autologous or heterologous proteins to become immunogenic. New LMW agents are continuously recognized as inducing OA, in most cases through an IgE-independent mechanism.

Some low-molecular-weight agents, such as acid anhydrides, and some metals, such as platinum salts, induce asthma through an IgE-associated mechanism, but for a large number of agents of this class, the mechanisms of induction of asthma remain unknown.

Anhydrides

Trimellitic anhydride (TMA), phthalic anhydride, hexahydrophthalic anhydride, himic anhydride, and tetrachlorophthalic anhydride (TCPA) are highly reactive low-molecular-weight chemicals. They are important in the manufacture of epoxy resins, which have multiple uses in the production of plastics, adhesives, molding resins, and surface coatings. Exposure in the workplace to these chemicals may be in the form of either fumes emitted from heated resins or powdered chemicals that are added to reactions.

Phthalic anhydride has long been known to cause OA and rhinitis. TMA exposure is associated with a spectrum of lung diseases: asthma, rhinitis, late respiratory systemic syndrome, and pulmonary disease—anemia syndrome [79]. As many as 2.5% of workers exposed to TMA and 8.8% of workers exposed to various anhydrides may show work-related respiratory symptoms. A significant association has been found between HLA antigens DR3 and specific IgE antibodies to TMA.

Metals

Metals in the first series of the periodic table are more potent sensitizers compared with the rest, but cases of OA caused by metals mostly come from platinum and aluminum exposure. Complex platinum salts, particularly the halides, are more potent in inducing sensitization and asthma than any other metallic salts [80]. In some chemical plants, the cumulative risks for sensitization can be as high as 51% within 5 years [81]. Smoking is a strong risk factor for a positive skin prick test response to these, but not atopy or bronchial hyper-responsiveness. The HLA-DR3 phenotype has been associated with a significant increased risk of skin sensitization to platinum salts.

The prevalence of sensitization correlates closely with OA. Skin prick testing has a high sensitivity and specificity for detecting patients with complex platinum salt-induced OA. A low concentration of sodium hexachloroplatinate has been recommended for skin testing to avoid false-positive reactions [82].

Diisocyanates

Diisocyanates are highly reactive low-molecular-weight chemicals used in the manufacture of polyurethane foams, automobile and spray paints, and plastics. The more commonly used diisocyanates include toluene diisocyanate (TDI), methylene diphenyldiisocyanate, hexamethylenediisocyanate, and naphthalene diisocyanate. High concentrations of TDI can cause an acute inflammatory reaction. Symptoms may develop immediately or up to 8 h later and are characterized by cough, dyspnea, and chest tightness. Exposure to lower concentrations of TDI induces occupational asthma in up to an estimated 5–10% of exposed workers [83].

In many parts of the world, diisocyanates are the most common cause of OA. All these chemicals have N=C=O groups that are highly reactive and explain their sensitizing properties. The prevalence of diisocyanate-induced OA has been reported to be up to 5 to 10% but in recent years, lowering the permissible concentration from 20 to 5 ppb, and reduced use of the volatile diisocyanates may have reduced cases [84]. Dermal exposure has also been postulated as a reason for sensitization.

The pathogenesis of TDI-induced asthma is unclear. An IgE-mediated immunologic mechanism was suggested by some studies [85]. However, other studies demonstrated that only 3–18% of individuals with TDI-induced asthma had hapten-specific IgE antibodies to TDI conjugates [86].

Skin testing with diisocyanate-protein carrier extracts in groups of symptomatic exposed workers has shown low diagnostic sensitivity. Despite the failure to frequently demonstrate an IgE-mediated mechanism in TDI-induced asthma, the findings that individuals sensitized to TDI may react to very low levels, non-irritant and that there is a latent period between the beginning of exposure and the development of asthma symptoms are suggestive of an allergic mechanism.

Cleaning Agents

In many population-based studies, exposure to cleaning agents at work has consistently been shown to be associated with increased risks of asthma after adjusting for confounders [87]. Many cleaning and sterilizing agents can cause OA. The most notable example is glutaraldehyde, which is used extensively for disinfecting heat-sensitive equipment such as fiber-optic endoscopes and also for developing radiographs. Health care workers are known to be at risk for exposure to a number of sensitizers in addition to cleaning agents at work.

Relatively little is known about the risk factors, exposure levels, clinical features, and pathogenetic mechanisms of asthma related to cleaning agents. Professional cleaners are exposed not to one agent but to many, such as bleach, ammonia, and hydrochloric acid. Most cleaning agents are low-molecular-weight compounds, and it is not clear whether they induce the production of specific IgE antibodies. Many are irritants and may interact with sensitizers to induce asthma.

Wood Dusts

Various types of wood, including western red cedar, oak, mahogany, and boxwood have been associated with occupational asthma. Most cases of OA caused by wood dusts have been published as case reports, with the exception of OA caused by Western red cedar (*Thuja plicata*) [88]. The prevalence of work-related asthma in Western red cedar sawmills ranges from 1.6 to 13.5% and is directly related to the level of exposure. The permissible concentration of Western red cedar dust has currently been reduced from 10 to 1 mg/m^3.

The agent responsible for asthma from Western red cedar has been identified as plicatic acid, which is a low-molecular-weight compound. The clinical picture and outcome have been well described, and the pathology is similar to diisocyanate-induced OA. As for OA caused by diisocyanates, the mechanisms responsible for red cedar asthma are still unclear but are likely a combination of immunologic and nonimmunologic factors [89]. Certain HLA class II antigens are associated with predisposition and others with protection.

Summary

In recent years, there has been a global increase in the prevalence of asthma. This has coincided with many changes in outdoor and the home environment, resulting in changes to the quality of indoor and outdoor air. Management of asthma requires attention to environmental exposures both indoors and outdoors. Control of the environment requires attention to exposures that originate from both the outdoor and indoor environments. Urbanization, with its high levels of vehicle emissions and westernized lifestyle, tends to be more associated with the disease than rural living. The indoor and outdoor environments notably contain particulate matter, NO_x, secondhand smoke, O_3, and allergens from furred pets, dust mites, cockroach, rodents, and molds.

Many substances encountered in the workplace may induce asthma and rhinitis. Occupational allergens of high molecular weight include, among others, animal danders; urine proteins; enzymes of animal, plant, fungal, and bacterial origin; cereal grains; flour; and latex. Low-molecular-weight agents are often reactive chemicals that can act as haptens and require covalent binding to host proteins to become allergenic. These agents are less well-characterized as allergens and include diisocyanates, acid anhydrides, wood dusts, metal salts, and others.

This review provides a basis for understanding the interactions between health and the indoor, outdoor and occupational environment, enabling healthcare professionals to advise patients on the actions that can be taken to reduce exposure to triggers in homes and workplaces.

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Chapter 6
Hypersensitivity Pneumonitis

Lawrence Ho and Ware G. Kuschner

Abstract Hypersensitivity pneumonitis (HP) is a complex pulmonary disease caused by an immune reaction after respiratory exposure to a wide range of antigens including microbial, plant/animal protein, and low molecular weight chemicals. The diagnosis of HP is difficult and the disease likely remains under diagnosed. Symptoms typically develop after repeated exposure to an etiologic agent and can present abruptly or insidiously. Clinical suspicion and classic radiographic findings are usually sufficient to establish the diagnosis. However, lung biopsy may be required if the diagnosis is in question. The cornerstone of management is avoidance of the inciting antigen, but corticosteroids and even other immunosuppressive agents have been used in severe, rapidly progressing cases. When diagnosed early, HP may be reversible but chronically exposed individuals may develop pulmonary fibrosis and end stage lung disease.

Keywords Hypersensitivity pneumonitis • Extrinsic allergic alveolitis • Non-caseating granuloma • Farmer's lung

Introduction

Hypersensitivity pneumonitis (HP), also known as extrinsic allergic alveolitis, is an antigen-driven "allergic" and inflammatory lung disease that results from recurrent exposure and subsequent sensitization to a wide variety of organic aerosols and

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chemical antigens [1]. Acute HP is characterized by a constellation of signs and symptoms that mimic infectious pneumonia and include the abrupt onset of cough, dyspnea, chest tightness, fevers, chills, headaches, malaise, and myalgias upon exposure to the inciting agent. Acute HP includes a spectrum of pathological findings including granulomatous inflammation and interstitial, bronchiolar and alveolar filling processes. HP is often self-limited and reversible when the exposure is recognized early. However, unrecognized, persistent exposure to an offending antigen can result in the development of emphysema, granulomatous lung disease, and eventually interstitial fibrosis; features that characterize chronic HP. Initially associated with farming, HP was subsequently associated with a variety of environmental settings and etiologic antigens. Although many presentations and exposures related to HP have been described, diagnosis can be challenging, as there is neither a universally accepted case definition nor a "gold standard" diagnostic test.

Etiology

The list of potential causes of HP is vast and continuously growing with over 300 agents linked to HP [2]. Many occupational and environmental exposures have been implicated and workers in agricultural, veterinary, and the plastic-making industry may be at increased risk [3]. The major causes can be arranged into three broad categories, including microbial agents, animal proteins, and low molecular weight chemicals. Examples of some of these major causes are listed in Table 6.1.

Microbial Agents

Causative microorganisms include bacterial, fungal, and protozoan. One the most common bacteria are the thermophilic *Actinomycetes* [4]. These gram-positive filamentous bacilli thrive in moist and warm conditions (50–60 °C) [1]. They secrete enzymes that decay vegetable matter such as mushroom compost (mushroom worker's lung), sugar cane (bagassosis), and hay (farmer's lung disease). These bacteria and others are also often found in stagnant warm water such as humidification equipment or ventilation systems (humidifier lung). Many other bacteria have been implicated in HP, including gram negative rods and others [1]. For example, *Mycobacterium avium* colonization of heated water has been implicated in causing a presentation of HP known as hot tub lung [5].

Fungi are often found in indoor sites such as wallpaper, upholstery, shower curtains, window moldings, and garbage containers. Fungi commonly found in these locales, which have been implicated in HP, include *Aspergillus, Penicillium,*

Table 6.1 Examples of agents causing HP

Agent	Source	Disease
Microbial agents		
Thermophilic actinomycetes	Moldy hay	Farmer's lung
	Warm water	Humidifier lung
Thermoactinomyces sacchari	Sugar cane	Bagassosis
Thermoactinomyces vulgaris	Mushroom compost	Mushroom worker's lung
Mycobacterium avium complex	Warm water	Hot tub lung
Mycobacterium sp.	Metal-cutting fluid	Machine worker's lung
Aspergillus clavatus	Moldy barely	Malt-worker's lung
Aspergillus sp.	Tobacco mold	Tobacco-worker's lung
Penicillium casei	Cheese mold	Cheese-washer's lung
Penicillium frequentans	Moldy cork	Suberosis
Aureobasidium pullulans	Moldy sequoia dust	Sequoiosis
Trichosporon cutaneum	Mold in Japanese homes	Summer-type HP
Avian proteins		
Proteins in avian feces, feathers	Various birds	Bird fancier's disease
Animal fur protein	Animal fur	Furrier's lung
Mollusk shell protein	Mollusk shell dust	Oyster shell lung
Low molecular weight protein		
Isocyanates	Plastics, paint	Paint-refinisher's lung
Anhydrides	Paint	Plastic worker's lung

Cladosporium, Rhizopus, and *Candida* [6]. In Japan, a common form of this disease, summer-type HP, associated with *Trichosporon asahii*, results from water-damaged tatami mats [3]. *Aspergillus*, which is commonly found in nature, has been linked to disease in malt and corn workers as well as being associated with farmer's lung (*Aspergillus* species in hay). *Penicillium* has been associated with HP in cork, pear moss, and cheese workers.

Animal Proteins

Avian antigens are complex high and low molecular weight proteins found in bird droppings, serum, and feathers. These are the most common animal proteins associated with HP. The bloom (a fine dust that coats bird's feathers) of pigeons and parakeets is most frequently implicated [7]. Animal handlers such as veterinary and laboratory workers are at increased risk for exposure to the avian antigens. However, exposure to live birds is not required to develop the disease; HP has been associated with exposure to these proteins from duvets and feather pillows [8]. Other proteins that have been reported to cause HP are derived from animal fur used to make garments and mollusk shells [9].

Low Molecular Weight Chemicals

Low molecular weight chemicals appear to cause HP by binding with endogenous proteins to form haptens [4]. Although they are less commonly implicated than biological antigens in HP, some of these inorganic chemical antigens are widely used in industry. One such class of chemicals are the isocyanates, which are used in the production of adhesives, polyurethane foam, and paints. Other chemicals implicated include acid anhydrides, pyrethrum, and Pauli's reagent [3].

Epidemiology

Data pertaining to HP are relatively limited as there are only a small number of cohort or population-based studies and only a few countries with registries for HP or interstitial lung disease (ILD). Therefore, the worldwide prevalence remains unknown. Also, reports of disease incidence, prevalence, and attacks rates are varied and sometimes conflicting depending on the populations studied. Even investigations on the two most documented types of HP, farmer's lung and bird fancier's disease, are logistically difficult as the case definition of the disease is not firmly established and the at-risk population is unknown. HP is likely under diagnosed as only the most severe cases generally prompt further investigation such as radiographs, bronchoscopy, or lung biopsy [10]. In addition, there is likely misclassification of disease; a survey of hospital discharge final diagnostic classifications noted 73% of cases were falsely classified [11]. Given all of these intricacies, a complete understanding of the prevalence, mechanism, and presentation of HP have been elusive.

In one report, the most common exposure leading to HP was birds followed by hot tubs—accounting for 34 and 21% of the cases, respectively. Farmer's lung only accounted for 11% of those cases, and in a quarter of the cases, no cause was identified [12]. Population-based studies have estimated that HP composes 4–13% of all ILDs [13]. The prevalence is higher in high-risk populations with questionnaire surveys of farming communities noting prevalence rates from 2 to 20% [14]. There is a higher prevalence in non-smokers with occupations, lifestyles, or hobbies that repeatedly expose them to known inhalation antigens.

Pathogenesis

The pathogenesis of HP involves an interaction of immune-complex-mediated (type III) and T-cell-mediated (type IV) hypersensitivity reactions [15]. Inhaled antigenic particles with a diameter less than 3 μm can reach the distal pulmonary parenchyma. Repeated exposure to these airborne particles leads to antibody production. Binding with antibodies forms an immune complex which fixes complement and results in

the elaboration of inflammatory mediators by alveolar macrophages. The activated macrophages also secrete interleukin (IL)-12 and promote differentiation of T-cell lymphocytes to Th1. Th1 produces interferon-γ, which further stimulates macrophages to produce IL-1 and tumor necrosis factor-α (TNF-α) [3, 15–17]. Recent investigations have also suggested that IL-17 is involved as increased levels of IL-17 are found in the lungs of mice exposed to the HP antigen, *Saccharopolyspora rectivirgula* [18, 19]. Also, the genetic depletion or antibody-mediated depletion of IL-17 has been shown to protect against HP by reducing lung inflammation [20]. These reactions cause injury to the lung and promote the formulation of granulomas, and, if left untreated, result in parenchymal lung fibrosis.

The hallmark of HP is the presence of activated T lymphocytes in the bronchoalveolar lavage (BAL) [21] and lung biopsy evidence of interstitial mononuclear cell infiltrate. Recurrent antigen exposure leads to CD8+ as well as the aforementioned Th1-mediated inflammation. The CD4+/CD8+ ratio in the BAL is usually reduced. However, these ratios vary widely and may even be elevated in chronic disease, and thus are not helpful diagnostic information [3, 21].

The sequence of cellular events that occur in the lung has been evaluated through analysis of BAL constituents. Initial contact with the offending agent leads to an influx of neutrophils. The neutrophilic predominance generally peaks at 48 h [22, 23]. Neutrophils are essential in granuloma formation as well as in the development of emphysema. They have been found to secrete soluble factors leading to granuloma formation [24] and elastase which breaks down elastic fibers and can lead to emphysema [25]. Between 48 and 72 h, there is an influx of lymphocytes and macrophages [23]. These macrophages play an important role throughout this process as they act as antigen presenting cells and secrete cytokines which enhances the inflammatory response [26, 27]. The lymphocytes are notable in BAL long after exposure ceases, while neutrophils usually subside within weeks [28]. Both neutrophils and macrophages produce reactive oxygen species which contribute to the tissue damage and eventually fibrosis [29].

Host factors also appear to play both a protective and promoting role in the development of HP [10]. The observation that HP is more prevalent among nonsmokers has led to speculation that there may be a protective mechanism associated with cigarette smoking. Nicotine decreases total BAL cells such as lymphocytes and also decreases the expression of several inflammatory mediators such as tumor necrosis factor (TNF)-α [30, 31]. However, cigarette smokers who develop HP generally have a worse prognosis, perhaps attributable to the elevation of CD4+ T cells and free oxygen radicals [32–34]. Viral infections may be a promoting factor as many patients with HP present initially with symptoms similar to a respiratory infection. Viral antigens have been expressed more readily in lung tissue of patients with HP compared to normal individuals [35]. Also, mice infected with a parainfluenza virus are more responsive to *S. rectivirula* antigens [36]. Other factors that may influence susceptibility to developing HP include genetic polymorphisms of class II human leukocyte antigen (HLA), TNF-α, transporter associated with antigen processing protein-1 (TAP-1), and tissue inhibitor of metalloproteinase-3 (TIMP-3) [37–39].

Clinical Features

The clinical manifestations of HP have been classically defined into three temporal categories: acute, subacute, and chronic. However, there is significant overlap among these groups. A cluster analysis of a large group of HP patients failed to identify the three categories in the HP study group protocol. Given difficulties such as this, there have been suggestions of reclassifying the disease into two groups based on clinical findings, pulmonary function studies and computed tomography (CT) findings [40]. In this chapter, the clinical features are described based on the classic definitions.

In acute HP, symptoms are attributed to intense and intermittent antigen exposure. Symptoms typically occur 4–12 h after exposure and peak at 6–24 h. These symptoms include the abrupt onset of influenza-like respiratory and constitutional symptoms including cough, dyspnea, chest tightness, fevers, chills, headaches, malaise, and myalgias. Physical examination findings include a distressed appearance, fever, tachypnea, tachycardia, and inspiratory crackles. Laboratory findings include peripheral leukocytosis and neutrophilia. Symptoms generally last from hours to days without repeat exposure to the offending antigen; however, acute respiratory failure may occur in severely ill patients. The acute form of HP has been reported to be the most common clinical presentation [39, 41], although these cases may also be more easily detected and diagnosed.

Subacute and chronic forms usually have insidious presentations and their distinction is often blurred [42]. Some differences include the length of symptom development. In subacute HP, symptom onset ranges from weeks to 4 months while the chronic form takes over 4 months for symptoms to develop [3]. Others have distinguished chronic HP from subacute by describing an irreversible and fibrotic progression [39, 43]. Cough and exertional dyspnea are the most common symptoms in both forms, while fatigue and weight loss are more prominent in chronic HP. Physical examination reveals basilar crackles in subacute HP. In progressive forms of chronic HP, cyanosis, clubbing, severe dyspnea, and evidence of right-sided heart failure have been reported [4].

Radiographic Features

A chest radiograph is usually the first step in the clinical investigation of patients presenting with symptoms of HP. Radiographic findings differ depending on the stage of the disease and can be essentially normal, particularly in early disease. Diffuse ground glass opacities (GGO) or a fine micronodular pattern is seen in acute disease. These abnormalities resolve over 4–6 weeks with discontinuation of the exposure. In contrast, in the chronic form of HP, the findings include reticular opacities, honeycombing, and volume loss with a gradual progression of fibrosis in the mid and upper lung zones [44, 45].

CT scanning has improved sensitivity over traditional chest radiography. Abnormalities are seen in greater than 90% of patients with HP, but may be minimal

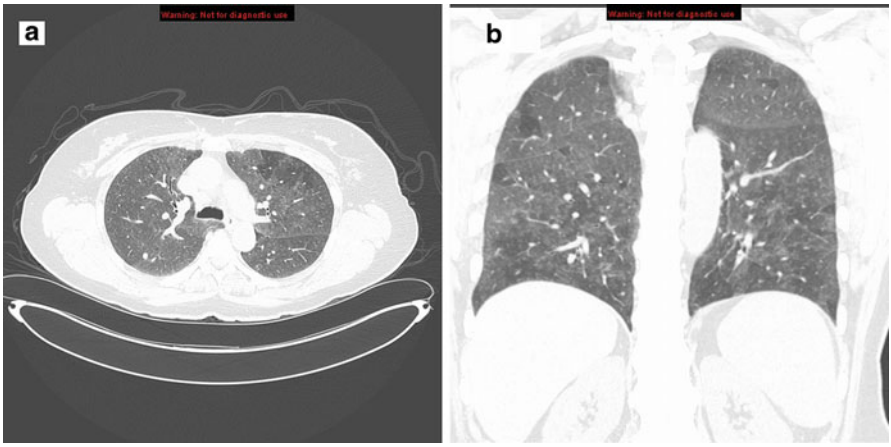

Fig. 6.1 A 66-year-old woman with HP. (**a**) Poorly defined centrilobular nodules right upper lobe, ground glass opacities, and areas of airtrapping (**a**). (**b**) Coronal reformat with ground glass opacities and airtrapping predominately at the bases. (Courtesy of Dr. Ann Leung, Stanford Medical Center, Stanford, CA)

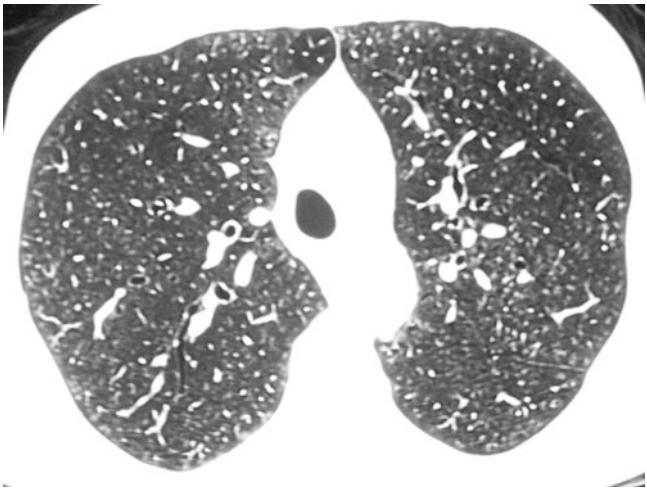

Fig. 6.2 A 30-year-old man with subacute HP. His CT demonstrates multiple small centrilobular nodules with accompanying subtle ground glass opacities. (Courtesy of Dr. Paul Stark, San Diego VA Medical Center, San Diego, CA)

in early disease [46]. Classic findings on CT scan include GGO, air trapping with mosaic attenuation, and centrilobular nodules (Figs. 6.1 and 6.2). Generally, these findings are noted in an upper/middle lung distribution. Sometimes, GGO may be the only finding noted on CT scan and represents active alveolitis or fine fibrosis.

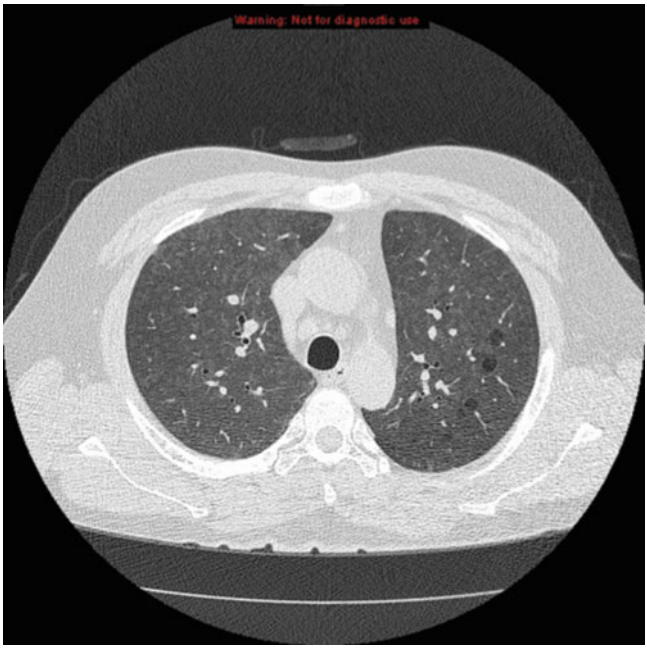

Fig. 6.3 A 45-year-old man with mushroom worker's lung demonstrating ground glass opacities and cysts. (Courtesy of Dr. Ann Leung, Stanford Medical Center, Stanford, CA)

The GGO are usually bilateral and symmetric [47] (Fig. 6.3). Bronchiolar inflammation and obstruction cause the hypoattenuated regions on CT scan that represent air trapping. The centrilobular nodules are poorly defined and less than 5 mm in diameter. The centrilobular nodules likely represent peribronchiolar interstitial inflammation and/or cellular bronchiolitis [48]. Occasionally focal consolidation can be present representing organizing pneumonia. Mediastinal lymphadenopathy is rare but is occasionally noted [4].

Chronic HP is associated with reticular lines, fibrosis, honeycomb changes, and traction bronchiectasis in a bronchovascular distribution. There may be relative sparing of the extreme apices and bases (Fig. 6.4). These findings may be often indistinguishable from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonitis. Emphysema may be a more common finding in chronic HP, especially for farmer's, than fibrosis; however, fibrosis on CT scan portends a poorer prognosis [47, 48].

Pathologic Features

The cardinal histopathological manifestations of hypersensitivity pneumonitis include the classic triad of (1) interstitial, poorly formed, non-necrotizing granulomas; (2) mononuclear bronchiolitis; and (3) diffuse cellular interstitial infiltrates.

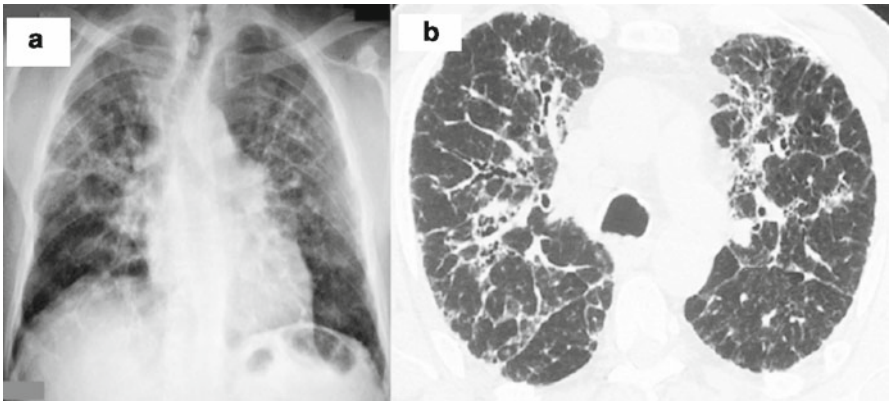

Fig. 6.4 A 75-year-old man, bird fancier with chronic HP. Images show upper lobe scarring and fibrosis. (**a**) The chest radiograph shows coarse bilateral mid and upper lung scarring with architectural distortion. (**b**) The CT show coarse reticular opacities with mild traction bronchiectasis and subtle centrilobular and peri-lymphatic nodules. (Courtesy of Dr. Paul Stark, San Diego VA Medical Center, San Diego, CA)

At scanning magnification, the bronchiolocentric and interstitial distribution is appreciated along with the temporal uniformity of the process (Fig. 6.4). Areas of uninvolved parenchymal can be discerned except in severe cases. The interstitium is expanded by modest accumulations of lymphocytes and plasma cells along with the loosely formed granulomas. Both the peribronchiolar and alveolar interstitium are affected. Granulomas can also be found within the interstitium, near small veins and arteries or within the mucosal layer of the bronchioles. They may lack the well-delineated arrangements of sarcoid-type granulomas and typically are composed of scattered epithelioid histiocytes and mononuclear inflammatory cells, although well-formed granulomas may also be observed [49–51] (Fig. 6.5). Other cell types include multinucleated giant cells, and giant cells with cholesterol clefts and giant cells with clustered calcifications or Schaumann bodies (Fig. 6.5). The airspaces are usually devoid of cells or debris but clusters of foamy macrophages indicating airway obstruction can be occasionally seen. The inflamed bronchioles display moderate numbers of mononuclear inflammatory cells within the mucosa and walls of the terminal bronchioles (so-called lymphocytic bronchiolitis) (Fig. 6.5). In more than half the cases, foci of organizing pneumonia with loose granulation tissue plugs in the distal airways are found. Features that are typically not found in HP include eosinophils, necrosis, and hyaline membranes and their presence should raise other diagnostic considerations.

The constellation of findings is similar irrespective of the inciting agent; however, the complete triad is not always present. Careful examination of all the biopsy pieces often yields the diagnostic findings. Pathologic features also vary depending on the stage of the disease. For example in the acute stages, neutrophils, fibrinous exudates, and vasculitic injury has been reported, while in the chronic phase, granulomas are seen in less than 50% of chronic cases [52–54].

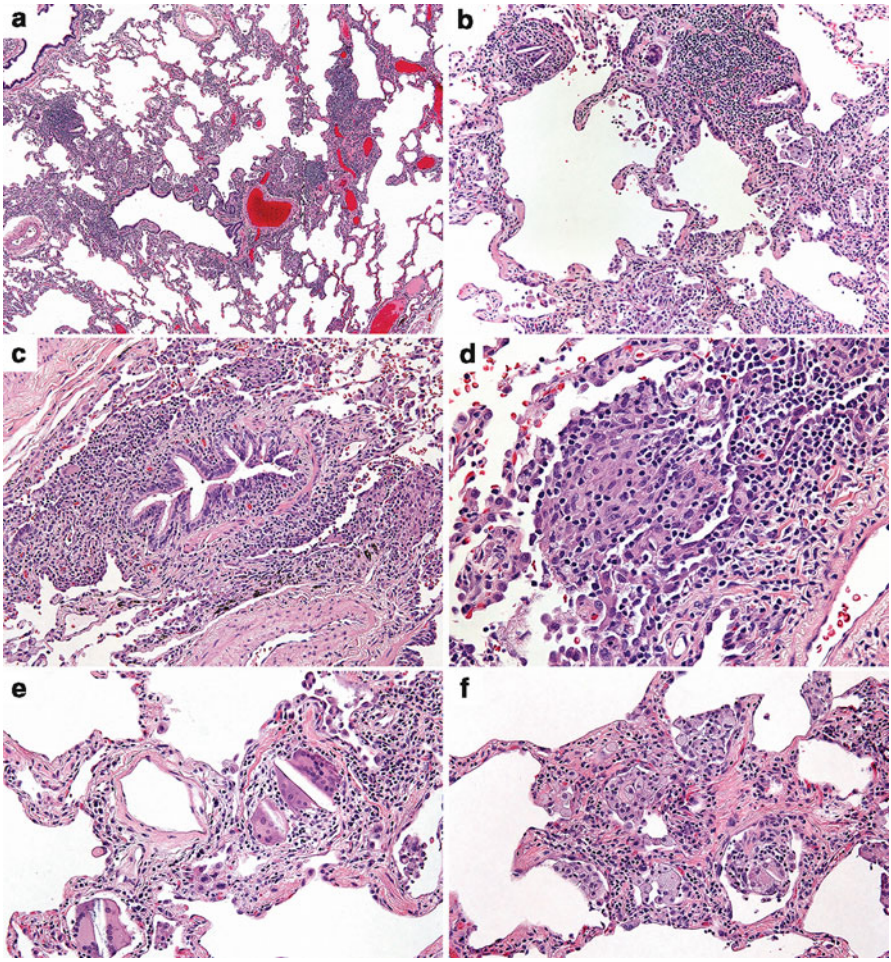

Fig. 6.5 Subacute HP: (**a**) low-power magnification showing bronchiolocentric and interstitial distribution of inflammatory infiltrates (H&E×60). (**b**) Interstitial expansion of lymphocytes and giant cells with cholesterol clefts (H&E×100). (**c**) Lymphocytic bronchiolitis exhibiting moderately dense mononuclear cells within the mucosal and mural layers of the terminal bronchiole (H&E×200). (**d**) Poorly formed non-necrotizing granulomas composed of scattered epithelioid histiocytes, macrophages, and lymphocytes within the alveolar interstitium (H&E×400). (**e**) High-power magnification of multinucleated giant cells containing either cholesterol sterols or calcified debris (Schaumann body) (H&E×400). (**f**) Airspace accumulations of foamy macrophages reflect the obstructive changes produced by bronchiolar inflammation (H&E×400). (Courtesy of Dr. Gerald Berry, Stanford Medical Center, Stanford, CA)

In the chronic fibrotic form of HP, there is an overlap of histopathological findings with other forms of chronic idiopathic ILD and their distinction can be problematic. The lungs are contracted and fibrotic (Fig. 6.6). The distribution of honeycomb change can be variable and in one post-mortem study the cystic spaces ranged from

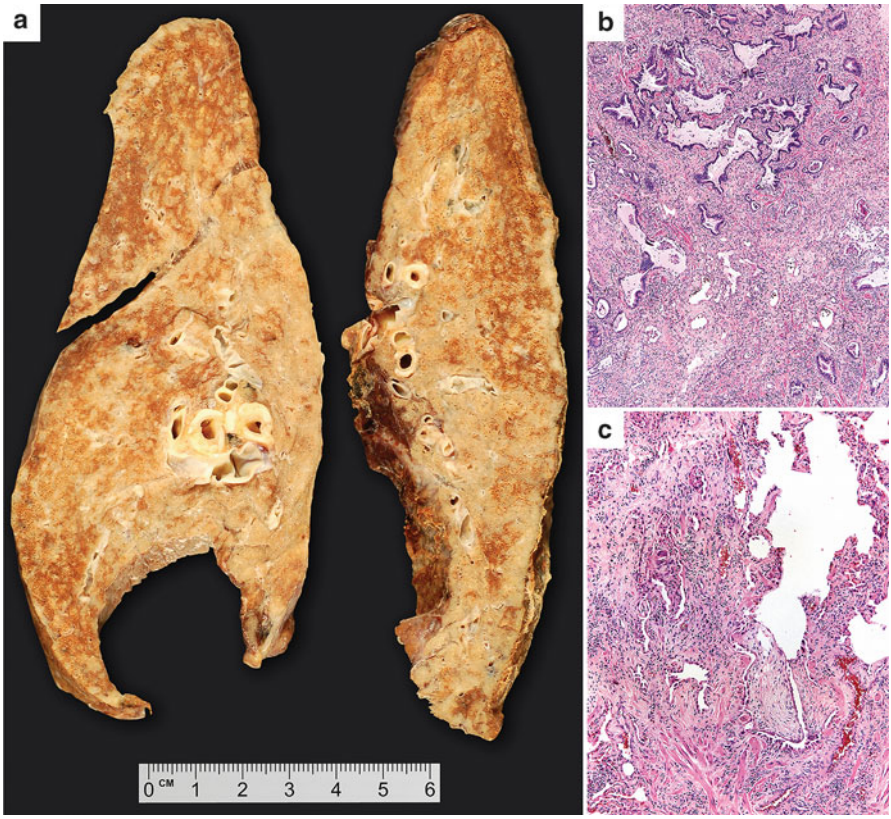

Fig. 6.6 Chronic fibrotic phase of HP: (**a**) sagittal sections of right and left lungs at transplantation. Both lungs are uniformly fibrotic, noncompliant, and contracted. Diffuse fine fibrosis and honeycomb changes are seen throughout all the lung fields. (**b**) Low-power magnification showing honeycomb change with restructured airspaces lined by bronchiolar metaplastic epithelium and dense collagenous fibrosis (H&E×60). (**c**) Foci of fibroblastic activity admixed with chronic inflammation and mature fibrosis (H&E×200). (Courtesy of Dr. Gerald Berry, Stanford Medical Center, Stanford, CA)

2 to 4 mm in diameter [52]. In most cases, the honeycomb changes predominantly involved the lower lobes or both upper and lower lung zones. Subpleural or interlobular fibrosis was present in most of the cases. Churg et al. described three histological patterns in chronic HP: (1) homogenous linear fibrosis resembling fibrotic nonspecific interstitial pneumonia (NSIP); (2) usual interstitial pneumonia (UIP)-like pattern with a patchy subpleural distribution, fibroblastic activity, and honeycomb change (Fig. 6.6); and (3) irregular fibrosis in a peribronchiolar distribution [55]. The airway-centered interstitial fibrosis commonly involves the respiratory bronchiole while fibroblastic foci are frequently observed at the margin of peribronchiolar and alveolar duct fibrosis. These findings may suggest continuous antigen exposure [49]. Bridging fibrosis between peribronchiolar and perilobular areas is

the histopathologic hallmark of chronic disease. In one study, bridging fibrosis was found in 70% of cases with chronic summer-type HP [49, 55, 56]. In the fibrotic stage, granulomas may be either sparsely scattered or absent. Finally, emphysema is also a prominent histopathologic component in patients with insidious onset of symptoms, specifically chronic farmer's lung [57].

Diagnostic Approach

The diagnosis of HP remains a challenge given the varied presentation and wide spectrum of environmental and occupational exposure settings. Numerous diagnostic criteria and recommendations have been published [15, 41, 58, 59], but there remains no validated criteria or gold standard. Therefore, the diagnosis depends on a firm clinical suspicion, detailed exposure history, and a combination of imaging, histopathologic, and physiologic findings.

A careful clinical history is paramount as it often suggests a temporal relationship between symptoms and certain activities. The history should also include a detailed work history together with a chronology of current and previous occupations. Exposure to pets and other domestic animals, recreational activities, medications, use of humidifier, and hobbies including gardening or lawn care should be carefully assessed.

Pulmonary Function Tests

Pulmonary function tests (PFTs) are utilized primarily to describe the physiologic abnormalities and associated impairment as well as guide therapy by aiding in the selection of who should receive corticosteroids [8]. There are no factors to differentiate HP from other ILDs based on PFTs alone [59]. The abnormality on PFTs is typically restrictive in acute disease with decreased forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity (DLCO) [58]. However, obstructive patterns may be present, especially in cases of farmer's lung and subacute or chronic disease states. Hypoxemia is also often present. After an acute episode, PFTs can normalize. Therefore, once the diagnosis of HP is established, serial PFTs should be performed to assess response to therapy and guide future treatment decisions [1].

Laboratory Tests

Peripheral leukocytosis as well as elevated serum inflammatory markers is often noted. These inflammatory markers include erythrocyte sedimentation rate, C-reactive protein (CRP), and immunoglobulins—IgG, IgM, and IgA. Specific IgG

precipitating antibodies can be helpful in diagnosis. Once thought to be the hallmark finding in HP, these precipitating antibodies are neither sensitive nor specific for the disease and the absence of these antibodies does not exclude HP [4]. They indicate potential exposure and are currently utilized as supportive evidence for the diagnosis. The fact that antibodies are not always identifiable suggests that some are still unknown. There are several methods used to test for these serum-specific precipitating antibodies, including immunodiffusion, immunoelectrophoresis, or enzyme-linked immunosorbent assay. Antigens available for testing include pigeon and parakeet sera, dove feather antigen, *Aspergillus* sp., *Penicillium, S. rectivirgula*, and *Thermoactinomyces viridians* [10].

Inhalation Challenge

Inhalation challenges have been performed to determine if there are any reactions to specific antigens or environments in patients with suspected HP. During the antigen challenge, the patient inhales allergens via a nebulizer or is placed in an environment where the antigen is present [60]. This test lacks standardization in both inhalation protocols and the criteria to define a positive response. The criteria for a positive response usually include respiratory or systemic findings, especially fever 4–10 h post-exposure. Other findings include decreased DLCO, decreased FVC, increasing radiographic abnormalities, worsening alveolar-arterial oxygen gradient, and elevation of CRP. Due to these difficulties, inhalation challenges are rarely used except in research settings [60, 61].

Bronchoalveolar Lavage

BAL is both a safe and sensitive test to confirm the presence of alveolitis [62]. There is usually a striking lymphocytosis, without neutrophilia or eosinophilia. The lymphocytosis is usually 30–70% in nonsmokers and >20% in smokers [63]. A normal lymphocyte count essentially rules out all but residual disease [64]. Lymphocytosis, however, is not specific and seen in a host of other diseases including sarcoidosis, interstitial pneumonia associated with collagen vascular disease, silicosis, cryptogenic organizing pneumonia, human immunodeficiency virus pneumonia, and drug-induced pneumonitis. CD4+/CD8+ lymphocyte ratios may be reduced in HP and may help distinguish the BAL lymphocytosis of HP from the BAL lymphocytosis of sarcoidosis in which increased CD4+/CD8+ ratio may be present. Parenthetically, HP associated with *Mycobacterium avium* complex is often characterized by elevated CD4+/CD8+ ratios [2]. Limiting the usage of BAL is the lack of correlation between BAL lymphocytosis and other clinical parameters as lymphocytosis can persist for years despite symptomatic improvement [62–65].

Lung Biopsy

Among patients who present with a classic history of antigen exposure, typical CT findings and a positive serum specific antibody test, a lung biopsy is not necessary. Accordingly, lung biopsy is only indicated in cases where a definitive diagnosis is not readily available [66]. Transbronchial biopsy frequently does not show all the specific histological changes of HP, especially the poorly formed, non-necrotizing granulomas and mononuclear bronchiolitis, in part due to the small tissue samples obtained by the biopsy forceps. Surgical lung biopsy may be considered to confirm the diagnosis, especially if transbronchial biopsy has not provided a diagnostic yield. The diagnostic yield of video-assisted thoracostomy surgical biopsy is increased if biopsies are obtained from multiple lobes [67].

Natural History and Prognosis

The duration of exposure, concentration of antigen, exposure frequency, and interval between exposures affect the presentation, latency, and severity of disease. Symptoms are often alleviated by prolonged avoidance from the offending agent and single acute episodes are self-limited with symptoms disappearing within days. Single episodes usually do not require treatment other than avoidance of the exposure. Subacute and chronic HP is caused by intermittent or continuous exposure to the antigen. Symptoms are insidious and develop over weeks to months. The prognosis of subacute and chronic HP is worse than the acute form. Acute exacerbations in chronic disease have also been reported, particularly in patients with bird fancier's lung [68].

Rapid improvement in lung function, including measurement of FVC and DLCO capacity, may occur within 2 weeks of cessation of antigen exposure [1]. Specific forms of HP may have different natural histories. For example, patients with farmer's lung generally have a rapid improvement compared with bird fancier's lung after removal of the offending agent [69, 70]. The prognosis is worse in the elderly, in patients with increased duration of antigen exposure, and those with radiographic evidence of fibrotic HP. When the disease has progressed to chronic HP, the prevalence of lung cancer may be increased, with a recent study observing a rate of nearly 11% [71]. In a recent study, patients with fibrotic disease have a median survival of around 2 years compared to 22 years in patients with non-fibrotic HP [72, 73].

Treatment

The most important therapeutic intervention in the management of HP is ensuring cessation of exposure to the offending antigen either by eliminating the antigen or avoiding the setting in which the exposure took place. Once the antigen has been

determined, if elimination of the antigen is not possible, removing the patient from that environment should be advocated under most circumstances. An experienced industrial hygienist may be able to provide onsite investigation of work and home environments to help in exposure remediation or to delineate potential sources of HP. Unfortunately, the etiology of HP may not always be easily apparent.

Treatment with corticosteroids may be considered. Most reports supporting the administration of corticosteroids include anecdotal observations. No prospective randomized controlled trials demonstrating efficacy and safety of corticosteroids in the management of HP have been published. Steroids are indicated in acute, severe or progressive disease. Older studies suggest that the normal starting dose is 60 mg/day [74], although lower doses are often used. Steroids are continued until there is significant symptomatic and functional improvement [39]. A 4 week course appears to be sufficient based on studies which have compared a 4 week course with a 12 week course showing no added benefit in the longer course [75]. While on corticosteroids, PFTs should be checked within the first 4 weeks and should be followed serially afterward. Cytotoxic agents including azathioprine, cyclophosphamide, and cyclosporine have been tried in patients with refractory disease but their efficacy is unclear [76]. In refractory cases that progress to end-stage ILD, lung transplantation is an option. In patients with airflow limitation, chest tightness and cough, inhaled steroids, and beta agonist are beneficial [1].

Hypersensitivity Pneumonitis in Children

There has been a growing literature on the subject of hypersensitivity pneumonitis in children. Previously, HP had been considered a disease of adulthood due to the increased occupational exposures of adults; however, HP has been reported in infants, children, and adolescents [77]. The published literature is limited and there are little epidemiologic data on HP in children. A recent Danish Cohort study estimated 4 cases per 1,000,000 children [78]. Given the uncommon nature of HP in children, it may often be misdiagnosed as asthma [78]. While the causes of HP are similar to that of adults, children may have a different set of exposures and may be at higher risk for certain types of HP. Currently, the most common type of HP in children is bird fancier's disease associated with avian antigens [79–82]. Other exposures have been reported including farmer's lung secondary to children performing chores in a farm home setting [83, 84] as well as HP from exposure to a shower contaminated with the fungus *Epicoccum nigrum* [85].

The clinical presentation including symptoms, physical examination, histopathologic findings, radiographic findings, and diagnosis of HP in children are similar to adults. The clinical features of HP in children are also classified into similar categories: acute, subacute, and chronic. If the offending antigen is not removed, or if there is continued exposure, HP in children can progress into a fibrotic stage [77]. Treatment of HP in children also centers on elimination of the inciting antigen. In severe attacks, oral corticosteroids have been used—usually prednisone 0.5–1 mg/kg/day

for 2–3 weeks [77]. In another report, intravenous methylprednisilone was used for severe acute episodes [78]. Further investigations are warranted to evaluate prognosis of HP in children.

Summary

HP is a type of ILD caused by exposure to a wide range of antigens including microbial, plant, and animal protein and low molecular weight chemicals. HP can be challenging to diagnose. Symptoms develop after repeated respiratory exposure to an etiologic airborne agent and can present acutely or insidiously. Symptoms mimicking infectious pneumonia can be abrupt in onset and develop within hours of exposure in cases of acute HP. In contrast, chronic HP is characterized by chronic exposures resulting in the insidious development of dyspnea, cough, diminished exercise tolerance, and weight loss.

The diagnosis of HP requires a high clinical suspicion and a thorough history. Typical CT findings include GGO, centrilobular nodules, and mosaic attenuation. Lung biopsy is not necessary unless the diagnosis is in question after review of clinical radiographic data. Typical pathologic findings include mononuclear cellular interstitial infiltrates, cellular bronchiolitis and small, loosely formed non-necrotizing granulomas. Treatment requires avoidance of the offending antigen. Oral corticosteroids have been used in severe cases. When diagnosed early, HP is usually reversible. However, unrecognized chronic exposure to etiologic agents can result in the development of chronic HP with irreversible features, including pulmonary fibrosis.

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Chapter 7
Air Pollution and Lung Diseases

Yuh-Chin T. Huang and Ellen Volker

Abstract Epidemiological studies continue to show associations between adverse health effects and outdoor air pollution despite tighter regulation in recent years. These adverse effects occur at levels of pollutants much lower than those encountered in earlier air pollution disasters and, in some studies, at concentrations near or below the national standards. Although the relative risk tends to be low, the population attributable risk is significant due to the large number of people exposed to air pollutants. The adverse health consequences primarily are those related to respiratory and cardiovascular systems. Respiratory effects include decline in lung function, increases in respiratory-related hospital admissions, exacerbation of asthma and COPD, and elevations in the rates of respiratory infection. This chapter reviews the respiratory health effects associated with particulate matter (PM) and gaseous pollutants and briefly discusses clinical approaches to managing air pollution-associated lung disease, especially in susceptible populations, such as patients with pre-existing cardiopulmonary diseases.

Keywords Air pollutant • Ozone • Nitrogen dioxide • Sulfur dioxide • Carbon monoxide • Particulate matter

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Introduction

Outdoor pollution became a public health problem with larger urban centers. Both Greek and Roman society noted that air pollution was a potential source of health problems. While cities of antiquity used wood as a fuel until deforestation, London was the first city to use coal (in the thirteenth century). The domestic use required an effective chimney and these were common only in the better houses of the early medieval period. By Elizabethan times, effective chimneys were more common and coal was adopted as a domestic fuel by the poor. However, very high concentrations of air pollution were common in cities. Black was the color of the fabric widely used for umbrellas since rain was ink-colored. English women did not favor white clothes because of soot (the color cream was in vogue) and businesses were set up to refurbish materials that had been smoked. Building leases required repainting every 3 years to hide the effects of smoke and wallpaper was dark-colored to conceal the effects of the air pollution inside. By Victorian times, air pollution was a serious concern and it challenged normal health. Doctors noted the debilitating effects of urban air and frequently advised sensitive patents to leave for extended stays in the countryside. In the nineteenth century, interest in cities grew and there was a passage of numerous laws concerning smoke abatement (in England "Health of Towns Act" resulted, 1853). Despite this, urban air quality remained poor with fogs (particles from coal burning associated with sulfuric acid) in London increasing in both frequency and intensity throughout the nineteenth century. Only in retrospect was it observed that these fogs (dating back to seventeenth century) were associated with increased mortality until the London smog of 1952 in which 4,000 excess deaths were documented.

Efforts to reduce air pollution ensued in the 1960s and 1970s. In the United States, the federal government enacted a series of Clean Air Acts, which required the Environmental Protection Agency (EPA) to set National Ambient Air Quality Standards (NAAQS) for pollutants considered harmful to both the public health and the environment (see Table 7.1). Despite these efforts, epidemiological studies continue to show associations between adverse health effects and air pollutants, even at concentrations near or below the current national standards. The relative risk is generally low, but the population attributable risk for pollution-related health effects is significant due to the large number of people exposed to air pollutants. The World Health Organization estimates that outdoor air pollution causes approximately two million premature deaths worldwide per year.

Background

Air pollution is a complex mixture of particles and gases that originate from both anthropogenic (e.g., combustion of fossil fuels) and natural (e.g., soil resuspension) sources with secondary physicochemical modifications in the atmosphere. In an urban environment, the majority of air pollutants are secondary to emissions. These pollutants are emitted from several sources, including large stationary fuel combustion

Table 7.1 Current national ambient air quality standards (Adapted from U.S. Environmental Protection Agency. http://epa.gov/air/criteria.html. Last accessed 27 August 2011)

Pollutant	Type of standards	Level	Averaging time
CO	Primary[a]	35 ppm (40 mg/m^3)	1-h
	Primary	9 ppm (10 mg/m^3)	8-h
Pb	Primary and secondary[b]	0.15 μg/m^3	Rolling 3-months
		1.5 μg/m^3	Quarterly
NO_2	Primary and secondary	0.053 ppm (100 μg/m^3)	Annual
PM_{10}	Primary and secondary	150 μg/m^3	24-h
$PM_{2.5}$	Primary and secondary	35 μg/m^3	24-h
	Primary and secondary	15 μg/m^3	Annual
O_3	Primary and secondary	0.12 ppm (235 μg/m^3)	1-h
	Primary and secondary	0.075 ppm (150 μg/m^3)	8-h
SO_2	Primary	0.14 ppm (365 μg/m^3)	24-h
	Primary	0.030 ppm (80 μg/m^3)	Annual
	Secondary	0.5 ppm (1,300 μg/m^3)	3-h

[a]Primary standards set limits to protect public health

[b]Secondary standards set limits to protect public welfare from any known or anticipated adverse effects of a pollutant

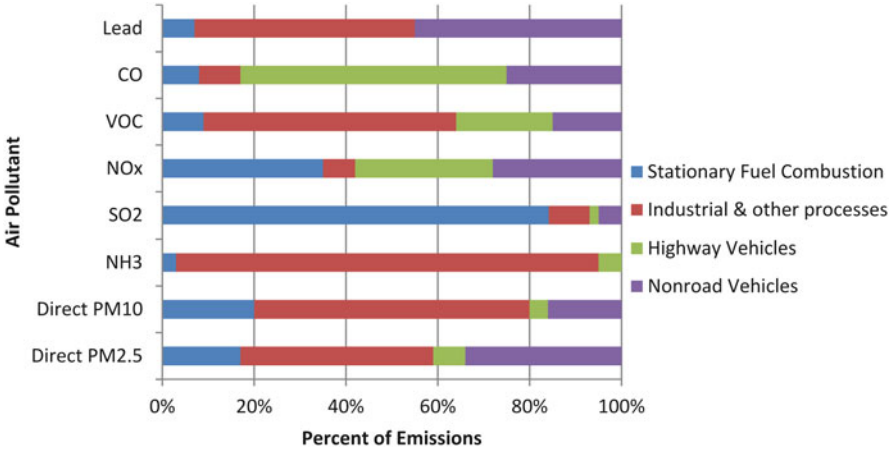

Fig. 7.1 Distribution of national total emissions estimates by source category for specific pollutants, 2008. (Adapted from U.S. Environmental Protection Agency. http://www.epa.gov/airtrends/2010/report/airpollution.pdf. Last accessed 27 August 2011)

sources (e.g., electric utility plants), industrial emissions (e.g., smelters and oil refineries), and transportation modalities (e.g., automobiles, aircraft, and locomotives). Gaseous pollutants include carbon dioxide (CO_2), carbon monoxide (CO), nitrogen oxides (NO_x), ozone (O_3), and sulfur dioxide (SO_2), volatile organic compounds (VOCs), and various air toxics (i.e., benzene, formaldehyde, and lead). Particulate matter (PM) is a mixture of sulfate, nitrate, elemental (black) carbon, organic carbon, and crustal material. Figure 7.1 displays the distribution of total emissions for the United States by source and for specific pollutants in 2008. The EPA has set standards

for six of the most common air pollutants, called criteria pollutants, and they include ground-level ozone, particulate matter, lead, NO_2, CO, and SO_2 (see Table 7.1).

Exposure to air pollution depends upon many variables. Ambient concentrations of pollutants are susceptible to seasonal and meteorologic conditions (e.g., hot, dry air increases O_3 production). The concentrations of air pollutants also have significant spatial and geographic variations. Proximity to a source of emissions (e.g., power plant, major road or highway), as well as time-activity patterns, will influence exposure to pollution. The level of some air pollutants near a busy highway may be several times higher than those measured by a monitor station located away from the road. There is a strong association between the traffic intensity near a home and mortality with increases of 5–10% [1]. The near-road air pollution has become a major public health issue since approximately 16% of US housing units (approximately 48 million people, mostly non-white and economically disadvantaged) are located within 300 ft of a major highway, railroad, or airport.

Respiratory Effects of Air Pollution

Exposure to outdoor air pollution is associated with many adverse health effects. The respiratory system is uniquely affected as it is the predominant portal of entry. The association of human adverse effects to outdoor air pollution comes from a large body of epidemiologic (cohort and time series) and experimental (controlled exposure) studies, most providing level II evidence. The adverse effects caused by air pollutants range from subtle biochemical and physiological changes to overt clinical symptoms. This exposure may cause both acute and chronic effects. Acute effects, such as cough and bronchospasm, usually occur within minutes or hours after exposure and often are reversible when the exposure ends. Chronic effects, such as decline in lung function and lung cancer, are associated with years of exposure and may not be reversible even if the exposure to the pollutant ends. The severity of air pollution-induced health effects varies from person to person. Elderly, pregnant women, children, and patients with cardiopulmonary diseases are generally considered more susceptible. Individuals with certain genetic polymorphisms may also have altered sensitivity to air pollution. The following section describes respiratory health effects following specific pollutants.

Pulmonary Toxicity by Air Pollutant

Ozone

Ozone (O_3), is an ambient gas formed as a result of a chemical reaction between NO_x and volatile organic compounds (VOCs), emitted during combustion, in the presence of sunlight ($h\upsilon$):

$$\mathrm{VOC} + \mathrm{NO} + h\upsilon(\lambda \leq 410\mathrm{nm}) \rightarrow \mathrm{NO_2} + \mathrm{O_3} \tag{7.1}$$

This reaction also produces many secondary species that, along with O_3, form photochemical smog. NO_2 produced in this reaction can form more O_3 via the following reactions:

$$NO_2 + h\upsilon(\lambda \leq 410\,nm) \rightarrow NO + O \tag{7.2}$$

$$2NO + O_2 \rightarrow 2NO_2 \tag{7.3}$$

$$O + O_2 \rightarrow O_3$$

The ozone produced in the above reactions can be removed by the following mechanism:

$$O_3 + NO \rightarrow NO_2 + O_2$$

The efficiency of this O_3 removal mechanism is decreased if NO reacts with other elements, such as hydroxyl radicals, present in the smog. Motor vehicle exhaust, industrial emissions, gasoline vapors, and chemical solvents are primary sources for increased O_3 concentration in the metropolitan areas. In rural areas, biogenic VOCs emitted from vegetation may also be a source.

Numerous epidemiological studies have reported associations between excessive O_3 in the air and respiratory morbidity, primarily hospital admissions, and emergency department (ED) visits in patients with preexisting lung diseases during the warm season [2]. O_3 exposure is also associated with increased mortality, especially from respiratory causes [3–6]. A study on 95 large urban communities in US showed that a 10-ppb increase in the previous week's ozone was associated with a 0.52% increase in daily mortality and a 0.64% increase in cardiovascular and respiratory mortality. Another recent study estimated that each 10-ppb increase in daily ozone is associated with a 0.87% increase in total mortality. Panel studies, which make individual-level exposure assessment feasible, generally confirm the adverse effects of O_3 on respiratory symptoms, lung function and use of asthma medication in individual patients [2, 7]. In human-controlled exposure studies, short-term exposure to O_3 at ≥0.08 ppm consistently showed induction of respiratory symptoms (cough and chest pain), an acute but reversible decrement in lung function, and increases in nonspecific airway reactivity [2]. The responses are generally accentuated by exercise or increased duration of exposure, however. The acute pulmonary response demonstrates considerable individual variability. About 20–50% of the individuals showed a decrement of FEV_1 >10% at 0.08–0.12 ppm of O_3. The variability decreased at lower O_3 concentration. Younger individuals and obese subjects tend to have a greater response to O_3 [2]. Individuals carrying certain genetic polymorphism may have increased sensitivity to O_3 exposure. These genotypes include GSTP1 105Val variant, the HMOX1 long (GT)n repeat, GSTM1-null/NQO1 Pro187Pro-combination genotype, NQO1wt, GSTM1null, and TNF-308 G/G [8–11]. Individuals appear to develop some tolerance in lung function and symptoms to O_3 after repeated exposures, but not in the inflammatory response. It is unclear if there is a threshold level of O_3 below which there are no detrimental health effects. One recent controlled exposure study showed no acute effect at 0.04 ppm but a small FEV_1 decrement at

0.06 ppm [12]. If true, this indicates that the health effects would continue to be present even at exposure levels below the current EPA standards.

Patients with asthma show similar or increased functional and inflammatory airway response to O_3 exposure. Exposure to ozone at 0.27 ppm for 2 h enhanced both FEV_1 decrement and sputum eosinophilia to inhaled allergen in subjects with asthma [13]. The O_3 response does not appear to correlate with the severity of asthma. The health effects of exposure to O_3 on children are of particular concern since their lungs are growing. Studies have linked long-term O_3 exposure to increased prevalence of childhood asthma, reduced lung function and increased asthma symptoms in schoolchildren [14–16]. Patients with COPD did not show excessive sensitivity to acute (1 h) exposure to low levels O_3 up to 0.3 ppm, however, when the exposure is more prolonged (4 h) combining with exercise, patients with COPD did show FEV_1 decrements which were 2–3 times greater than those observed in control subjects [17].

The basis for O_3 toxicity is likely due to its strong oxidant properties allowing it to directly oxidize cellular components such as unsaturated and polyunsaturated lipids, and thiol groups of proteins. Reactions with lung lining fluids also produce various secondary oxidants, such as peroxides, aldehydes and organic radicals, which may promote further oxidative damage. These reactive oxygen species can further activate redox-sensitive transcription factors such as nuclear factor-κB (NF-κB) and activator protein-1 (fos and c-jun) resulting in more extensive cellular effects, including gene changes [18]. The oxidative stress created by O_3 inhalation also causes dysregulation of the innate immune response [19] and adaptive immunity. Acute inhalation of O_3 stimulates the release of proinflammatory cytokines and chemokines, including (but not limited to) tumor necrosis factor-α, keratinocyte chemoattractant, interleukin-1, interleukin-6, prostaglandins, leukotrienes, and complements; all of which play a role in airway hyperresponsiveness, lung inflammation and injury. There was, however, no correlation between the inflammatory response and the magnitude of FEV_1 responses, suggesting different mechanisms responsible for the two effects.

Particulate Matter

Particulate matter (PM) is a complex mixture of solid and liquid particles suspended in air. PM contains multiple chemical constituents, including metals in the forms of oxides, soluble salts (e.g., ammonium nitrate and sulfates) and organic materials (e.g., elemental carbon and hydrocarbon compounds). The specific composition and relative abundance of these constituents depend on the sources and vary from place to place. For example, PM from combustion of fossil fuel, e.g., oil fly ash, contains a large amount of soluble transition metals. This is in contrast to PM derived from crustal sources, e.g., Mount St. Helen dust, which has almost no metals.

Ambient PM is commonly categorized by size fraction based on its mass median aerodynamic diameter (MMAD). Particles <10 μm are the respirable fraction of air particulates. Coarse PM has MMAD between 2.5 and 10 μm ($PM_{10–2.5}$) and fine PM

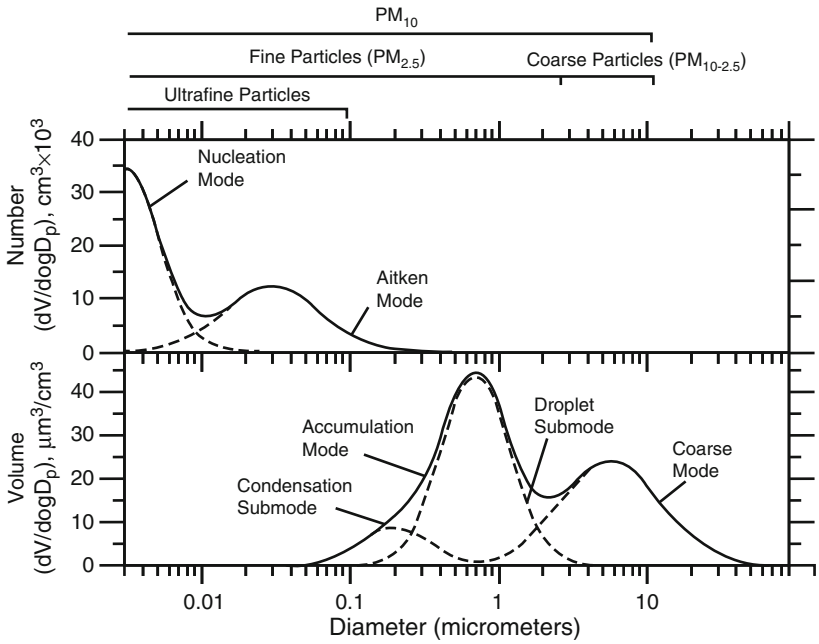

Fig. 7.2 Particle size distributions by number and volume. *Dashed lines* refer to values in individual modes and *solid lines* to their sum. Note that ultrafine particles are a subset of fine particles. (Modified from Pandis [91])

has MMAD <2.5 μm ($PM_{2.5}$). The ultrafine PM (particles with MMAD ≤0.1 μm) is a subset of fine PM. Each size fraction possesses unique physical and chemical properties. Coarse PM mainly derives from natural sources, including resuspended crustal material, suspended residues from brake pads, tire wear, and road usage, sea spray, and biological materials (e.g., pollen, mold, spores, and other plant parts). Fine PM derives primarily from fuel burning, such as power plants and automobiles. Ultrafine PM also primarily derives from fuel combustion; however, these particles are highly unstable and tend to grow through coagulation and/or condensation after a few hours to form larger complex aggregates. Fine PM tends to travel a longer distance from the source than coarse PM. There is a significant spatial variability in PM concentrations which is particularly important for PM from mobile sources. People who live near a busy highway may be exposed to higher concentrations of PM. PM concentration and composition also show significant seasonal variation. EPA currently regulates the levels (mass) of PM_{10} (MMAD <10 μm) and $PM_{2.5}$, but not ultrafine PM. The particle number and size distributions for coarse, fine and ultrafine PM are shown in Fig. 7.2. The largest single source of airborne PM from motor vehicles is diesel exhaust. The combustion of diesel fuel produces up to 100 times as many particles as gasoline combustion [20].

Numerous epidemiological studies have demonstrated an association between PM and adverse cardiopulmonary health effects [21–24]. This association is remarkably

consistent across the different geographic regions. While healthy individuals may experience symptoms from exposure to elevated levels of PM, subjects with heart or lung diseases, children and older adults, subjects with certain genetic polymorphism and subjects in low socioeconomic status are particularly susceptible.

$PM_{2.5}$

Short-term exposure to $PM_{2.5}$ increases respiratory symptoms, respiratory morbidity, reductions in pulmonary function, and medication use and respiratory-related hospital admissions/emergency room visits among both asthmatics and those patients with COPD [25–27]. The risk for all respiratory diseases combined as well as COPD admissions is approximately 2.0–6.0% per 10 μg/m^3 increases in $PM_{2.5}$. The excessive risk was also observed in children with asthma. For example, exposure to $PM_{2.5}$ was associated with severe respiratory symptoms and decreased lung function in asthmatic children, particularly those who were not taking anti-inflammatory medications [28, 29]. Controlled human exposure studies using adult volunteers have demonstrated increased markers of pulmonary inflammation following exposure to a variety of different particles, including concentrated ambient air pollution particles (CAPs), woodsmoke, and diesel exhaust (DE) [30–32]. Other acute respiratory effects associated with $PM_{2.5}$ exposure include desaturation in COPD patients, oxidative stress, lung function decline, and airway hyperresponsiveness in allergic and nonallergic patients [27, 33–36].

Exposure to $PM_{2.5}$ increases the risk of mortality from all causes and cardiopulmonary diseases [1, 37–39]. The risks for cardiovascular and respiratory mortality were approximately 0.60% and 1.68% per 10 μg/m^3 increase in $PM_{2.5}$ respectively. Long-term exposure to $PM_{2.5}$ also has been linked to lung cancer. Interestingly, most of the adverse health effects associated with PM exposure have been seen with cigarette smoking also, indicating the two pollutants may share common pathophysiologic mechanisms.

Ultrafine PM

More recently, ultrafine PM has received increased attention due to its large reactive surface area and the putative ability to permeate the alveolar-capillary barrier. Many of the health effects observed with $PM_{2.5}$ exposure may be due to its ultrafine fraction. To date, controlled human exposure studies have provided the majority of the evidence for health effects in response to short-term exposure to ultrafine PM, especially to diesel exhaust, as it typically contains a large number of ultrafine particles. These studies have consistently demonstrated changes following exposure to relatively high concentrations of UFPs in healthy adults as well as patients with cardiopulmonary diseases [30, 40, 41] Epidemiologic and panel studies found an association between UFPs and hospital admissions for cardiovascular disease, asthma/COPD, subclinical cardiovascular measures (i.e., arrhythmias and supraventricular beats),

respiratory symptoms, decline in respiratory function and mortality [42, 43]. These health effects described by controlled exposure and observational studies were similar to those seen with $PM_{2.5}$ exposure. There are, however, several factors that make it more difficult to ascertain that these observations are specific to ultrafine PM. A systematic network is not in place to measure ultrafine PM. The number concentrations of ultrafine PM are highly variable (e.g., concentrations drop off quickly from the road), therefore, the errors in exposure estimates may be greater. In addition, ultrafine PM tends to form aggregates when inhaled and physical characteristics are erratic. Thus it is unclear if the effects are due to UFPs themselves, larger particles (i.e., $PM_{2.5}$), or gaseous components (in DE studies).

$PM_{2.5\text{-}10}$

Although there were epidemiological studies showing health effects of $PM_{2.5–10}$ on mortality and cardiopulmonary morbidity, others failed to substantiate them. One reason for the variability may be that $PM_{2.5–10}$ is not directly monitored in the national network, and thus ambient concentrations of $PM_{2.5–10}$ have to be estimated by the subtraction of PM_{10} and $PM_{2.5}$ measurements using various methods. The errors introduced by the procedures may lead to a greater uncertainty and misclassification of health effects associated with $PM_{2.5–10}$. In positive studies, the relative risks associated with $PM_{2.5–10}$ were similar to those with $PM_{2.5}$ at concentrations near or below current national standards. The relatively few controlled human exposure studies have observed alterations in heart rate variability and mild pulmonary inflammation in young health individuals and older patients with coronary artery disease [44, 45].

Nitrogen Dioxide

Nitrogen dioxide (NO_2) belongs to a family of reactive gases known as nitrogen oxides (NOx). NO_2 facilitates the formation of ground-level O_3 via the chemical reactions described earlier (7.1) and (7.3). NO_2, by reacting with ammonia, moisture, and other compounds, also contributes to the formation of fine PM. NO_2 is frequently considered a traffic-related surrogate. In-vehicle concentrations of NO_2 can be 2–3 times higher than the ambient level measured at nearby outdoor monitors. Near-roadway (within about 50 m) concentrations of NO_2 have been measured to be approximately 30–100% higher than concentrations away from the roads.

Exposure to NO_2 has been linked to adverse health effects although the association is less consistent relative to those with ozone and PM. Most studies reported small, albeit positive, health effects from exposure to low levels of NO_2, including all cause mortality, reduced lung function in children, respiratory symptoms, such as cough and rhinorrhea, respiratory infection and hospitalization for respiratory and cardiac diseases [46, 47]. Ambient NO_2 was shown recently to increase cardiovascular mortality in regions with a concentration of 20–25 ppb [48]. Asthmatics, children and the elderly were more susceptible. Controlled exposure studies of NO_2

generally showed very little measurable biological effects at dose <1 ppm and small effects when the dose was higher [49]; there appears to be a response threshold of approximately 0.6 ppm. Since NO_2 facilitates the production of O_3 and PM, its health effects are also linked to those produced by these two pollutants.

Carbon Monoxide

Carbon monoxide (CO) is formed primarily by incomplete combustion of carbon-containing fuels. In metropolitan areas in the United States, as much as 75% of outdoor CO emissions originates from the exhaust of gasoline-powered vehicles. CO emissions from mobile sources have decreased by approximately 5% per year since the early 1990s. Nationwide ambient CO data from the EPA Air Quality System for the years 2005–2007 show that the median 1 h daily maximum concentration across the US was 0.7 ppm, although CO exposure levels in the vehicle and in the near-road environment may be 2–5 times higher than the ambient concentrations.

The most well-known mechanism for the toxicity of CO is tissue hypoxia as a result of its high-affinity binding to hemoglobin (Hb) producing carboxyhemoglobin (HbCO). The formation of HbCO reduces the O_2-carrying capacity of the blood and impairs the release of O_2 in the peripheral tissues. The increase in HbCO resulting from ambient CO exposure, however, is usually quite small, and insufficient to affect oxygen-carrying capacity in healthy individuals. CO also binds to other heme proteins, such as myoglobin, cytochrome c oxidase, nitric oxide synthase, and cytochrome P_{450}. The interactions with these proteins change downstream signaling that may be responsible for the "non-hypoxic" mechanisms of the CO toxicity. Exposure to ambient CO has been associated primarily with adverse effects in the cardiovascular system, including increased cardiac-related ED visits and hospital admissions [46, 50].

Sulfur Dioxides

Sulfur dioxides (SO_2) is a major member of the sulfur oxides (SO_X) that derive primarily from combustion of fossil fuels. The sources of SO_2 emissions include power plants (~66%), other industrial facilities (29%) and transportation-related sources (~5%). SO_2 can also come from natural sources, such as volcanic eruptions and wildfires. SO_2, along with NO_X, are the main precursors of acid rain. Control measures that reduce SO_2 generally also decrease all gaseous SO_X. The measures also indirectly lead to reduction in the formation of fine sulfate particles, which also pose significant public health threats.

Healthy individuals can develop increased airway resistance and decreased FEV_1 with exposure to 1.0–5.0 ppm SO_2. Children, the elderly and asthmatics are more susceptible and showed increased visits to emergency departments and hospital admissions for respiratory illnesses at lower concentrations [46]. Asthmatics may also show decrements in lung function, bronchoconstriction, increased airway

hyperresponsiveness, increased sputum eosinophilia and increased wheezing and chest tightness after short-term (5 min to 24 h) exposure to concentrations <1.0 ppm [46, 51]. Individuals with COPD are considered more susceptible to SO_2-induced respiratory health effects; however, this group has not been extensively studied. Chronic exposure to SO_2 can produce a syndrome very similar to chronic bronchitis associated with cigarette smoking. As a result of a high incidence of bronchiolitis in soldiers exposed to smoke from a sulfur-mine fire [52], SO_2 was thought to be a possible contributor to this specific lung disease.

Non-criteria Pollutants

Toxic air pollutants (TAPs), also known as hazardous air pollutants and "air toxics," are 188 pollutants known or suspected to cause cancer or other serious health effects, as well as adverse environmental effects. Common TAPs include benzene, perchlorethlyene, methylene chloride, dioxin, asbestos, toluene, and metals such as cadmium, mercury, chromium, and lead compounds. Some of these TAPs are emitted by motor vehicles when gasoline evaporates or passes through the engine as unburned fuel. Several TAPs are potentially carcinogenic and others affect neurological, reproductive, developmental, respiratory systems.

Polycyclic aromatic hydrocarbons (PAHs) are another group of non-criteria air pollutants. Anthracene is the simplest example of a PAH. The main source of PAHs seems to be incomplete combustion of carbon-containing fuels such as diesel, wood, coal, fat, tobacco, and incense. The toxicity of PAHs varies widely and is very structurally dependent. Some PAHs, such as benzo[α]pyrene (which is also present in cigarette smoke), have been implicated as a cause of lung cancer. PAHs may be responsible for some of the adverse health effects associated with exposure to DE. Detailed information regarding PAHs can be found in the website of Agency for Toxic Substances and Disease Registry (ATSDR) of the Center for Disease Control (http://www.atsdr.cdc.gov/substances/toxsubstance.asp?toxid=25).

Non-emissions Pollution

While the majority of our air pollution is secondary to emissions, other sources have demonstrated negative respiratory health consequences. These sources include natural disasters such as wildfires, terrorist attacks, and living near burn pits. Studies of wildfires across the world in the past decade have demonstrated a significant association between wildfires and increased emergency department presentations and hospitalizations for respiratory issues including asthma exacerbations and dyspnea [53–55]. Wildfires produce elevated levels of particulate matter of all sizes and a recent review found wood smoke particles are at least as detrimental for respiratory disease as combustion-derived particles [56]. Exposure of mice to PM collected during the California wildfires of 2008 initiated a neutrophilic inflammation in lung tissue [56]. Wildfires may likely become an increasingly worrisome and more

frequent contributor to overall air pollution and exacerbation of respiratory symptoms due to changes in the climate and land use practices. The terrorist attacks on the World Trade Center (WTC) serve as a significant example of disaster-related respiratory consequences. An estimated 525,000 people, including residents, rescue workers, and clean-up workers, were exposed to pulverized building materials and combustion-derived air pollutants. The alkaline dust included silicates, asbestos, glass fibers, heavy metals, and PCBs [57–60]. The fires at Ground Zero released PAHs, benzene, sulfur compounds, naphthalene, dioxins, and VOCs [57–60]. Exposure to the air in and around the site has contributed to a number of respiratory health issues including WTC cough (chronic sinusitis, asthma, and/or bronchitis), bronchiolitis obliterans, sarcoid-like granulomatous disease, and interstitial lung disease, as well as decline in FEV_1 and FVC [58, 61–65]. Finally, some soldiers returning from service in Iraq and Afghanistan have complained of exertional dyspnea and decreased exercise tolerance, without significant spirometric declines or radiographic changes. Exposures included a 2003 sulfur-mine fire in Iraq and the burn pits common to large military bases in the region. Thoracoscopic lung biopsy of a sample of these soldiers revealed diffuse constrictive bronchiolitis [52]. Exposure to the burn pits is not limited to the military, but includes contractors and local populations as well. While air pollution due to emissions creates the bulk of exposure and respiratory disease, disasters and burning of biomass and trash may also produce significant pulmonary morbidity in certain locations.

Clinical Implications and Management of Air Pollution-Induced Respiratory Effects

Recognition of outdoor air pollution as a significant contributor to respiratory health is important in clinical practice. As described above, exposure to specific air pollutants, such as O_3 and NO_2, may provoke respiratory symptoms and exacerbate existing chronic pulmonary disease. Long-term exposure to air pollution has also been suggested as a risk factor for incident asthma in both children and adults, but the literature on development of COPD and allergic rhinitis after exposure to pollution is weaker [66–81]. Acute and chronic exposure to air pollution may also increase the risk for respiratory infections [82–84]. One small cohort study of cystic fibrosis patients demonstrated exacerbations of the disease with increased levels of O_3 and PM, as well as a decrease is $FEV_1$with increased $PM_{2.5}$ [85]. Finally, air pollution has been positively associated with lung cancer in nonsmokers, although direct causation requires further inquiry [81, 86–89].

Patients with chronic pulmonary disease, such as asthma and COPD are more susceptible to the respiratory effects of air pollution. Therefore, it is important to identify these susceptible patients in clinical practice. The exposure assessment should be conducted during clinic visits, monitoring air quality and environmental disasters (e.g., forest fire) can be a way for both the physicians and the patients to anticipate potential respiratory complications and adjust medications. The current

AQI Range	Level of Health Concern	Meaning
0 - 50	Good	Air quality satisfactory and air pollution poses little or no risk.
51 - 100	Moderate	Air quality acceptable; there may be a moderate health concern for people unusually sensitive to air pollution.
101 – 150	Unhealthy for sensitive groups	The general public likely not effected; members of sensitive groups may experience health effects.
151 – 200	Unhealthy	Everyone may begin to experience health effects; members of sensitive groups may experience more serious health effects.
201 – 300	Very unhealthy	Health alert; everyone may experience more serious health effects.
301 – 500	Hazardous	Health warnings of emergency conditions; the entire population is likely to be experience serious health effects.

Fig. 7.3 Air quality index guide. (Adapted from U.S. Government cross-agency. http://www.airnow.gov/index.cfm?action=aqibasics.aqi. Last accessed 3 September 2011)

and forecasted air quality index (AQI) can be obtained in the EPA website (http://www.airnow.gov/). The air quality index uses concentrations of the five criteria pollutants that impact cardiopulmonary health and calculate an index value. The calculated value has a range from 0 to 500. A value less than 100 is generally considered satisfactory air quality for all people; above this, symptoms may occur for sensitive populations initially, followed by greater numbers of the population affected as the index increases. Figure 7.3 shows a guide to the AQI. Air quality is reported online, with local weather reports, on the *Weather Channel*, and in the national newspaper, *USA Today* [90]. It may also be helpful to identify the primary residence and its distance to major roadways, power plants, or other industrial facilities as part of the exposure assessment. This may be particularly important in patients whose respiratory symptoms are poorly controlled or who have frequent exacerbations. As always, occupational exposures should be identified as well.

Counseling patients with chronic cardiopulmonary disease about air pollution and the associated risks should be part of the regular management plans. Shofer et al. recommend an approach that includes the mnemonic AIR (Ask, Inform, React) [90]. Ask patients with chronic respiratory illnesses at every office visit if they know air pollution can exacerbate their symptoms, cause acute illness, and even be fatal. Inform patients that general respiratory symptoms such as cough, wheeze, phlegm, shortness of breath, or chest discomfort may be related to air pollution. Educate patients about how to follow air quality using the AQI and where to find it. Finally, patients should have a plan to react to air quality information. If air quality level is unhealthy, sensitive patients should avoid prolonged or heavy exertion outdoors. Patients should also carry a short-acting beta-agonist rescue inhaler for use should symptoms arise. Medication compliance should be reinforced, especially during the high pollution times, in an effort to decrease the exacerbation of symptoms such as wheezing or cough. Corticosteroids, and perhaps inpatient admission should be recommended early in the event that exacerbations are not sufficiently managed by rescue albuterol inhaler or nebulizer at home.

Conclusion

Despite efforts in the developed world to decrease emissions of pollutants, outdoor air pollution remains a significant public health concern. Exposure to traffic emissions and the associated individual pollutants have been extensively studied through epidemiologic and toxicologic investigations. Air pollution is associated with significant respiratory morbidity and even mortality. As the number of vehicles on the road increases across the world and global temperatures continue to rise, the burden of outdoor air pollution-associated respiratory disease will continue to increase. Identifying susceptible patient populations and educating them about air quality and its associated risks, exposure risk-reduction, and timely management of symptoms is essential to good clinical practice.

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Chapter 8
Unanswered Questions Regarding Asbestos Exposure: Concerns for the Next Generation

Daniel E. Banks

Abstract Despite the numerous manuscripts published on the respiratory health effects of asbestos over the past 50 years, there are a number of clinically relevant issues that remain unresolved. In this report, the author addresses aspects of pleural disease, interstitial lung disease, lung cancer, and mesothelioma attributable to asbestos exposures and attempts to present reasonable evidence for his conclusions. In general, the worldwide use of asbestos has lessened over time and one is buoyed by the number of countries that have "banned" asbestos. Yet, this is not clearly the case in all countries. This worldwide initiative to "ban" asbestos leads one to be optimistic that the burden of illness that we recognize at present and which is the result of exposures of past generations will be lessened in the next generations.

Keywords Asbestos • Unanswered questions • Asbestosis • Mesothelioma • Pleural plaques • Pleural thickening

Introduction

Asbestos mining in the United States ceased in 2002, and, over the past generation, the importation of asbestos has lessened and the utilization of asbestos has dramatically declined. At its peak in 1951, the United States utilized 723,000 mt of asbestos. These values have varied year-by-year but remained similarly high until the decade of the 1980s when utilization began to substantially decline [1]. Over these years, the great percentage of asbestos utilized was imported from Canada. In 2010, US consumption was reported to be 1,040 mt, an increase from 869 mt in 2009 [2].

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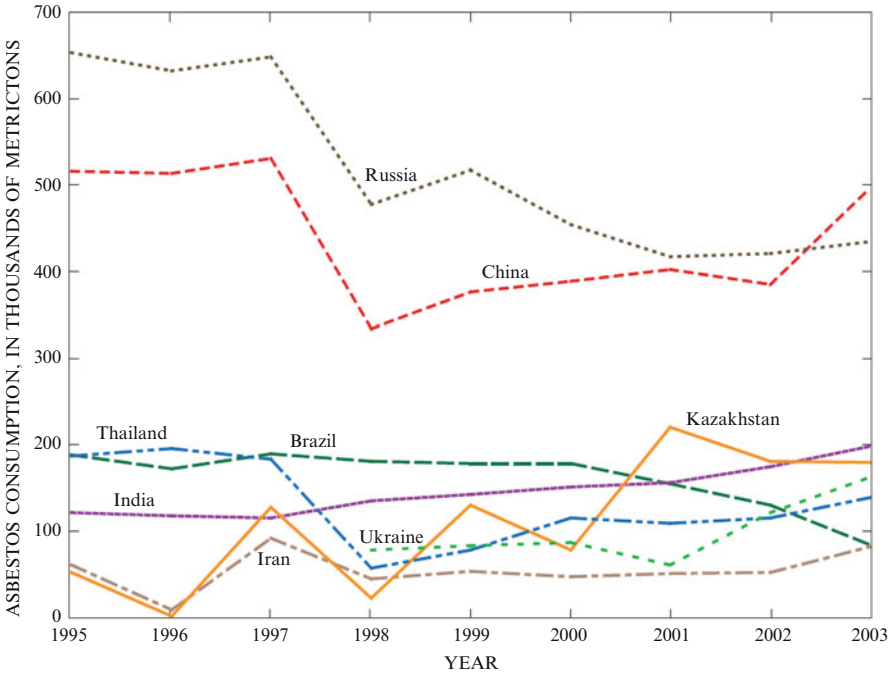

Fig. 8.1 Changes in asbestos consumption by country (1995–2003). (Reprinted from Worldwide asbestos supply and consumption trends from 1900 to 2003. Circular 1298. United States Department of the Interior. United States Geologic Survey (USGS). http://pubs.usgs.gov/circ/2006/1298/c1298.pdf. Accessed October 15, 2011)

All imported asbestos in 2010 was chrysotile in fiber type. Nearly 2/3 was used in roofing products, with the rest nearly entirely used for diaphragms and valves in manufactured products.

This dramatic decline is not uniformly the picture in the rest of the world. Although numerous other countries have lessened their use of asbestos (and a number of countries have completely banned the use of asbestos in the past 10 years), some countries, notably India, China, and Russia, continue to mine asbestos and/or have an increased importation of this material [3]. The most common usage in these countries is corrugated asbestos-cement sheets. The continued usage presents health challenges to the populations of these countries and prolongs the resolution of this worldwide problem (Fig. 8.1). The impact of these different policies means that the global burden of asbestos-induced illnesses over time will be uneven.

Although much of the aforementioned information is, on the whole, encouraging and provides a suggestion that asbestos use in the world has gradually diminished, the reality is the asbestos-related illnesses that we recognize today are the result of the asbestos exposures that have occurred over the past 40, or even more, years. These health problems will likely persist for several more generations. When one compares the mortality associated with asbestos exposure to that of coal dust and

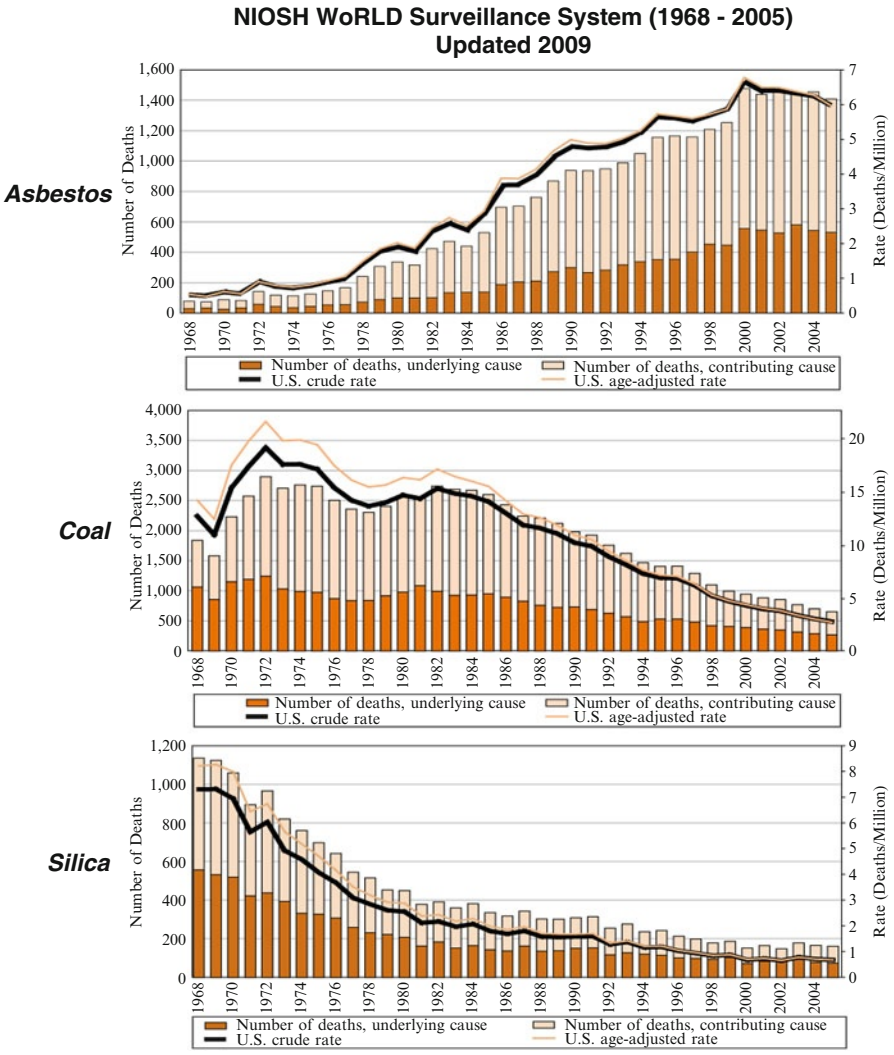

Fig. 8.2 Changes in mortality associated with asbestos, silica, and coal dust exposure over time. (Reprinted from National Institute for Occupational Safety and health. Work-Related Lung Disease (WoRLD) Surveillance System. http://www2.cdc.gov/drds/WorldReportData/. Accessed October 28, 2011)

silica exposures, it is clear that asbestos-related health effects that occurred years ago remain a contributor to the exposed worker's risk of mortality (Fig. 8.2). Recent reports show that mortality rate attributable to asbestosis continues to increase in such a way that it is likely to be 10 or 15 more years before the annual mortality rate due to this disease begins to decline [4].

Table 8.1 Selected issues relevant to the health of workers with asbestos exposure

One criterion for attributing an asbestos recognized effect (such as asbestosis or lung cancer) to asbestos exposure is clinically significant exposure. What does that mean?
Are small airway flows rates (as measured by spirometry) attributable to asbestos exposure in a worker so exposed?
Is asbestosis necessary for the development of lung cancer?
What approach should a physician take when a worker presents following an acute excessive exposure to asbestos?
What is the mechanism for the development of pleural abnormalities in asbestos exposed individuals?
Has the decline in exposure levels to asbestos in the workplace altered the frequency of mesothelioma?
How should workers with asbestos exposure be evaluated with imaging studies ?

Workers with asbestos-related exposures will continue to present to clinicians for medical help. Although there are many reports addressing the health effects of asbestos exposed workers, a number of clinical concerns remain. This report has attempted to address a number of what may be considered to be unresolved clinical questions (Table 8.1).

One of the Criteria for Attributing Interstitial Lung Disease (Asbestosis) to Asbestos Exposure Is Clinically Significant Exposure: What Does "Clinically Significant Exposure" Mean?

There are three criteria for the diagnosis of asbestosis. These include the following:

1. Radiographic features consistent with the interstitial fibrosis
2. A sufficient duration of exposure and latency period sufficient to explain these features
3. The absence of another clinical explanation to explain the radiographic features

Neither the presence of respiratory symptoms nor abnormalities in physiologic testing are necessary to make the diagnosis of asbestosis, although there is little question that the addition of this clinical evidence increases the strength of the argument that asbestosis is present.

The meaning of the term "sufficient exposure and latency period" has changed over the past 50 years, beginning when epidemiologic studies on populations of asbestos workers were first reported. The driving determinant of change has been the recognition that exposures need to be monitored and the initiation and enforcement of a protective permissible exposure limit (PEL). The Occupational Safety and Health Agency (OSHA) serially decreased the PEL over time and, in 1986, the date of the implementation of the current standard, mandated that the PEL for asbestos in the workplace be 0.1 fibers/cm^3 of air averaged over an 8-h shift of a 40 h work

week. In addition, OSHA requires workers who are exposed to asbestos above the PEL and who are employed in certain asbestos industries to use personal protective devices, to undergo medical surveillance in order to identify signs of asbestos-associated disease and to use this information as a basis for removing workers from further exposure, and to provide documentation for work-related injury claims. Components of the required medical surveillance include a standard questionnaire, a physical examination, a spirometric test, and a chest X-ray.

With the recognition of the extent of the workers' asbestos exposure as well as an understanding of the latency period, changes in the PEL have been reflected in the prevalence of disease described in respiratory health surveys recorded over the past generations. In 1965, Selikoff et al. reported on a population of 121 asbestos workers with a 40 year latency of asbestos exposure. In this group, 94.2% showed radiologic evidence of asbestosis [5]. This population had a lifetime of work in workplaces where asbestos exposures had not been controlled. No exposure regulations were in effect. In 1979, Polakoff et al. evaluated 359 present and retired shipyard workers with 10 or more years of exposure. Of this group, 44% had parenchymal interstitial disease. This population was a combination of workers who had worked and retired prior to the establishment of exposure recommendations and those hired after regulations had been initiated [6]. In 1998, Hessel et al. studied the respiratory health of electricians in Edmonton, Alberta, Canada. In this population, the prevalence of small opacities (findings consistent with asbestosis) was 2.1% [7]. In a similar vein, the prevalence of interstitial lung disease in sheet metal workers in 1985 was 13.7% and in those studied in the years 2000–2004 was 5.9%. In both categories, the mean duration of employment in the sheet metal trade was 33 years [8].

In summary, not surprisingly, absolute values describing a "sufficient exposure and latency period" cannot be presented, but the decline in asbestosis (a dose-related interstitial lung disease) in populations where exposure has been recognized suggests that the regulations have been effective and the physician may need to consider greater years of exposures and longer latency periods than previously. As a practical consideration, in 1997, the Helsinki Criteria stated that the latency period must be at least 10 years [9]. In the absence of recognized persistent excessive exposures, it may require a working lifetime of exposure in a workplace where asbestos exposure has been recognized in order to be considered of "sufficient duration and latency period" to explain the illness. Yet, cases may even develop after "a working lifetime." Follow-up evaluations may need to go for many more years as a worker who had no radiographic evidence of asbestosis after 30 years of work may retire and then be shown to have this disease 5 years later.

Is Asbestosis Necessary for the Development of Lung Cancer?

Of particular interest is the failure of experts [10] to agree on whether asbestos exposure or asbestosis is the cause of the increased risk of lung cancer in asbestos workers. To begin, the facts that most asbestos-associated cancers occur in cigarette smokers, that smoking represents the strongest identifiable lung cancer risk

(even stronger than asbestos exposure), and that lung cancer is a relatively common malignancy in industrialized societies make an analysis of the relationship between smoking and asbestos exposure complex [11]. It should be noted that all types of commercially produced asbestos fibers are carcinogenic [12].

The argument was initially presented by Mereweather [13], who showed that lung cancer occurred in 35 of the 235 (13.2%) deaths of asbestos exposed workers where asbestosis was identified. In 1955, the first mortality study of a cohort of asbestos-exposed workers showed that among 105 deaths, lung cancer was found in 18 instances, 15 times in association with asbestosis. In the three instances without asbestosis, the latency periods were 2, 12, and 11 years, leading one to question the relevance of dust exposure in these individuals [14]. Conclusions from these and other reports were crystallized by Browne [15], who reported there was sufficient evidence to justify the hypothesis that lung cancer in asbestos-exposed workers was due to asbestosis and not asbestos exposure per se. A meta-analysis by Weiss [16] provided support for this hypothesis. Yet, because few studies cited by Weiss were designed to test the interaction among asbestos exposure, asbestosis, and lung cancer, these studies could be reasonably criticized [17].

Despite the difficulties in sorting this out, it remains a great public health consequence that we understand how lung cancer develops in these workers. Specifically, if asbestos exposure, in the absence of asbestosis, is sufficient to increase the risk of lung cancer, then the emphasis must be on absolute avoidance of asbestos fiber inhalation, not just maintaining exposures below the PEL. Alternatively, if asbestosis (be it radiologically or pathologically recognized) is essential for the development of lung cancer, then reasonable avoidance measures, such as those currently in effect, should effectively prevent the contribution of asbestos fiber inhalation to the development of lung cancer.

What are the manuscripts that lead us to attribute lung cancer to asbestos exposure in the absence of asbestosis? Wilkinson et al. performed a case–control study comparing the work history and chest radiographic features of lung cancer patients (with or without asbestos exposure and with or without pulmonary fibrosis) to a comparable group of other patents in the hospital. They showed that lung cancer was not only statistically more frequent in patients who had pulmonary fibrosis, but also in those with asbestos exposure, in general, regardless of the presence or absence of interstitial changes [18]. Important work by Hillerdal showed an increase in lung cancer in workers with pleural abnormalities (but without asbestosis) on the chest radiograph [19, 20]. One concern about this work has been the notoriously difficult problem of accurately identifying pleural changes on the chest radiograph. Since only 50–80% of cases of documented pleural thickening demonstrated by autopsy, conventional CT, or high-resolution CT (HRCT) are detected by chest radiograph, the difficulty in identifying changes on the radiograph may result in miscategorizing the participants [21, 22]. Finkelstein studied asbestos cement workers in Ontario. He showed that the lung cancer standardized mortality ratio was 5.3 times baseline at 20 years of latency for exposed workers without asbestosis. The rate was nearly twice as high for those with asbestosis; however, the sample size was small and confidence intervals overlapped [23]. Hessel et al. presented a

summary of nine mortality studies assessing whether lung cancer required asbestosis for causation or could be attributed to asbestos exposure with a sufficient latency period. This group found limitations associated with all of the reports, but noted seven showed asbestos exposure was sufficient while just two showed that asbestosis was necessary for causation of lung cancer [24].

In summary, the manuscripts cited and others reviewed were written to define the pulmonary health of a population. None were designed to assess the interaction between asbestos exposure, asbestosis, and lung cancer. Perhaps the primary problem in accepting the results of these studies correlating routine chest radiographic features of pleural plaques and/or pulmonary fibrosis with asbestos exposure is our inability to be confident that we can accurately diagnose these abnormalities. Finally, asbestosis, pleural plaques, and lung cancer are dose-related, so it is only logical that in those followed long enough, a clear relationship between these variables will be recognized. Furthermore, in asbestosis, the end-product is fibrosis, not malignancy. The fibrogenic mechanisms critical in the initiation of transformation to malignancy remain largely unknown.

In the end, although the weight of the evidence appeared to favor the conclusion that asbestosis was necessary for the development of lung cancer in many of the earlier reports, most now accept that sufficient asbestos exposure with latency allows one to attribute lung cancer to this exposure.

Are Declines in Small Airway Flows Rates Attributable to Asbestos Exposure in a Worker so Exposed?

The 1986 statement by the American Thoracic Society did not address small airway flow rates in its discussion of the pulmonary function features of nonmalignant manifestations of asbestos exposures [25]. The 2004 American Thoracic Society statement on the diagnosis and initial management of nonmalignant diseases related to asbestos exposure noted that "epidemiologic studies have demonstrated a significant association between asbestos exposure or asbestosis category as defined radiographically and reduction in FEV_1, FEV_1/FVC ratio and mid-expiratory flow rates." Furthermore, although the authors note that the decrease in small airway flow rates is not likely to produce clinically relevant impairment, they suggest that this may indicate an increased probability that this effect will occur later in life [26]. Finally, in the 2009 American College of Chest Physicians statement, experts disagreed on the validity of the statement "a decline in small airway flow rates can be attributed to asbestos exposure in a worker so exposed" [10].

The $FEF_{25–75\%}$ is the most commonly used parameter in discussing small airway flows. This is the average rate of airflow during the mid-portion of the FVC maneuver. It may be reduced in both obstructive and restrictive lung disease. It is perhaps the best of the small airway flow rate measurements because it excludes the first 25% of the expiratory effort, typically affected by the elastic recoil of the chest and

the last 25% affected by diminishing expiratory effort. Importantly, it is highly dependent on the validity of the FVC measurement and the worker's effort.

When this parameter is reviewed in asbestos-exposed cohorts, there appears to be differences in outcomes. To begin, a report of 2,611 long-term employed insulators who began their work in the 1970s was reported in 1994. The mean exposure duration was 35.1 years. 515 workers were non-smokers. Although the FEV1/FVC ratio was decreased in only 3.3% of this population and the mean $FEF_{25–75\%}$ was 96.4% predicted, this flow rate was diminished in 19.2% of the participants [27]. In reports by Wright and Churg, descriptions of pathologic lesions in the walls of the respiratory bronchioles were present in long-term chrysotile miners without asbestosis [28, 29]. Perhaps the weakness of the work is that no non-smoking asbestos workers were in the autopsied population, although the workers were matched by age, years of asbestos exposure, and amount of cigarettes smoked.

In the most recent summary addressing whether asbestos exposure causes airway obstruction, a group of French authors evaluated a cohort of 3,660 retired or unemployed workers previously exposed to asbestos (mean age = 63.2 years and mean exposure duration 27.7 years) as a part of a nationwide study. The mean $FEF_{25–75\%}$ for 893 non-smokers was 97% predicted (compared to 86.4% for the smokers). The authors concluded that their data "did not support the hypothesis of a causal role of asbestos exposure in the pathogenesis of airways obstruction" [30]. In the time between these earlier and most recently cited studies, there were numerous reports and while some convincingly showed that small airway flow rates were affected by asbestos, others showed this less likely to be the case [31–35].

How can this difference in conclusions be reconciled? One may consider changes in the PEL over time and the associated changes in exposures over a worker's career. When workers finished a lifetime of work in the dusty trades in the 1960s, 1970s, and 1980s, it is likely that the exposures, and the associated physiologic effects, were much greater then than in recent reports addressing lung function in asbestos-exposed workers. The effect may be less today. Such a perspective has been alluded to previously [36]. Future epidemiologic studies may provide the opportunity to test this hypothesis.

What Action Should a Physician Take when a Worker Complains of an Acute Excessive Exposure to Asbestos?

When asbestos is removed (e.g., from an asbestos wrapped boiler), exposures may occur even when strict rules to prevent exposure are in place. In many older workplaces, such as steel mills and power plants, many pipes are wrapped in asbestos insulation. In most instances, the pipes are not disturbed and the asbestos remains captured in the pipe wrapping. Yet, on occasion, events occur and the worker presents to the health service following an exposure associated with the damaged pipe wrapping or a breach in protection protocol. In such instances, exposures must be reported. Physicians providing care to workers in these situations have exhibited a

broad range of responses—from noting the exposure and "observing" the worker to immediately undertaking spirometry and a chest radiograph. Workers exposed to such events or at risk for such exposures should be enrolled in clinical screening program [37].

Suggestions for a practical response to such events have been put forward. First, it is important to recognize the worker's concern. The physician should then attempt to understand how the accidental exposure occurred and the type of work associated with the event, as well as the duration of the exposure, whether protective gear was worn, and evaluate, if possible, the amount and types(s) of asbestos in the ambient air. The possible increase in cancer or lung fibrosis risk to the worker from such an exposure is likely insignificant. It is essential to fully report, document, and investigate the incident, as well as enter this in the worker's record, yet there is no reason to subject workers to the ionizing radiation associated with a chest radiograph or computerized tomogram scan of the chest. The solution to this episode is making sure that this does not recur by implementing engineering controls [38].

What Is the Mechanism for the Development of Pleural Abnormalities in Asbestos-Exposed Individuals?

Asbestos fibers have a natural, unexplained predilection for transport to the pleura. The result is an unusual array of benign and malignant manifestations of exposure—these changes are not seen in any other disease. Although there have been rare cases of silica exposure associated with pleural changes, exposure to no other fibrogenic dust is associated with these outcomes on such a regular basis. In addition to mesothelioma, asbestos-induced pleural disease includes the non-malignant entities of pleural plaques, benign asbestos pleurisy, diffuse pleural thickening, and rounded atelectasis. These non-malignant disorders are important because they are common and, in some instances, result in abnormal lung function and symptoms. Intriguingly, these benign pleural changes may occur in the absence of a radiologically or pathologically visible lung response.

It is not known how asbestos fibers are transported to the pleural space. Investigators have presented numerous theories [39–41]. One that remains relevant was proposed by Taskinen et al. a number of years ago [42]. This group considered three potential mechanisms of how dust may be handled in the lung: (a) penetration through the lung, the visceral pleura, and the pleural cavity with uptake into the parietal pleura; (b) propagation through the blood vessels; and (c) transport via lymphatic vessels. In a worker exposed to coal and siliceous dust, they showed autopsy evidence of linear pigmentation along the intercostal vessels, the location of the lymphatic vessels, just anterior to the parietal pleura. They proposed that particles from the lung were first carried in macrophages or transported free in the lymphatic vessels into the lymph nodes of the lung. When the nodes were full, this contaminated lymph flowed retrograde into the intercostal lymphatic vessels anterior to the parietal pleura. They dismissed penetration of particles through the pleural cavity as the outline of the lymphatic vessels was "clear-cut" and dismissed penetration of

particles through the blood vessels because the particles were not visible in the blood vessel wall. Coal and silica particles were identified in the lymphatic vessels. Acceptance of this theory requires that fibers should travel against the normal flow of lymph.

More recently, Miserochi et al. explained how fibers are translocated from the airway into the interstitium and from there into the pleural space using principles of fluid dynamics [43]. First, fibers in the alveolar lining fluid reach the interstitium through phagocytosis by type I alveolar lining cells which allow a "pass-through" into the interstitium by combined osmotic (through active sodium absorption) and hydraulic (the interstitial pressure is less than the airway) pressure gradients. Alveolar epithelial cell injury also damages fibroblasts and myofibroblasts and results in an inflammatory response with the laying down of increased amounts of extracellular matrix; the start of the pathologic process of asbestosis. Second, asbestos fibers can exit the lung through lymphatic vessels. Very fine fibers can be cleared in 24 h [44]. The lymphatic circulation inevitably drains into the blood and, in that way, fibers may be dispersed to all organs [45]. Fibers in lymphatic vessels and in the blood can enter the pleural space dragged by water flux gradients. Third, movement of fibers from the lung parenchyma into the pleural space can occur directly. If there is an inflammatory response in the lung (such as asbestos-induced alveolitis), the interstitial pressure is raised and this can drive fibers in the lung parenchyma through minute pores in the visceral pleura into the pleural space.

Although fibers are transported into the pleural space (be it via the lymphatic vessels, the systemic circulation, or through direct pleural penetration), the differing pleural responses are unexplained. Diffuse pleural thickening and pleural plaques frequently co-exist. For example, the intense inflammatory features of an exudative pleural effusion which resolves and scars to form diffuse pleural thickening are very different from the insidiously progressive essentially acellular and avascular pleural fibrosis [46]. Furthermore, it appears that diffuse pleural thickening is considerably more frequent than plaques in crocidolite workers, suggesting the role of amphibole fibers in its etiology [47]. Finally, it should be noted that the "cause and effect" relationship of an exudative pleural effusion with clinical features of acute pleurisy leading to diffuse pleural thickening is often presumptive, with the effusion never recognized but thought to have occurred on a subclinical basis [48, 49].

How pleural plaques develop is poorly understood. First, the relationship between exposure and the development of plaques is not clear. Using chest radiographs, work from British shipyard population surveys showed that the prevalence of plaques increased with increasing doses of asbestos inhaled [50]. In direct opposition to this conclusion, using CT scanning of the chest, there was no relationship between the plaque surface area and cumulative amount of asbestos exposure, smoking history or time since first asbestos exposure [51]. Asbestos bodies are not typically found in the pleural abnormality. Unlike diffuse pleural thickening, plaques appear to be more likely related to chrysotile compared to amphibole exposures [52].

Despite some insights in how fibers enter the pleural space, an explanation for the very different responses has been elusive. Whether the pleural features associated with asbestos exposure occur (or fail to occur) and whether the changes will be

diffuse pleural thickening following an exudative pleural effusion, pleural plaques or even rounded atelectasis appears to be unable to be predicted.

Has the Decline in Exposure Levels to Asbestos in the Workplace Altered the Frequency of Mesothelioma?

As noted earlier, there remains considerable discussion regarding whether lung cancer occurring in an asbestos-exposed worker requires the presence of asbestosis for causation or can be attributed to asbestos exposure alone. Mesothelioma, on the other hand, is recognized as the most sensitive and specific marker of adverse health effects attributed to asbestos [53]. It is sensitive because this tumor can develop from lesser exposures [given substantial (usually more than 30 years) latency] and specific as the great percentage of those with this disease can provide a history of workplace or environmental asbestos exposure. In addition, exposures to amphibole fibers increase this adverse asbestos effect.

The concern is whether the rate of mesothelioma is declining and reflecting the exposure changes that have been made over the past generations. In the United States, for example, a series of changes in the PEL for asbestos resulted in the current standard for exposure being established in 1986. Furthermore, in the United States, the rate of importation and utilization of asbestos has dramatically lessened. Using 2005 data, a review of the annual rate of mesothelioma deaths in 31 countries showed no clear-cut decline compared to 1996 data [54]. In seven countries, the mortality rate increased (in five, this occurred in a statistically significant manner). The mortality rates were equivocal in 24 countries (in five of these countries, rates declined but were not statistically different from the 1996 rates). There was no change in the US rate of change over these 10 years. Countries that banned asbestos showed the greatest declines in annual mortality rates. Not surprisingly, with what is known about the latency effect for the development of mesothelioma, countries with the greatest decline in asbestos utilization during 1970–1985 showed the greatest annual rate of mesothelioma decline.

Even though the data describing mesothelioma rates are presented as age-adjusted, it should be noted that the life span of a population may dramatically affect the mesothelioma mortality rate by decreasing the potential latency period. As an example, the US male life expectancy averages 75–76 years, while in India, the mean span is 60–61 years. Most noticeably, in South Africa, the annual mortality rate for mesothelioma was 40.5 per million white men deaths in 1984. From 1995 to 2007, this rate has held steady at approximately 15 per million deaths per year. Importantly, from 1991 to 2004, the average life expectancy declined from 60.1 to 49 years in black men and from 66.5 to 61.7 years in white men [55]. Because of the well-recognized long latency period of mesothelioma, the many premature deaths due to other illnesses (notably tuberculosis and HIV infection) may well explain the suspected fewer cases of mesothelioma. In this example, the decrease in the number of mesothelioma cases may not be associated with the implementation of dust control measures.

In summary, investigators from many countries are optimistic that the worldwide mortality rate for mesothelioma will change from essentially "holding steady" to substantially declining over time. This has not yet clearly begun. Yet, these same investigators also caution that the persistence of the most fibrogenic and carcinogenic fibers (specifically, the amphiboles amosite and crocidolite) in the environment in existing structures, the release of asbestos fibers from older buildings during demolition or renovation, and the ongoing mining, importation (as well as the continued utilization of chrysotile asbestos in selected countries) [56] is likely to slow the projected worldwide decline.

How Should Workers with Asbestos Exposure Be Evaluated with Chest Imaging?

The current OSHA standard mandates that workers with recognized exposure to asbestos fibers which are at or exceed the PEL for asbestos must participate in a screening program. This includes a medical and work history, complete physical examination with emphasis on the respiratory, cardiovascular and digestive system, a chest radiograph, lung function tests, and a standardized respiratory questionnaire. Based on the worker's age and years of employment in the workplace, the frequency of such testing varies and as the worker ages and has a longer duration of potential exposure, screening decreases from every 5 years, to every 2 years to yearly [37]. The intent, of course, is to protect the worker's health and to recognize early changes associated with asbestos exposure.

During the decades of the 1960s, 1970s, and 1980s, investigators undertook a number of randomized trials of lung cancer screening of heavy cigarette smokers using either more frequent chest radiographs alone or in association with the relatively frequent routine use of sputum cytology. Although several of these trials showed that more lung cancers could be recognized with the implementation of these screening procedures, this improvement in early detection did not translate into a significant decline in mortality rate [57–61]. A trial comparing annual chest radiograph screening for 4 years to usual care in more than 150,000 participants in middle age and older allowed a mean follow-up of 13 years was recently reported. There was no difference in lung cancer mortality rate in these two groups [62].

With the introduction of more sophisticated screening methods has the "earlier diagnosis" of malignancy altered the outcome of asbestos-associated pulmonary malignancy? An affirmative answer to this question is of great consequence in view of the long-standing dismal outlook for lung cancer; the current 5 year survival of 15.6% when all stages and histological cell types are included [63]. Asbestos exposure is thought to contribute to up 15% of all lung cancers [64].

Low-dose CT (LDCT) allows a low-resolution image of the entire thorax in a single breath hold with low-radiation exposure. Nodules as small as 2–3 mm in diameter are routinely recognized. LDCT identifies many more nodules than the chest radiograph. Although the number of nodules that turn out to be malignant (typically in an early and therefore resectable stage) are increased, the vast majority

of these nodules are benign. Indeed, this has been the experience in asbestos-exposed populations [65–67]. Often, using a 3D reconstruction of images, the physician can gain insight into nodules more likely to be malignant. Yet, overall, this screening approach yields an assessment that is much more sensitive than specific for lung cancer and, until recently, early detection of lung cancer had not been shown to affect mortality [68, 69].

A recent report of more than 50,000 participants showed annual LDCT screening to be more effective than annual chest radiography in prolonging survival in middle aged and older individuals with at least 30 pack years of smoking. On the LDCT scan, any nodule greater than 4 mm in any diameter, and on the chest radiograph any non-calcified nodule or mass was considered suspicious for malignancy. Such abnormalities provoked further clinical investigations as determined by their physicians. Screening was performed in 2002–2004 and mortality outcome assessed in 2010. The authors reported that the power of the study, the high rate of adherence to the screening protocol (approximately 90% of participants), the fact that few participants received screening outside of the study, and a thorough follow-up process were the keys to showing changes in mortality.

This report did not address the risk of cancer attributable to asbestos. Because of the large number of participants needed to show this effect, the clearly defined lung cancer risk associated with 30 pack years of cigarette smoking, and the decline in the prevalence of lung fibrosis associated with asbestos exposure in the United States, it does not appear to be likely that a program to test the hypothesis that LDCT scanning will lessen the mortality rate of malignancy in asbestos-exposed patients will be undertaken. Nevertheless, it may be reasonable to consider the aforementioned screening results in asbestos-exposed cigarette smokers with a high risk for lung cancer.

Conclusion

Dr. Montague Murray is generally credited with reporting the first fatal case of asbestos-related disease in 1907 [70]. It is now more than 100 years since the saga of the health effects due to asbestos began. Despite many reports describing the tragic rates of illness associated with this exposure over this past century, workers in a number of countries continue to have exposure to these fibers. In other countries, the complete banning of this agent will likely alter the natural history of asbestos-related diseases in their country. We hope to see this more clearly as the latency time from the initial ban increases. Finally, although there are issues that may be discussed about asbestos health effects, the great many manuscripts available provide clear insight into the illnesses associated with this exposure.

In the end, one cannot help but conclude that all of these diseases are dose-related. Minimizing, and even better, completely avoiding exposure, is the most effective way to lessen the effects discussed earlier. Even with mesothelioma, an illness often attributed to community environmental exposures to asbestos or to

relatively brief periods of asbestos exposure in the workplace, one cannot help but think that the long latency period would have less of an impact if fewer fibers had been inhaled into the lung.

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Chapter 9
Pneumoconiosis in the Twenty-First Century

Andrew J. Ghio

Abstract While defined pathologically, it is uncommon that the diagnosis of pneumoconiosis necessitates tissue biopsy. The approach initially used by physicians for diagnosis of asbestosis has been extrapolated to all pneumoconioses. This requires meeting criteria of (1) evidence of structural pathology consistent with dust-related disease as documented by imaging, (2) evidence of causation by dust exposure as documented by the occupational and environmental history or markers of exposure, and (3) exclusion of confounders. The first criterion for the diagnosis requires evidence of structural pathology consistent with dust-related disease, and this is most frequently met using chest X-rays interpreted by either a radiologist or a B reader. If there are abnormalities on the chest X-ray, these should be confirmed using a CT scan of the chest. The second criterion requires evidence of causation by dust demanding the physician to obtain a detailed history into all full and part jobs and potential environmental exposures from hobbies. The third and final criterion for the diagnosis of pneumoconiosis requires exclusion of confounders. The most frequent confounders for pneumoconiosis include cigarette smoking, granulomatous disease, aging, and obesity. Therefore, evaluation of the patient for pneumoconiosis must include a history (with emphasis on the history of respiratory illness, past medical history, occupational history, and smoking history), physical examination, pulmonary function tests (including spirometry, lung volumes, and diffusing capacity), and a chest X-ray; a CT scan of the chest may be obtained depending on the interpretation of the posteroanterior film.

Keywords Silicosis • Anthracosis • Asbestosis • Chronic obstructive pulmonary disease

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Introduction

Pneumoconiosis is an interstitial lung disease occurring after inhalational exposure to an inorganic dust (either a particle or a fiber). The responsible exposures most frequently are occupational but can occasionally be environmental [1]. Pathology includes both fibrosis and inflammation with the former predominating. The most common pneumoconioses are silicosis, coal workers' pneumoconiosis (CWP), and asbestosis (i.e., the "classical pneumoconioses"), which are also covered in another chapter in this book.

While pneumoconiosis is defined pathologically, it is uncommon that their diagnoses should necessitate tissue biopsy. The current model used by physicians for diagnosis of pneumoconiosis evolved from the criteria provided by the American Thoracic Society statement on diagnosing nonmalignant disease after asbestos exposure [2]. In the absence of pathologic examination of lung tissue, these criteria recommend that the diagnosis of pneumoconiosis be established after careful consideration of all relevant clinical findings, and there had to be both a reliable history of exposure and an appropriate time interval between exposure and detection. The Ad Hoc Committee of the Scientific Assembly on Environmental and Occupational Health regarded the following clinical findings to be of recognized value: chest roentgenographic evidence of small opacifications, a restrictive pattern of lung impairment with a forced vital capacity below the lower limit of normal, a diffusing capacity below the lower limit of normal, and bilateral later of pan inspiratory crackles at the posterior lung bases not cleared by coughing. However, the findings on the chest roentgenogram were considered the most important. Based on this statement, it became standard practice to require (1) chest X-ray evidence of fibrosis and (2) a significant history of exposure for the diagnosis of pneumoconiosis. These criteria were later amended to include a lack of alternative plausible causes (confounders) [3]. In 2004, the American Thoracic Society again addressed diagnosing nonmalignant disease after asbestos exposure, and the same three criteria were recommended for the diagnosis of asbestosis to be established [4]: (1) evidence of structural pathology consistent with dust-related disease as documented by imaging; (2) evidence of causation by dust exposure as documented by the occupational and environmental history, markers of exposure, or other means; and (3) exclusion of confounders for the findings.

This approach to diagnosis has been extrapolated to all pneumoconioses. For the physician to apply the diagnosis to a patient without available pathology, all three criteria must be fulfilled. The first criterion for the diagnosis requires evidence of structural pathology consistent with dust-related disease, and this is most frequently approached using chest X-rays. The chest X-ray should be interpreted by either a radiologist or a B reader with experience evaluating radiographs for the presence of pneumoconiosis. The diagnosing physician should be cautious in accepting a positive B read obtained during a mass screening as evidence of structural pathology consistent with a dust-related disease since some investigations have shown that approximately 97% of all positive B reads in these mass screenings can be incorrect [5, 6]. The diagnosing physician should be both familiar with the radiologist or B reader

from whom the interpretation is being provided and trustful of her or his judgment. Alternatively, an opinion should be requested from a university-based radiologist or B reader.

If there are abnormalities on the chest X-ray, these should be confirmed using a CT scan of the chest. While there is a higher dose of radiation used by the CT scan, the procedure is both more sensitive and more specific for pneumoconiosis than the radiograph [7]. If a potentially life-threatening diagnosis is to be applied to a patient, there must be confidence in the diagnosis, and CT scan imaging will provide this.

The second criterion requires evidence of causation by dust. This demands the physician obtaining a detailed occupational history into all full and part-time jobs from the first to the present. It is best to begin by inquiring what jobs the patient had during school and did the patient graduate high school. From the time of graduation, she or he should be allowed to progress through the years reporting what jobs were held and what exposures potentially occurred. Under certain circumstances, the parents' and spouse's occupations may also be significant. It is rarely adequate to have the job title and industry the individual worked in. The products, the manner of manipulation, frequency of the operation, and duration of such work should be recorded. However, these subjective estimates of dust exposure are recognized to be fraught with difficulties because an individual's estimate of exposure is subject to poor recall of what conditions were really like decades prior to the development of disease, poor appreciation of what was in the dust to which she or he was exposed, and perhaps exaggeration because of the prospect of compensation [8]. Potential exposures of the home environment should be examined by asking if the patient has any hobbies that expose her or him to dusts or fumes. With asbestos exposure, objective evidence of exposure can be and should be searched for (i.e., pleural plaques and asbestos bodies in sputum and lavage fluid).

The third and final criterion for the diagnosis of pneumoconiosis requires exclusion of confounders. The most frequent confounder for pneumoconiosis that every physician must exclude is cigarette smoking. Pathologically, an increased deposition of collagen and fibrosis can be observed in the lungs of many cigarette smokers [9, 10]. Irregular opacities reflecting fibrosis (comparable to those in pneumoconiosis) can be observed on their chest X-rays [11–14]. Such misinterpretation of the smoker's chest X-ray as supporting pneumoconiosis reveals its lack of specificity. While it frequently assists in clarifying whether dust-related lung disease is truly present, abnormalities consistent with pneumoconiosis can be present even on the CT scan in cigarette smokers [15]. These can include ground glass opacities (indicating inflammation and early fibrosis), micronodules (indicating respiratory bronchiolitis), and bronchiolectasis [16–19].

A feasible approach to evaluating the patient for pneumoconiosis is to include a history (with emphasis on the history of respiratory illness, past medical history, occupational history, and smoking history), physical examination, pulmonary function tests (spirometry, lung volumes, and diffusing capacity), and chest X-ray (Fig. 9.1). An arterial blood gas can also be obtained and should be when either the clinical presentation or finger oximetry suggests hypoxemia. If the chest X-ray is supportive of pneumoconiosis, a CT scan of the chest should be obtained.

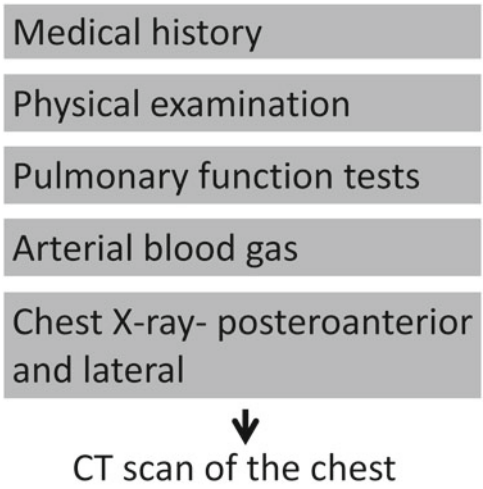

Fig. 9.1 Recommended evaluation for pneumoconiosis

Silicosis

Silicosis is one of the most ancient of diseases with its description first being reported among those working with rock during the Greek Empire. This pneumoconiosis became a greater public health problem after the industrial revolution introduced mechanization (e.g., use of power drills), which increased both dust levels and the number of exposed workers. Outbreaks in the United States included the Joplin, Missouri, epidemic from 1911 to 1916, and this further delineated the strong relationship between silica exposure, lung disease, and human mortality [20]. It was the scandal at Hawk's Nest Tunnel in Gauley Bridge, West Virginia, during 1930 and 1931 that thrust silicosis into the spotlight of the media and introduced the general public to the disease [21, 22]. In an 18-month period between 1930 and 1931, 5,000 workers assembled in rural West Virginia to drill a tunnel through Hawks Nest Mountain at Gauley Bridge. The tunnel diverted water from the New River for purposes of energy and necessitated drilling and blasting 16,250 ft through rock that was identified and confirmed to consist of industrial grade silica (>90% crystalline content). Despite prohibition by law, dry drilling was employed. Extreme dust levels resulted, and an unknown number of workers (700 by one estimate) suffered silicosis and died. Silicosis was then recognized as the "King of Occupational Diseases" [22]. In the 1960s, after being declared a disease of the past in the United States, widespread silicosis was documented among workers at the Avondale Shipyards in Louisiana [23]. Cases of silicosis (hundreds per year in the United States) have continued to be reported especially in foundry work, tunneling, and mining, sandblasting, and quarrying. Most recently, an epidemic of silicosis was recognized by a group of Turkish pulmonologists among a very young group of jean sandblasters [24]. The disease persists in both developing and developed countries as a result of not applying dust protective measures.

Three forms of silicosis are recognized: chronic, accelerated, and acute [25, 26]. Chronic silicosis is the classic form of the disease (i.e., simple silicosis with fibrotic nodules or complicated silicosis/progressive massive fibrosis (PMF) with confluent lesions replacing lung parenchyma) that develops after 10 or more years of silica exposure. While clinical manifestations are comparable to chronic silicosis, accelerated disease presents within 10 years of the initial particle exposure. Acute silicosis occurs within weeks to 5 years after the initial exposure and, relative to chronic and accelerated forms, exhibits greater evidence of inflammatory injury and is associated with higher dust levels.

Almost exclusively, physicians in the United States are inquired regarding the diagnosis of chronic silicosis. It would be unusual to either have or require biopsy material for diagnosing this disease; the exception to this is a complicated lesion occurring with a lower profusion of small opacities resulting in a question of lung carcinoma and therefore biopsy would follow. If there is tissue considered diagnostic for silicosis, there must be silica nodules and fibrosis; the presence of polarizable material alone is inadequate.

Regarding diagnosis of silicosis when there is no pathology available, meeting the first criterion of evidence of structural pathology consistent with silica-related disease usually requires a chest X-ray interpreted by a radiologist or B reader. Some abnormal profusion (1/0 or greater) of rounded opacities (p, q, and/or r lesions) is observed in the superior aspects of the lungs. The involvement is bilateral and most commonly symmetrical in distribution. Irregular opacities in the bases should not be considered as supportive of silicosis. If the chest X-ray is positive, a CT scan of the chest should be obtained to confirm the presence of small, rounded opacities with greater involvement in the superior portions of the lungs. While pneumoconiosis can be evident on the CT scan of the chest and absent on the chest X-ray, my experience has been that this is unusual in silicosis (less than 5% of all individuals with silicosis). Complicated lesions present radiographically with a diameter >10 mm. While symptoms, loss of pulmonary function, and increased morbidity and mortality are unusual with simple disease, they are observed with some frequency in complicated disease.

To meet the second criterion of evidence of causation by silica exposure, there is the occupational history; objective indices of a significant silica exposure equivalent to either pleural plaques on the chest X-ray or lavage and sputum asbestos bodies following fiber exposure have not yet been defined. Those occupations most frequently associated with silicosis are foundry work and mining. A minimum of 10 years of exposure is usually required to increase the individual's risk for the chronic form of this pneumoconiosis. There are domestic products whose exposure can increase the risk for silicosis [27–29]. While amorphous silica can be associated with granuloma formation [30], only crystalline forms cause silicosis.

The final criterion for the diagnosis of silicosis requires exclusion of confounders. The major confounders for this diagnosis include smoking and granulomatous disease. It is common for individuals to have fibrotic residua from previous granulomatous disease, especially histoplasmosis and tuberculosis. Chest X-rays and CT scans of the chest that demonstrate conglomerate masses but no background profusion

of small opacities suggest old granulomatous disease. Similarly, calcification of lymph nodes, large lung masses, and small opacities can be observed with silicosis but are more frequently observed with granulomatous disease.

Accelerated silicosis is pneumoconiosis that occurs within 5–10 years of initial exposure [25]. Such disease requires higher levels of silica exposure relative to chronic silicosis. In accelerated silicosis, inflammation, scarring, and symptoms progress at a faster rate. These patients are at greater risk for complicated disease. Acute silicosis usually follows only weeks or months of exposure (or as long as 5 years after the exposure) to large concentrations of crystalline silica usually in unregulated occupational environments [31]. The clinical presentation can approximate that of patients with a pulmonary alveolar proteinosis. The lungs are extremely inflamed and fill with a fluid abundant in phospholipids. There is shortness of breath and low blood oxygen levels. The radiology reveals a diffuse alveolar filling with hazy, diffuse infiltrates, air bronchograms, and ground glass opacities.

All forms of silicosis (chronic, accelerated, and acute) can be complicated by an increased risk for mycobacterial infections including tuberculosis [32]. Patients with silicosis should be closely observed for any evidence of mycobacterial infection. Latent and active infection must be treated promptly. Treatment of active tuberculosis in an individual with silicosis may require prolonged, or even life-long, provision of antimycobacterial agents.

Finally, exposure to silica can also be associated with COPD comparable to numerous particles. Cough and phlegm production was previously recognized as an industrial bronchitis while emphysema is most frequently focal [33].

There are extrapulmonary diseases associated with silica exposure, and these are lung cancer and scleroderma [34]. The practicing physician is frequently called upon to opine whether there is a causal association between the lung cancer or scleroderma and the patient's exposure to silica. To suggest that this disease is attributable to silica, the patient must meet the criteria for the diagnosis of silicosis.

Coal Workers' Pneumoconiosis

The field of lung injury after exposure to coal mine dust is complicated by a lack of uniform definitions. CWP is interstitial lung disease following exposure of underground miners to coal dust, while Black Lung is a lay term used to refer to any lung disease associated with the same exposure, for example chronic obstructive pulmonary disease (COPD) after coal dust exposure. Lung disease associated with coal dust exposure was first reported in 1822 as "miner's asthma" (cough and shortness of breath). Mechanization with the introduction of drills into the coal mine produced higher dust levels. As a result of study among coal miners in Wales (initiated in 1937 by the British Medical Research Council), CWP was recognized in Britain in 1942. At this same time, there was little research conducted in the United States. However, following a mine explosion at Farmington, West Virginia, in which 78 miners died (on November 20, 1968), a movement erupted in Appalachia demanding

a federal health and safety law that would recognize and compensate Black Lung [35]. In the Coal Mine Health and Safety Act of 1969, allowable dust levels in mines were reduced, disease was compensated, and those suffering disease were transferred away from dust without changes in pay. The Black Lung Benefits Program pays monthly payments to disabled miners, widows, and dependents.

CWP is a condition characterized by permanent deposition of substantial amounts of particulate material in the lungs and the fibrotic reaction of the lung tissue to that deposition caused by dust exposure in coal mine employment. Biopsy is infrequent in CWP but, similar to silicosis, an exception would be a complicated lesion occurring with a lower profusion of small opacities presenting the issue of possible lung carcinoma. Pathologically, coal macules are required for the diagnosis; anthracotic material alone does not suffice.

The first criterion for the diagnosis of CWP, when biopsy material is unavailable, is evidence of structural pathology consistent with dust-related disease and this is metal almost always with a chest X-ray. The medicolegal definitions for this pneumoconiosis were written prior to widespread availability of CT scans and thus do not rely on CT scans. In addition, it is required by the regulations that the chest X-ray be interpreted by a B reader who is also a radiologist (e.g., an internist or pulmonologist who B reads may not suffice). Most frequently, the pneumoconiosis is evident as small, rounded opacities in the superior aspects of the lung (comparable to silicosis). If the radiograph is positive for the presence of pneumoconiosis (profusion 1/0 or greater), a CT scan of the chest is helpful to verify the disease. It is uncommon for the chest X-ray to be negative and the CT scan still demonstrates pneumoconiosis but this does occur.

The criterion of evidence of causation by coal dust exposure is met with ten years or more of underground mining. The jobs at greatest risk for CWP are those closest to the face of the mine and the continuous miner, which is a major source of the dust. Duration at the specific position and the proximity to the face should be noted.

The third criterion for the diagnosis requiring exclusion of alternative confounders is most frequently challenged by smoking and granulomatous diseases, comparable to silicosis. Chest X-rays and CT scans of the chest should be examined for the presence of simple pneumoconiosis and calcification. Large masses (>10 mm in diameter) alone are not usually associated with pneumoconiosis unless there is also a background profusion of small opacities; with no such background profusion, the X-ray may suggest granulomatous disease. Calcification of lymph nodes, large lung masses, and small opacities support the diagnosis of granulomatous disease. In addition, variability in the size of the individual nodules on the chest X-ray and CT scan and a lack of symmetry support granulomatous disease.

Comparable to silicosis, simple CWP is infrequently associated with symptoms, loss of pulmonary function, and increased morbidity and mortality. However, individuals displaying complicated disease (with a lesion having a diameter >10 mm) can have symptoms, respiratory impairment, and elevated risk for mortality. Recently, there have been reports that the incidence of simple and complicated CWP is increasing [36–38]. The reasons for the increase are unclear. The complicated disease appears to be in continuous miner operators and roof bolters and among

younger workers (both smokers and nonsmokers) in smaller underground mines. These exposures occurred following the implementation of the current federal dust regulations challenging their safety.

The Department of Labor (DOL) manages the Black Lung Benefits Program and defines what is required to meet the medicolegal requirements for their diagnosis of "medical pneumoconiosis". In addition to the history, physical examination, pulmonary function tests, and chest X-ray that would be obtained by physicians, the DOL insists on obtaining arterial blood gases both at rest and with exercise. The purpose of this additional testing is to determine respiratory disability (in contrast to the American Thoracic Society criteria for impairment that uses spirometry and diffusing capacity). While investigation has established that arterial blood gases are unnecessary in the diagnostic evaluation of coal miners for pneumoconiosis and determination of pulmonary disability [39–41], they must be obtained if the intent is to apply through the DOL for benefits.

Legal CWP

Unlike other exposures, coal mining requires the physician to consider what is called "legal pneumoconiosis." The DOL defines this as any chronic restrictive or obstructive pulmonary disease arising out of coal mine employment, including any chronic pulmonary disease or respiratory impairment significantly related to, or substantially aggravated by, dust exposure in coal mine employment. Based on this definition, COPD accounts for the most common diagnosis of "legal pneumoconiosis" among coal miners.

Medicine does recognize development of COPD after coal dust exposure. Complicated CWP can be associated with both obstructive and restrictive pulmonary function. In addition, there is evidence of an association between loss in forced expiratory volume in one second (FEV_1), airway obstruction, and coal dust exposure without evidence of either simple or complicated CWP. There were several studies conducted by the Pneumoconiosis Field Research Program/Institute of Occupational Medicine in Britain that defined a loss of function consistent with obstruction:

- Among 3,581 men, there was a reduction in FEV_1 in both smokers and nonsmokers with increasing dust exposure [42]. There was an average FEV_1 loss of 100 mL in relation to the mean dust exposure of the group studied.
- In 1,677 miners without progressive massive fibrosis (PMF), the decline in FEV_1 over approximately 11 years was greater in those with higher dust exposure [43]. Thus, a cumulative dust exposure of 117 ghm^{-3} was associated with an estimated additional reduction of 42 mL in FEV_1 over the next 11 years.
- In 4,059 men without radiological changes of PMF, lung function at the time of the follow-up survey was related to cumulative exposure to respirable dust [44]. Increasing cumulative exposure to dust was associated with lower FEV_1. Overall, the estimated reduction in FEV_1 was 0.76 mL/ghm^{-3} exposure to respirable dust.

- In 3,380 men who did not have PMF, cumulative exposure to respirable dust was related to risk of four end points: FEV_1 less than 80% predicted; symptoms of chronic bronchitis; symptoms of chronic bronchitis and FEV_1 less than 80% predicted; and FEV_1 less than 65% predicted [45].
- FEV_1 values in 1,286 miners from seven collieries in England who did not have pneumoconiosis on chest radiography were compared to those of 567 male residents in Nottingham [46]. After adjustment, FEV_1 was 155 mL lower in the miners than in the controls, the difference being greatest in younger men.

In the United States, the National Institute for Occupational Safety and Health (NIOSH) similarly conducted several surveys and observed evidence of obstruction:

- Decrements in FEV_1 and forced vital capacity (FVC) were noted in relation to years worked underground among nonsmoking miners who did not have complicated pneumoconiosis [47].
- After adjustment, there was a decline in FEV_1 over 9 years in 1,072 men aged 20–49 in association with work at the coal face, increasing number of years between the surveys spent working underground, increasing estimated average exposure to dust between the two surveys, and increasing years of work underground before the initial survey [48]. The extent of the decline in FEV_1 associated with previous underground work was broadly consistent with the effect of previous dust exposure previously estimated [43].
- After adjustment, exposure to dust was associated with lower FEV_1 in 7,139 white miners aged 25 years or older with the estimated reduction being 0.69 mL/ghm^{-3} [49].
- In 1,185 male miners who had entered the occupation in or after 1970, FEV_1 was lower in men with higher cumulative exposure to dust [50]. The strength of the relation (5.5 mL/mg/year/m^3 or approximately 3.4 mL/ghm^{-3}) was greater than in earlier analyses.
- A further investigation concentrating on 977 men confirmed the association of FEV_1 with cumulative dust exposure [51].

Based on these investigations, it can be concluded that, physiologically, coal miners can demonstrate an accelerated loss of FEV_1. This can occur in the absence of radiographically detected pneumoconiosis. However, these changes in pulmonary function are small. It has been estimated that under the current 2 mg/m^3 federal dust limit, the estimated loss in FEV_1 would be 2–3 mL/year. Therefore, the total loss attributable to coal dust exposure over a career could approximate 100 mL [49]. Such a loss in lung function could potentially result in a mild COPD but not moderate or severe obstructive disease.

The question that the medical field has repeatedly addressed is whether there is a range of severity among individuals exposed to coal dust including some sufficiently severe to be clinically important. It has been suggested that coal dust could lead to disabling airways obstruction in the absence of complicated CWP [52]. Even allowing for individual variation, it appears almost impossible for these losses in pulmonary function described above to ever be of clinical significance. In support of this,

Table 9.1 Clinical presentation of COPD after coal dust exposure and cigarette smoking

	COPD with coal dust	COPD with cigarette smoking
Respiratory symptoms	Cough/phlegm, dyspnea (usually mild)	Cough/phlegm, dyspnea, wheeze, paroxysmal nocturnal dyspnea, orthopnea
Lung examination	Abnormal findings are infrequent	There can be increased hyperinflation, decreased breath sounds, wheezes, rales
Pulmonary function tests	Mild obstruction usually	Mild, moderate, or severe obstruction with increased volumes and decreased diffusing capacity
Arterial blood gas	Hypoxemia is infrequent	Hypoxemia and hypercarbia are common
Chest X-ray/CT scan	No evidence of hyperinflation	Hyperinflation, increased bronchovascular markings at bases
Treatment	Usually not required	Therapy can include inhaled agents, theophyllines, corticosteroids, and home oxygen
Patient's course	Not complicated by exacerbations requiring hospitalization or respiratory failure	Complicated by exacerbations requiring hospitalization and respiratory failure

in an evaluation of 611 Black Lung claimants, there was only one subject who was a nonsmoker and had sufficient airways obstruction to render it difficult for him to carry out hard labor [52]. The conclusion from this investigation was that, in the absence of smoking and complicated CWP, if the inhalation of coal dust ever induces sufficient ventilatory impairment to preclude a miner from working, it is indeed rare.

In industrialized nations, severe COPD is most frequently associated with cigarette smoking. COPD after coal dust exposure can be differentiated from COPD after smoking in many cases based on severity (Table 9.1).

Asbestosis

The commercial exploitation of asbestos began after 1870, and the first description of asbestosis followed in 1906. This was a report by Dr. H. Montague Murray to a British parliamentary committee of a 33-year-old man who had worked for 14 years in the carding section of an asbestos textile plant. Cooke recorded additional reports of pulmonary fibrosis in asbestos workers in 1924 and 1927 and coined the term "asbestosis" [53, 54].

Following asbestos exposure, different lung injuries can occur, and a dependence on the magnitude of fiber exposure has repeatedly been demonstrated (Fig. 9.2). Lower intensity exposures can result in pleural plaques. Higher levels of exposure can be associated with an increased risk of mesothelioma. Finally, the greatest

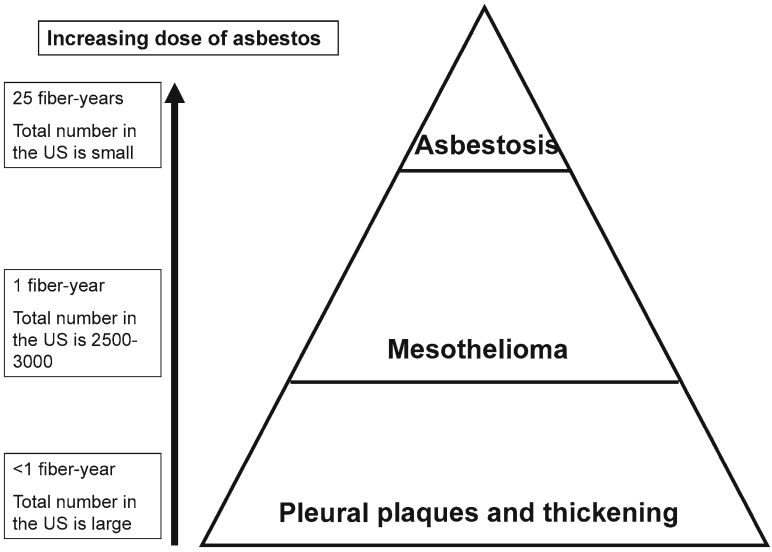

Fig. 9.2 Dose response for asbestos-related disease

exposures to asbestos can elevate the risk for both lung cancer and asbestosis. The total number of individuals diagnosed to have asbestosis must consequently be less than that of those with mesothelioma. It is difficult to calculate with certainty how many cases of asbestosis are expected on a yearly basis in the United States. However, an estimate can be obtained. Because mesothelioma is closely associated with asbestos exposure and rarely escapes medical attention, the rate of this cancer can be used to estimate the number of cases of asbestosis expected in a population. In a recent surveillance of work-related respiratory disease, the ratio of mesotheliomas to cases of asbestosis approaches 3-to-1 [55]. Using this ratio, the number of asbestosis cases per year in the United States is estimated to be 1,000 or less.

Pathologic diagnosis of asbestosis is very rarely obtained but requires evidence of an interstitial lung disease with asbestos bodies (2 or more per cm^2 on the slide). Regarding the first criterion for the diagnosis of asbestosis when tissue is not available (i.e., evidence of structural pathology consistent with fiber-related disease), the chest X-ray must be interpreted by either a radiologist or a B reader with experience evaluating radiographs for the presence of pneumoconiosis. If the posteroanterior film is abnormal, a CT scan of the chest should be obtained to confirm asbestosis. Radiographic procedures will demonstrate irregular, rather than rounded, small opacities bilaterally with involvement of the lower lung fields. It is not possible to diagnose asbestosis solely based on either unilateral disease or interstitial markings in the superior aspects of the lung. Complicated disease does not occur in asbestosis.

The occupational history should clearly support evidence of causation. Among all the asbestos-related diseases, asbestosis is the injury associated with the greatest exposures to asbestos. Prior to the 1980s in the United States, insulators, shipyard work,

plumbers, pipefitters, boilermakers, and electricians frequently had a significant exposure to asbestos great enough to increase the risk for asbestosis [56–61]. Much of this exposure resulted from a manipulation of amphiboles in thermal insulation. However, cases are now being reported among workers in industries that have never previously been associated with an elevated risk of asbestosis by any study in the medical literature. The reason for this lack of an increased risk in certain jobs is that, while asbestos is employed, fiber levels have never been reported in these occupational settings to approach values associated with asbestosis (approximately 25 fiber-years). These occupations include

- *Railroad workers*. Fiber exposure in the railroad industry (chrysotile and amosite) was significant in the steam engine era as a result of its use in insulation. Workers had to apply and periodically remove magnesia blocks (85% magnesium and 15% asbestos) in the locomotive repair shop. Asbestos was also used to insulate pipes and cars. With the introduction of diesel engines, the risk for asbestosis was greatly diminished, if not eliminated, in this industry.
- *Power plants*. Potential exposures to asbestos in power plants included insulation on turbines, generators, boilers, and pipes carrying steam. Asbestos-related disease, including asbestosis, was previously shown to be elevated among power plant workers [62–64]. More recent investigation demonstrated no relationship between employment in a power plant and lung cancer, suggesting that the higher levels of fibers required to increase the risk for asbestosis and asbestos-related lung cancer might not be present [65, 66].
- *Oil refineries*. Asbestos was employed in thermal insulation, boilers, pumps, gaskets, and valve packing in oil refineries. However, exposure to fibers at an oil refinery does not include those higher levels associated with asbestosis and asbestos-related lung cancer [67, 68].
- *Paper and pulp mills*. Asbestos is not a raw material used in paper and pulp production but can be found in pipe insulation, boilers, in brakes, in gaskets, felts, and as a contaminant in talc (utilized in the industry as filler or to prevent the deposition of pitch). Accordingly, some exposure of workers to fibers does result. Reflecting this, there have been reports in the literature showing an increased incidence of mesotheliomas [69, 70]. However, workers in the paper and pulp mill industry have not been shown to be at increased risk for lung cancer and asbestosis [69, 71–73].
- *Aluminum workers*. There is little published data to support the contention of an exposure to asbestos among aluminum workers great enough to increase the risk for asbestosis. While one investigator raised the possibility of asbestosis in aluminum workers [74], these results were not verified by other studies. Epidemiologic investigation has not demonstrated an elevated risk for lung cancer among aluminum workers with 30 years exposure [75] suggesting that elevated fiber levels are unlikely to be observed in this occupational setting.
- *Rubber and tire workers*. While thermal insulation is employed in this industry, there has been no report of asbestosis. Evaluating for asbestos-related lung cancer, which requires approximately the same level of exposure, there have been

conflicting studies [76, 77]. Levels of asbestos were reported to be below the permissible exposure limit.

- *Garage mechanics.* While preliminary results were reported describing a possible increased risk for asbestosis among mechanics [78], other investigations of asbestosis in this group have convincingly demonstrated a lack of risk [79, 80].

In addition to the occupational history, there are objective measures of a significant asbestos exposure, and these include pleural plaque and thickening and asbestos bodies in the sputum and lavage. Pleural plaques tend to occur 20–30 years following a worker's exposure. The classic distribution on the chest radiograph is at the posterolateral chest wall between the seventh and tenth ribs; the apices and the costophrenic angles are typically spared. Calcification is reported in 10–15% of cases. Among patients with asbestosis, 80% will have co-existent pleural disease on the chest X-ray, and this number rises to 100% with the use of high-resolution CT scans [81, 82]. If asbestos bodies are observed in sputum and bronchoalveolar lavage, this defines a significant exposure [83, 84]. However, such ferruginous bodies are rarely observed in respiratory fluids.

Finally, the major confounders of the diagnosis of asbestosis are cigarette smoking, aging, obesity, and congestive heart failure.

Frequently, there is an issue of a possible association between a patient's lung cancer and any asbestos exposure she or he might have had. To associate a lung cancer with exposure to asbestos, physicians employ different criteria but many use the "Helsinki Criteria" [85]. The Helsinki Criteria stated that lung cancer can be attributed to asbestos based on the following:

1. The exposure history reports one year of heavy exposure (e.g., manufacturing of asbestos products, asbestos spraying, insulation work with asbestos materials, demolition of old buildings) or 5–10 years of moderate exposure (e.g., construction and shipbuilding).
2. Estimated cumulative exposures to mixed asbestos fibers of 25 fiber years.
3. A lung fiber burden within the range recorded for asbestosis in the same laboratory.
4. Retained fiber levels of two million amphibole fibers (>5 μm) per gram of dry lung tissue or five million amphibole fibers (>1 μm) per gram of dry lung tissue as determined by electron microscopic analysis.
5. Asbestos body concentrations determined by light microscopic analysis greater than 10,000/g of dry lung tissue.

Anecdotal estimates of fiber exposure (included in the criteria 1 and 2) are recognized to be fraught with difficulties because an individual's assessment of exposure is subject to poor recall of what conditions were really like decades prior to the development of the lung cancer, poor appreciation of what was in the dust to which he or she was exposed, and perhaps exaggeration because of the prospect of compensation [8]. If there is no quantified lung fiber burden available, physicians will evaluate for the presence of asbestosis to attribute a lung cancer to fiber exposure [86]. Readers are also referred to Chapter 8 for further discussion on asbestos-related lung diseases.

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Chapter 10
Inhalation Injury

David J. Prezant, Dorsett D. Smith, and Lawrence C. Mohr, Jr.

Abstract Chemicals with potential toxicity are regularly used and produced in a variety of industrial processes. Individuals may suffer inhalation exposures to potentially toxic gases in the workplace, the general environment, including the home or as smoke inhalation during a fire, or as weapons of mass destruction. In this chapter we review the basic determinants of inhalation exposure as well as the pathophysiology, diagnosis, and management of inhalation lung injury caused by chemical asphyxiants and irritant toxic gases.

Keywords Acute inhalation injury • Toxic gas • Asphyxiants • Irritants • Particulates • Smoke inhalation

Overview

Chemicals with potential toxicity are regularly used and produced in a variety of industrial processes. If inhaled, they may cause asphyxiation or lung injury. Although there is increased concern that toxic gases may be used as weapons of mass destruction, accidental exposures remain the greatest health threat [1]. Individuals may be exposed to the accidental release of toxic gases in the workplace [2] or in the general

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Table 10.1 Toxic products of combustion in residential fires

Acetaldehyde	Hydrogen fluoride
Acrolein	Hydrogen sulfide
Ammonia	Isocyanates
Carbon monoxide	Metals (Pb, Zn, Mn, Cd, Co)
Chlorine	Oxides of nitrogen
Hydrogen chloride	Phosgene
Hydrogen cyanide	Sulfur dioxide

environment, including the home [1] or as smoke inhalation during a fire [3]. Smoke inhalation is a multi-chemical and particulate matter exposure, where large amounts of carbon monoxide, hydrogen cyanide, hydrogen chloride, acrolein, sulfur dioxide, phosgene, and other toxic irritant gases are produced (Table 10.1).

Toxic agents can be inhaled in different physical states. A gas is a substance that, at standard temperature and pressure (STP), has the ability for its molecules to diffuse freely and be distributed uniformly throughout any container. The denser the gas compared to air, the heavier it is and the more likely exposures are to occur in low areas. Cold gases are denser than the same gas at higher temperatures. A vapor is a substance in the gaseous state that normally exists as a liquid or solid and is formed when a substance is heated above its critical temperature. Dusts are fine particles of a solid organic or inorganic material that are small enough to be airborne, typically ranging from 0.1 to 25.0 μm in diameter. Dusts can be coated with chemicals. Fumes are extremely fine solid particles that are dispersed into the air by the combustion or melting of solid materials, particularly metals. Fumes usually consist of particles that range from 0.001 to 1.0 μm in diameter. Smoke consists of airborne particles resulting from the incomplete combustion of organic materials. These particles either contain or are coated with multiple chemical substances resulting from combustion and range in size from less than 0.3 μm to greater than 10 μm in diameter.

This chapter's focus is on the diagnosis and treatment of acute inhalation injury resulting from asphyxiant gases, toxic irritant gases, and smoke.

Asphyxiant Gases

Background

Asphyxiants are gases that cause tissue hypoxia. They are classified as either *simple asphyxiants* or *chemical asphyxiants* based on their mechanism of toxicity. Simple asphyxiants displace or dilute oxygen in the ambient atmospheric air causing a decrease in the fraction of oxygen in inspired air (Fio_2). They can be lighter or heavier than air. Those lighter than air (e.g., acetylene, ethylene, methane, neon, and nitrogen) accumulate and displace oxygen in higher areas first, whereas those that

are heavier than air (e.g., argon, butane, carbon dioxide, ethane, natural gas, and propane) accumulate and displace oxygen in low-lying areas first.

In general, once the Fio_2 has decreased to 0.15, acute signs and symptoms of hypoxia begin to appear within minutes. These include dyspnea, tachypnea, tachycardia, confusion, incoordination, and dizziness. As the Fio_2 decreases below 0.10, lethargy or coma may develop as a result of cerebral edema, and cardiopulmonary arrest may occur. Brain damage sustained as a result of extensive cerebral edema or prolonged hypoxia may be permanent in individuals with these conditions who are resuscitated and survive.

Chemical asphyxiants interfere with physiological processes associated with the uptake, transport, or utilization of oxygen. Agents that decrease oxygen carrying capacity include carbon monoxide, hydrogen sulfide, and oxides of nitrogen. Agents that inhibit cellular oxygen utilization include acrylonitrile, hydrogen cyanide, and hydrogen sulfide.

Carbon Dioxide

Pathophysiology

Carbon dioxide (CO_2) is the most common simple asphyxiant. It is produced by aerobic metabolism and is exhaled into the atmosphere by humans and other animals. It is also a byproduct of carbohydrate fermentation, the combustion of carbonaceous material, and the oxidation of coal contaminants in coal mines. It exists in the frozen form as dry ice. CO_2 is heavier than air and reduces Fio_2 simply by diluting and displacing oxygen in ambient air. Most deaths from CO_2 asphyxiation result from the confinement of an individual in enclosed or poorly ventilated space. Such closed-space confinement prevents air with a normal Fio_2 from entering while exhaled CO_2 is accumulating and displacing oxygen inside. Simple asphyxiation from CO_2 has also been reported from environmental exposures. In 1986, for example, simple asphyxiation caused approximately 1,700 deaths from a cloudy mist of CO_2 and water droplets that rose suddenly from a lake in Cameroon [4]. Asphyxiation from CO_2 has also been reported by off-gassing from dry ice in a confined space [5].

Diagnosis and Management

CO_2 asphyxiation should be considered in any patient who presents with clinical signs of hypoxia, is unconscious, or is found to be in cardiopulmonary arrest after removal from an enclosed space or another source of potential CO_2 exposure. Clinical signs are nonspecific and related to the magnitude of hypoxia. Arterial blood gases, serum electrolytes, and measurement of the anion gap should be obtained. During and shortly after CO_2 asphyxiation, arterial blood gas analysis would be expected to show decreased arterial oxygen tension (Pao_2) and elevated carbon dioxide tension ($Paco_2$). However, both Pao_2 and $Paco_2$ typically return to

normal shortly after the patient is removed from the source of CO_2 exposure. Once the patient breathes oxygenated air, CO_2 is rapidly excreted by hyperventilation. Most patients will be acidotic at the time of presentation as a result of respiratory acidosis from CO_2 retention and concurrent lactic acidosis from hypoxia. Lactic acidosis will cause an elevated anion gap. The respiratory acidosis typically resolves shortly after removal from the source of CO_2 exposure. The lactic acidosis will resolve once tissue oxygenation returns to normal, but usually takes longer to resolve than the respiratory acidosis. The hypoxia caused by CO_2 asphyxiation can cause cardiac arrhythmias and myocardial infarction, especially in individuals with underlying heart disease. Therefore, an electrocardiogram and serial cardiac biomarkers should be obtained.

Removal from the source of exposure and administration of oxygen are the only specific therapies for CO_2 asphyxiation. If the patient is alert, has spontaneous respirations, and has a patent airway, it is recommended that high flow oxygen be administered by a nonrebreather mask. Endotracheal intubation will be required if adequate oxygenation cannot be achieved by the use of a face mask or the patient has suffered mental status changes or cardiopulmonary arrest. Additional supportive care, such as cardiopulmonary resuscitation, hemodynamic support, manual ventilation, and mechanical ventilation should be used as required by the patient's overall condition. Cardiac arrhythmias and myocardial infarction should be aggressively treated. Most victims of CO_2 asphyxiation will recover completely if removed from the source of co_2 exposure prior to cardiopulmonary arrest and given medical treatment as soon as possible. Individuals who have experienced a prolonged period of hypoxia, however, may have irreversible brain damage and chronic neurological sequelae if they are successfully resuscitated.

Carbon Monoxide

Pathophysiology

Carbon monoxide (CO) is a colorless, odorless, tasteless, nonirritating gas. It is the most common chemical asphyxiant. CO is produced during incomplete combustion from fires, faulty heating systems, internal combustion engines (including gas-powered generators placed in poorly ventilated areas during electrical failures), wood stoves, charcoal grills, volcanic eruptions, and a variety of industrial processes. In vivo hepatic production of CO occurs in poisoning from methylene chloride that is commonly found in paint thinners and is easily absorbed through the skin.

Most deaths from CO poisoning in the United States are intentional from exposures to motor vehicle exhaust. CO poisoning is responsible for 80% of fatalities related to smoke inhalation [6, 7]. Twenty-five percent of fatalities from CO poisoning occur in persons with underlying cardiopulmonary disease [7, 8].

Once inhaled, CO easily diffuses across alveolar-capillary membranes in the lung and is rapidly taken up by erythrocytes in the pulmonary capillary blood. CO competes with oxygen for hemoglobin binding sites and, as a result of its greater affinity, 240 times that of hemoglobin for oxygen, displaces oxygen from hemoglobin.

Table 10.2 Clinical manifestations of carbon monoxide intoxication

%HBCO level	Clinical Manifestations
0–5	Normal non-smoker
5–10	Mild Headache, Shortness of breath with exertion, Decreased exercise tolerance, Decreased angina threshold
10–20	Moderate Headache, Fatigue, Dizziness, Blurred Vision, Nausea, Decreasing threshold for exertional shortness of breath with possibly shortness of breath at rest
20–30	Severe Headache, Confusion and impaired judgment, Vomiting, Shortness of breath at rest, Decreased cardiac arrhythmia threshold
30–40%	Muscle weakness, Incapacitation, Cardiac arrhythmias, Decreased seizure threshold
40–50	Seizures, syncope, Cardiac Arrest
50–60	Fatal

The binding of CO to the iron moiety creates an allosteric change in the hemoglobin molecule that inhibits the off-loading of oxygen in the peripheral tissues and causes a shift of the oxyhemoglobin dissociation curve to the left. CO also interferes with intracellular oxygen utilization by inactivating intracellular respiratory enzymes, such as cytochrome oxidase [9]. Thus, the cumulative effect on peripheral oxygen delivery and utilization is greater than that expected from decreased oxygen transport alone [10]. Reoxygenation injury of the brain has also been described [11]. Thus, CO toxicity involves four pathophysiological mechanisms: (a) a decrease in hemoglobin's oxygen-carrying capacity; (b) decreased oxygen delivery to peripheral tissues as a result of the left shift in the oxyhemoglobin dissociation curve; (c) mitochondrial dysfunction and impairment of cellular respiration by inhibition of cytochrome oxidase; and (d) brain cell injury during reoxygenation. It has also been suggested that an immunological response to myelin basic protein may be involved in the delayed neurological dysfunction that is seen in many patients with serious CO poisoning occurring between 3 days and 4 weeks postexposure [12].

The clinical signs of CO poisoning are highly variable (Table 10.2). Early symptoms include headache, dizziness, sore throat, nausea, shortness of breath, and fatigue. These symptoms mimic those of a nonspecific viral syndrome that occur in the winter at the very time when heating systems and generators are in use. Impaired ability to concentrate is a frequent symptom. Mental status changes, seizures, loss of consciousness, tachypnea, tachycardia, cardiac dysrhythmias, hypotension, and myocardial ischemia are likely to occur when the carboxyhemoglobin concentration exceeds 20% [13]. With such elevations, loss of consciousness may occur rapidly and without warning. The threshold CO level for cardiovascular disorders will be lower in subjects with preexisting cardiopulmonary diseases. Evidence of myocardial ischemia has been observed in one third of individuals with moderate to severe CO intoxication, and it has recently been reported that myocardial injury, as determined by elevation of serial cardiac biomarkers, is an independent predictor of mortality from CO poisoning [8, 14, 15]. Metabolic acidosis occurs as a result of increased lactate production from tissue hypoxia and anaerobic metabolism. Rhabdomyolysis can occur as a consequence of impaired aerobic metabolism in skeletal muscle cells. Carbon monoxide poisoning is almost always fatal when levels exceed 60% [6, 16].

Fetal hemoglobin has a much greater affinity for CO than adult hemoglobin. Therefore, during pregnancy the fetus is more susceptible to CO poisoning than the mother. Once the mother is removed from the source of CO, clearance of carboxyhemoglobin may take 4–5 times longer in the fetus than in the mother [17]. Risks include ischemic brain damage to the fetus and increase the risk of stillbirth [18, 19].

In 10–30% of survivors, carbon monoxide poisoning may result in a delayed neuropsychiatric syndrome presenting at any time between 3 days and 4 months postexposure [6, 20]. Symptoms include cognitive impairment, personality changes, Parkinsonism, incontinence, focal neurological deficits, dementia, and psychosis. Loss of consciousness during the acute illness phase, carboxyhemoglobin greater than or equal to 25%, duration of exposure, and age appear to be significant risk factors [13], but delayed neuropsychiatric syndrome can occur even after low level CO toxicity. Brain imaging studies have shown that the areas most affected are the globus pallidus and deep white matter [6]. The exact mechanism for the development of this syndrome is unclear, but may be the secondary to reoxygenation brain injury. Most affected individuals recover within 1 year, although some may have chronic, long-term neurological or psychiatric impairment [6].

Diagnosis and Management

Because CO poisoning can present with a variety of nonspecific signs and symptoms, a high index of suspicion is needed to make the diagnosis. Although cherry-red lips, cyanosis, and retinal hemorrhages are the classic signs of high-dose CO poisoning, this classic presentation is rare and the diagnosis depends on clinical history substantiated by elevated blood carboxyhemoglobin levels (arterial or venous sampling) [6]. Carboxyhemoglobin is most accurately measured by CO-oximeter because routine pulse oximetry cannot distinguish between carboxyhemoglobin and oxyhemoglobin. Pao_2 is also of little value since in the absence of coexistent lung injury it is normal. This is due to the fact that a CO partial pressure of only 1 mmHg in arterial blood can saturate over 50% of hemoglobin without affecting gas exchange or the amount of dissolved oxygen.

Recently, noninvasive CO-oximeter has become commercially available. Studies show that it has a high degree of specificity but poor sensitivity [21, 22]. Using a cutoff of 15% carboxyhemoglobin, noninvasive CO-oximetry had a poor sensitivity of 48% (correctly identified only 11 of 23 patients with elevated levels) but an excellent specificity of 99% (correctly identify 96 of 97 patients with levels below 15%) [22]. It is probably most useful in environments where it is difficult or not possible to obtain blood measurement such as by Emergency Medical Service units in the pre-hospital environment [23].

The evaluation of patients with CO poisoning should also include a thorough examination for evidence of thermal injury to the skin or airways. If CO poisoning is the result of a suicide attempt, a drug screen including serum ethanol, salicylate, and acetaminophen levels should also be obtained. Another advantage of measuring the arterial carboxyhemoglobin level is that it also allows for simultaneous measurement of arterial pH. The pH can be used in conjunction with the anion gap

and the serum lactate level to assess the degree of metabolic acidosis which when elevated is an independent predictor of poor prognosis [6]. The serum creatine kinase level will be elevated if rhabdomyolysis has occurred. An electrocardiogram and serial cardiac biomarkers should be obtained in all patients to evaluate the possibility of myocardial ischemia or infarction. CO lowers the threshold for ventricular arrhythmias and therefore, patients should be carefully monitored [24]. The chest radiograph is usually normal, but signs of noncardiogenic pulmonary edema can rarely be seen in cases of severe CO poisoning [16], especially if there is coexistent smoke inhalation. Computed tomography of the head is useful when there is suspicion of trauma or other causes of neurological impairment.

The initial treatment of CO poisoning is prompt removal from the source of exposure and administration of 100% oxygen via a nonrebreather mask to reduce the half-life of carboxyhemoglobin from 4–6 h to 40–80 min [6, 25]. Patients who are unconscious or have cardiopulmonary compromise should be intubated and receive 100% oxygen by mechanical ventilation and hyperbaric oxygen therapy (HBOT) be considered (see below). Oxygen should be administered until the carboxyhemoglobin level returns to normal. Pregnant women typically require oxygen for a longer period of time, because it takes longer for CO to be excreted from the fetus as a result of the greater affinity of fetal hemoglobin for CO [17].

Patients with severe CO poisoning, coexistent smoke inhalation, serious underlying diseases, neurologic or cardiopulmonary instability or whose poisoning was an intentional suicide attempt should be admitted to the hospital for treatment and close observation.

HBOT has been used to treat patients with either extreme levels of CO poisoning (equal or greater than 25% carboxyhemoglobin) or end-organ sensitivity to CO at elevated but lower levels. Examples of this might include neurologic abnormalities or hemodynamic instability that was felt to be caused by CO poisoning. HBOT is performed by placing the patient in a chamber that is highly pressurized with 100% oxygen. HBOT produces a large increase in the amount of dissolved oxygen in blood that in turn greatly increases the partial pressure of oxygen in the blood. The half-life of carboxyhemoglobin decreases as the partial pressure of oxygen in the blood increases. HBOT with 100% oxygen at a pressure of 2.5–3.0 ATA will reduce the half-life of carboxyhemoglobin from 4 to 6 h to approximately 20 min [6, 16, 25].

HBOT when available is currently recommended for patients with CO poisoning meeting any of the following criteria: any period of unconsciousness coma or persistent neurologic abnormalities including delayed neuropsychiatric symptoms [26]; a percent carboxyhemoglobin level exceed 20–25% [26, 27]; metabolic lactic acidosis; or cardiac arrhythmias [6, 8, 13, 20, 28–30]. If myocardial ischemia is present, most experts believe cardiac catheterization with stenting of the blocked vessel to be the urgently required procedure rather than HBOT. In a pregnant patient, fetal distress even at lower % carboxyhemoglobin elevations prompts consideration for HBOT if available.

The clearance of CO can also be accelerated by use of normocapnic hyperoxic hyperpnea. In this technique, the patient breathes a hyperoxic gas mixture that contains an Fio_2 of 95.2–95.5% and a small amount of CO_2, in the range of 4.5–4.8%, through a nonrebreathing circuit. The resulting increase in minute ventilation

increases the partial pressure gradient for oxygen and CO between pulmonary capillary blood and alveolar gas, but does not increase the partial pressure gradient for CO_2. In a clinical study, normocapnic hyperoxic hyperpnea reduced the half-life of carboxyhemoglobin to 31 min in comparison to 78 min in individuals treated with 100% oxygen at normal minute ventilation [31]. CO-poisoned patients in hospitals without access to hyperbaric chambers might benefit from this technique.

In addition to controversy concerning which patients with CO intoxication might benefit most from HBOT, there also exists controversy surrounding the need to also treat for hydrogen cyanide toxicity (see below) in patients suffering severe CO poisoning from smoke inhalation. The likelihood for cyanide toxicity in smoke inhalation victims increases with increasing carboxyhemoglobin levels and increasing acidosis [32].

Hydrogen Cyanide

Pathophysiology

Hydrogen cyanide (CN) is a chemical asphyxiant produced by the combustion of nitrogen-containing polymers during fires [32–34]. It is also part of jewelry making and various manufacturing processes (metal plating) and in the reclamation of silver from photographic and radiographic film. It has the potential to be used as a chemical weapon of mass destruction in a terrorist attack [35]. It is a colorless, volatile liquid at room temperature, but readily vaporizes into a gas. The gaseous form of CN easily diffuses across the alveolar membrane after inhalation. Inhaled CN is lethal in high doses, and its inhalation during a fire can contribute to the mortality of smoke inhalation victims [32–34].

After inhalation, CN is rapidly distributed to tissues throughout the body. At the cellular level, CN molecules bind to iron-containing sites on cytochrome a_3 in mitochondria that inhibits the enzyme's activity toxicity and decreases the cellular utilization of oxygen [32–35]. Cytochrome aa_3 is a key enzyme in the cytochrome oxidase system that is important for carrying out and sustaining aerobic metabolism within cells. Inhibition of cytochrome a_3 by CN will stop cellular respiration and oxidative phosphorylation, forcing affected cells into anaerobic metabolism. The binding of CN to cytochrome a_3, and the resulting inhibition of cellular respiration, occur very rapidly, with clinical signs and symptoms typically occurring within 15 s after inhalation.

The clinical effects of CN intoxication are directly related to its ability to stop cellular respiration. They are nonspecific and identical to the signs and symptoms typically seen from hypoxia. Hyperpnea, dyspnea, tachycardia, agitation, anxiety, dizziness, headache, confusion, nausea, muscle weakness, and trembling are common. Lactic acidosis occurs as a result of anaerobic metabolism and may be severe. Hypotension, flushing, seizures, and Parkinson-like symptoms may occur in cases of severe intoxication. Coma, apnea, and cardiac arrhythmias are poor prognostic signs unless prompt treatment is given [35, 36].

Diagnosis and Management

The diagnosis of CN poisoning requires a high index of suspicion and should routinely be suspected in victims of (1) smoke inhalation, (2) industrial accidents in which cyanide could have been released, and (3) terrorist attacks or (4) when there is no obvious cause for the signs and symptoms of severe hypoxia. Blood and urine cyanide concentrations can be obtained but because this test is not routinely performed in most laboratories, results can only be used to confirm the diagnosis. Treatment for this potentially life-threatening poisoning must be initiated based on diagnostic suspicion alone.

There are several important clues that can be helpful in making a clinical diagnosis of CN intoxication. In smoke inhalation victims, the likelihood for CN poisoning increases with increasing carboxyhemoglobin levels, especially when there is a high anion gap metabolic acidosis from elevated serum lactate [32]. Arterial and venous blood gases can provide potentially useful information by demonstrating "arteriolarization" of venous blood. Arterial oxygen tension is usually above 90 mmHg, whereas venous oxygen tension may be significantly elevated above the normal range of 35–45 mmHg because of poor cellular extraction and utilization of oxygen. Similarly, arterial oxygen saturation is typically in the normal range of 95–100%, whereas the oxygen saturation of mixed venous blood may be in the vicinity of 85% or greater. Thus, the mixed venous oxygen saturation may be significantly higher than the normal range of 60–80%. This so-called "arteriolarization" of venous blood can be a useful clue in the diagnosis of CN intoxication [37].

The effects of CN poisoning progress rapidly and treatment must begin as soon as possible in patients presenting with seizures, coma, hypotension, or cardiac arrest in whom CN toxicity is suspected [38, 39]. The United States Food and Drug Administration has approved two forms of therapy for cyanide toxicity. The newest is the Cyanokit antidote consisting of hydroxycobalamin, a precursor to vitamin B12. It is a relatively benign substance with few side effects and more rapid onset of action when compared to the older less expensive therapy—the cyanide antidote kit (CAK) consisting of sodium nitrite and sodium thiosulfate [40, 41]. Hydroxocobalamin has no adverse effect on the oxygen carrying capacity of the red blood cells and no negative impact on the patient's blood pressure; these are significant benefits when treating victims of smoke inhalation. Hydroxocobalamin binds to cyanide, forming vitamin B12 (cyanocobalamin), a nontoxic compound excreted in the urine. Quickly passing side effects include reddish color to the skin, urine, and mucous membranes which may interfere with some colorimetric laboratory tests (i.e., blood glucose, iron levels, creatinine, total hemoglobin concentration, carboxyhemoglobin, oxyhemoglobin, methemoglobin, etc.) [42, 43]. Victims presenting with seizures, hypotension or a coma in a setting consistent with cyanide toxicity should be considered candidates for empiric administration of hydroxycobalamin administered intravenously (5 g over 15 min). A pretreatment blood sample should be obtained whenever possible for subsequent analysis for CN and for baseline laboratory tests that could be interfered with by the presence of hydroxycobalamin.

The CAK, consisting of sodium nitrite and sodium thiosulfate for intravenous administration and ampules of amyl nitrate inhalant, also effectively treats CN poisoning. Sodium nitrite generates methemoglobin by changing the normal ferrous state of iron in the heme molecule of hemoglobin (Fe^{+2}) to the ferric state (Fe^{+3}). The ferric heme molecules in methemoglobin have a high affinity for CN. Thus, CN molecules preferentially bind to the methemoglobin generated by sodium nitrate, which in turn prevents CN from entering cells and inhibiting cellular respiration. The adult dose of sodium nitrite is 300 mg of sodium nitrite in 10 mL of diluent (30 mg/mL) administered intravenously [35, 36]. Following the administration of sodium nitrite, sodium thiosulfate should be administered intravenously. Sodium thiosulfate acts as a substrate for, rhodanese, a detoxifying mitochondrial enzyme found in the liver. Rhodanese catalyzes the conversion of cyanide to thiocyanate that is then excreted in the urine [35, 37].

The inhalation of amyl nitrite from ampules is used as a temporizing measure until venous access for the intravenous administration of sodium nitrite and sodium thiosulfate is obtained. The inhalation of amyl nitrite should never be considered a substitute for the administration of intravenous sodium nitrite and sodium thiosulfate. In fact, amyl nitrite can itself be associated with serious reactions such as hypotension, syncope, methemoglobinemia, and hemolysis in G6PD-deficient patients. These effects are more pronounced in children, the elderly, and in patients with cardiopulmonary diseases. Dose regimen is difficult to control and could even result in exposure of the healthcare provider with adverse effects. For these reasons, administration of amyl nitrite may be unwarranted, especially since hydroxycobalamin is now available [44].

Oxygen, 100% FiO2 should be administered to all patients with CN poisoning in order to maximize the oxygen carrying capacity of blood. Ventilatory support should be provided as needed. The administration of sodium bicarbonate should be considered for the treatment of severe lactic acidosis in patients who are unconscious or hemodynamically unstable.

Hydrogen Sulfide

Pathophysiology

Hydrogen sulfide (H_2S), a chemical asphyxiant, is a colorless, highly flammable gas that is produced in a variety of settings, most commonly sewer systems, manure pits on farms, oilfields, and petroleum refining plants [45–47]. Its characteristic noxious, "rotten eggs" odor is detectable by smell at low concentrations, but may be undetectable at high concentrations or after prolonged exposure because of olfactory fatigue. It can produce a variety of clinical effects related to severe hypoxia including central nervous system dysfunction [48], cardiac arrhythmias, and pulmonary edema. In contrast to CN, H_2S is also an irritant affecting the eyes, mucous membranes, and respiratory tract.

As a chemical asphyxiant, H_2S is similar to CN blocking the cellular utilization of oxygen by inhibiting the activity of cytochrome aa_3, a mitochondrial enzyme of the cytochrome oxidase system. As with CN intoxication, disruption of aerobic metabolism by H_2S causes a shift to anaerobic metabolism within affected cells that, in turn, leads to metabolic acidosis and an elevated anion gap due to increased lactate production. Inhalation is the primary route of H_2S toxicity. H_2S is lipid soluble, readily crosses the alveolar membrane, easily dissolves in the blood and is rapidly distributed to tissues throughout the body. The respiratory system and organs with high oxygen demand, such as the brain and heart, are particularly vulnerable.

The severity of clinical signs and symptoms associated with H_2S toxicity depend on the exposure dose. Signs and symptoms of asphyxiation and mucosal irritation typically exist simultaneously. Irritant effects dominate at low exposure doses, whereas pulmonary edema and life-threatening chemical asphyxiation dominate at higher exposure doses. Low dose exposures in the range of 50–200 ppm are typically characterized by burning of the eyes, increased lacrimation, sore throat, nausea, cough, and occasional wheezing. Because olfactory function is lost at around 100–200 ppm, if exposed individuals can still smell the "rotten eggs" odor of H_2S, the concentration is usually not high enough to cause severe asphyxiation or irritant injury. At exposure concentrations of 200–250 ppm, olfactory function is lost and H_2S produces intense mucous membrane irritation, corneal ulceration, bronchospasm, pulmonary edema, and dyspnea. At concentrations greater than 500 ppm chemical asphyxiation of the brain produces headache, seizures, delirium, confusion, and lethargy. The central nervous system effects of H_2S toxicity may be exacerbated by hypoxemia secondary to severe pulmonary edema. In survivors, long-term neurologic sequelae, such as ataxia, intention tremor, sensorineural hearing loss, muscle spasticity, and memory impairment may occur [46]. Concentrations in the range of 750–1,000 ppm will cause severe inhibition of aerobic metabolism within the central nervous system and heart. Myocardial ischemia, arrhythmias, and dilated cardiomyopathy have been reported [49, 50]. As doses increase, loss of consciousness, cessation of brainstem function, and cardiopulmonary arrest occur [51].

Diagnosis and Management

Once again, a high index of suspicion is the key to making the diagnosis of H_2S intoxication and should be suspected based on exposure history. Although blood levels of thiosulfate are helpful in confirming the diagnosis of H_2S poisoning [49], these tests are not readily available in most clinical laboratories. When available, atmospheric measures of H_2S concentration can be used to increase diagnostic suspicion and in classifying the expected severity of exposure and intoxication. In the absence of specific exposure information, signs of ocular irritation, inflammation of mucosal membranes, and the smell of "rotten eggs" on the clothing or breath of a patient should suggest the diagnosis of H_2S intoxication.

As with CN toxicity, the inhibition of cytochrome aa_3 by H_2S toxicity causes a decrease in the extraction and utilization of oxygen by affected cells and an

"arteriolization" of venous blood. There may also be a "saturation gap" between the arterial saturation of oxygen (Sao_2) calculated from arterial blood gas data and the Sao_2 measured by CO-oximetry as a result of sulfide ions binding to some oxygen binding sites on hemoglobin molecules, forming molecules of sulfhemoglobin. In addition, both methemoglobin and sulfhemoglobin are produced during the treatment of H_2S poisoning with sodium nitrite and amyl nitrite, as discussed below. Therefore, if H_2S poisoning is known or suspected, Sao_2 should be measured by CO-oximetry. A rapid decline in either Pao_2 or Sao_2 could indicate the development or progression of pulmonary edema. Serum lactate concentration is elevated due to inhibition of aerobic metabolism. Elevated lactate causes a high anion gap metabolic acidosis.

The treatment for H_2S intoxication has important similarities and differences when compared to the treatment of CN intoxication. Oxygen, 100% FIO2, should be administered and assisted ventilation provided as clinically indicated. Sodium nitrite can be used as an antidote to generate methemoglobin by changing the normal ferrous state of iron in the heme molecule of hemoglobin (Fe^{+2}) to the ferric state (Fe^{+3}). The ferric heme molecules in methemoglobin have a high affinity for H_2S [52]. The preferential binding of H_2S molecules to methemoglobin results in the formation of sulfhemoglobin that prevents circulating H_2S from entering cells and inhibiting cellular respiration. Sodium nitrite should be administered as soon as possible after exposure. Inhalation of amyl nitrite from ampules contained in cyanide antidote kits can be administered as a temporizing measure until venous access is obtained for the administration of sodium nitrite. The detoxifying enzyme rhodanese is not involved in H_2S metabolism, as it is in CN metabolism. Therefore, sodium thiosulfate should not be given for the treatment of H_2S intoxication. Likewise, hydroxocobalamin has no role in the treatment of H_2S intoxication as its use in CN toxicity is to bind to CN. Several case reports argue for a beneficial effect of HBOT in H_2S intoxication [53, 54]. Basic supportive measures should not be forgotten and include irrigation of the eyes with sterile saline and the treatment of irritant-induced bronchospasm with inhaled β_2 agonists. Consideration should be given to the administration of sodium bicarbonate for the treatment of severe metabolic acidosis in unconscious or hemodynamically unstable patients. A benzodiazepine, such as diazepam, or a barbiturate can be given to control seizures if present but patients should be carefully monitored for signs of respiratory insufficiency after such use.

Irritant Gases

Irritant gases are those that cause chemical injury to the airways and lung tissue upon inhalation. The nature, location, and severity of respiratory tract injuries associated with the inhalation of an irritant gas are dependent on the physical and chemical properties of the gas, exposure dose, and host factors. The most important physical and chemical properties are water solubility and density. Exposure dose is

Table 10.3 Determinants of severity of lung injury

Duration of exposure
Proximity to source
Density of gas and height of victim
Temperature of gas
Toxicity of gas
Water solubility of gas
Particle size of mist, fog, or vapor
Age of victim
Minute ventilation
Breathing pattern—oronasal vs. mouth breathing
Host factors (e.g., preexisting lung or heart diseases)
Orthopedic problems that effect the ability to evacuate quickly

determined by the concentration of the gas in the environment and the duration of exposure. Minute ventilation, age, and the presence of preexisting respiratory disease are the most important host factors (Table 10.3).

The sites of injury produced by inhalation of an irritant gas are dependent on its water solubility. Highly soluble gases, such as ammonia, methyl isocyanate, and sulfur dioxide, mostly cause irritant damage to exposed mucous membranes of the eyes and upper airway (nose, lips, pharynx, and larynx), while sparing the lower airways. At high concentrations, however, a highly soluble irritant gas can overwhelm the upper respiratory tract, and thereby producing lower airway injury. Irritant gases of intermediate solubility, such as chlorine, may produce significant upper airway injury, especially in the mid-upper airway (pharynx and larynx), but the mucous membrane irritation is usually not as intense as that caused by highly soluble gases. Because of its intermediate solubility, the irritant effects of chlorine can extend more distally at higher concentrations. Thus, high concentrations of inhaled chlorine can produce both upper and lower airway injury, as well as pulmonary edema due to alveolar damage. The inhalation of low-solubility irritant gases, such as phosgene and oxides of nitrogen, produce minimal upper airway irritation, but can cause intense lower airway and alveolar damage. As a result of lung tissue injury, the development of non-cardiogenic pulmonary edema is more likely following inhalation of a low-solubility irritant gas or at high concentrations of gases with intermediate solubility. Examples of irritant gases that are associated with the development of pulmonary edema include acrolein, ammonia, chlorine, mercury, oxides of nitrogen, ozone, paraquat, phosgene, and smoke from fires. The inhalation of gases that are lipid soluble, such as chloroform, ether, or other halogenated hydrocarbons, can also produce central nervous system effects and little, if any, respiratory injury.

Irritant gases damage the airways and lung tissues by direct cellular injury, secondary injury from free radical production, and as a result of the inflammatory response. Direct cellular injury is typically produced by irritant gases that are highly acidic or a highly alkaline pH. When in contact with the water found in mucous membranes, chlorine, and phosgene, for example, produce hydrochloric acid while ammonia forms a strong alkali, ammonium hydroxide. Oxides of nitrogen cause the

production of free radicals that cause cellular damage by lipid peroxidation. Both direct cell damage and cell damage secondary to free radical formation result in the release a variety of inflammatory mediators that elicit an inflammatory response, thereby causing further oxidant damage to respiratory tract cells. In the airways, the damage caused by irritant gases is manifested by mucosal edema, mucus production, increased smooth muscle contraction, and airway obstruction. At the alveolar level, damage of type 1 pneumocytes occurs followed by capillary leakage due to epithelial cell damage, disruption of epithelial cell tight junctions, endothelial damage, and increased vascular permeability.

Specific Irritant Toxic Gases

Ammonia

Ammonia (NH_3) is a colorless, pungent, alkaline gas that is less dense than air and highly soluble. Most inhalational injuries from NH_3 occur as a result of exposures occurring during fertilizer production [55], chemical manufacturing, oil refining, and the use of cleaning solutions [56] or during the illicit production of methamphetamine [57]. The strong, pungent smell of NH_3 is easily detected at low concentrations and few individuals can tolerate concentration greater than 100 ppm without experiencing nasal congestion and cough.

As a highly soluble gas, NH_3 primarily causes irritation to the eyes, mucous membranes of the nasal-oropharynx, and upper respiratory airways. The reaction of NH_3 with water in the mucous membranes results in the formation of ammonium hydroxide (NH_4OH) that causes liquefaction necrosis and intense pain in the eyes, mouth, nose, and throat. The voice is lost shortly after exposure, and patients typically experience sensations of choking and suffocation. The eyes are erythematous, swollen, and may show signs of corneal opacification or ulceration. Edema, ulceration, necrosis, and sloughing of the mucous membranes are typically seen. Airway obstruction due to laryngeal edema, bronchial inflammation, bronchospasm, and plugs of sloughed epithelium may cause dyspnea, wheezing, and hypoxemia [58]. Death from laryngospasm can occur within 1 min after exposure to high concentrations (1,500 ppm or greater). With exposure to high concentrations, alveolar damage and pulmonary edema can occur within 24 h [58]. Secondary bacterial bronchopneumonia may occur several days later. Long-term sequelae of NH_3 inhalation include persistent airway obstruction from reactive airways dysfunction syndrome (RADS), asthma, bronchitis, bronchiectasis, and bronchiolitis obliterans [58, 59].

Chlorine

Chlorine (Cl_2) is a high density gas of intermediate solubility, and has the characteristic pungent odor of bleach detectable by smell at levels of 1 ppm. Industrial uses

of Cl_2 include the production of chemicals and bleaches, paper manufacturing, textile processing, and the production of polyvinyl chloride. Most Cl_2 exposures result from accidental releases at industrial sites, from ruptured tanks during its transportation or at swimming pools [60–62]. Accidental exposure to Cl_2 may also occur in the household when bleach is mixed with acid-containing cleaners during cleaning processes. The relatively high density of Cl_2 causes it to accumulate in low-lying areas, which should be avoided following its accidental release.

On contact with mucous membranes, chlorine reacts with water to produce hydrochloric acid (HCl), hypochlorous acid (HClO), and free oxygen radicals. Individuals exposed to low concentrations of Cl_2 typically experience burning of the eyes and mucous membranes, as well as choking and coughing due to inflammation of the nasal-oropharynx and upper airway. At higher concentrations, laryngeal edema, lower airway inflammation, bronchospasm, and pulmonary edema can develop. Stridor, if present, may reflect upper airway obstruction due to laryngeal or vocal cord edema and should be considered as a sign of impending respiratory distress which left untreated may progress to respiratory failure. However, in some cases, slight wheezing and erythema of the conjunctivae and mucous membranes may be the only physical findings that are evident within the first hour after exposure. Unfortunately, the initial paucity of significant signs and symptoms may not reflect the true severity of the inhalational injury, and exposed individuals may prematurely be sent home from the emergency department. For example, an exposure concentration of 50 ppm may produce relatively mild signs and symptoms initially, but can cause death from laryngospasm or massive pulmonary edema within 1–2 h after exposure. The onset of pulmonary edema may also be delayed up to 24 h after exposure. At any time within 2 days after Cl_2 exposure, airway inflammation and mucosal desquamation may cause plugging of medium and small bronchi, leading to airflow obstruction and atelectasis. Individuals with a history of asthma or airway hyperactivity may have particularly severe bronchospasm. Secondary bacterial bronchopneumonia may develop as a consequence of ulceration and desquamation of airway mucosa and/or alveolar damage. Fortunately, most exposed individuals will recover completely if they receive prompt medical treatment and survive the acute effects of Cl_2 exposure. However, chronic pulmonary problems may develop in some individuals, including RADS, asthma, bronchiectasis, and bronchiolitis obliterans [62–64].

Phosgene

Phosgene ($COCl_2$) is a low solubility, heavy (dense) gas that has the smell of freshly mown hay. Upon contact with water it hydrolyzes to form CO_2 and HCl. Phosgene was used as a chemical warfare agent during World War I [35]. Currently, phosgene is used as a chlorinating agent in a variety of industrial processes, including the production of isocyanates, pesticides, dyes, and pharmaceutical agents. Firefighters, welders, and paint strippers may be exposed to phosgene as a result of its release from heated chlorinated hydrocarbons, such as polyvinyl chloride [65]. Because phosgene is approximately four times as dense as air, it will accumulate close to the ground in low-lying areas.

As a gas with low solubility, phosgene is less irritating to the eyes and upper airway mucous membranes than NH_3 or Cl_2 and causes mostly irritant damage in the lower airways and cellular damage at the alveolar level. Immediate symptoms including eye burning, increased lacrimation, sore throat, rhinorrhea, coughing, choking, dyspnea, and chest tightness, are typically mild and resolve within minutes after cessation of exposure because of phosgene's low solubility. Laryngeal edema can occur shortly after high concentration exposures, with stridor and the potential for sudden death. Inhaled phosgene will eventually hydrolyze to form HCl in the lower airways and alveoli causing oxidative and inflammatory injury. As a result, bronchospasm and pulmonary edema typically develop between 2 and 6 h following exposure, but pulmonary edema may be delayed for up to 24 h. Most victims survive without long-term clinical effects if they receive prompt medical care. Pulmonary edema can progress to the acute respiratory distress syndrome (ARDS) and respiratory failure. Those with ARDS have the worst prognosis and will require assisted ventilation and circulatory support as needed. Chronic problems may develop in some individuals including RADS, asthma, bronchiectasis, and bronchiolitis obliterans [66].

Nitrogen Oxides

Oxides of nitrogen (e.g., nitrous oxide (N_2O), nitric oxide (NO), nitrogen dioxide (NO_2), and nitrogen tetraoxide (N_2O_4)) are used in the production of dyes, lacquer, and fertilizer. They are also generated in a variety of processes, including arc welding [65], chemical engraving, explosives, and the storage of fresh silage [67]. All oxides of nitrogen can produce serious acute respiratory tract injury upon inhalation. NO_2, the most common and clinically important toxicant in this group, is a low solubility, dense gas that forms nitric acid (HNO_3) and nitrous acid (HNO_2) upon contact with water.

NO_2 causes silo filler's disease which develops following exposure to this gas after its accumulation just above silage in recently filled, top-loading silos. During the first 2 weeks in the silo, carbohydrates in the silage ferment and produce organic acids which then oxidize nitrates in the silage into NO_2. NO_2 rapidly accumulates to toxic levels in the silo and then decreases 1–2 weeks later. Entry into a silo without proper respiratory protection, especially within the first 2 weeks of the silo being filled with fresh silage, can cause a rapid loss of consciousness and sudden death. The incidence of this disorder is estimated to be five cases per 100,000 silo-associated farm workers per year [67].

The lower airways and lung are the primary sites of injury. The low solubility of NO_2 results in minimal eye and upper airway irritant symptoms. The most significant effects occur in the lower airways and lungs as a result of the conversion of NO_2 to HNO_3 upon contact with water in bronchial mucosa and alveoli. The clinical response to inhaled NO_2 occurs in three phases [67, 68]. The first phase is the *acute illness,* typically occurring within the first hour postexposure. Symptom severity in the first phase is dose-related. At doses up to 100 ppm, cough, wheezing, dyspnea,

and chest pain develop as a result of lower airway irritation and bronchospasm. Hypotension may occur in severe cases. At doses greater than 100 ppm, pulmonary edema may develop within 1–2 h after exposure. The hypoxemia resulting from pulmonary edema is further exacerbated by NO_2-induced methemoglobinemia.

Without further NO_2 exposure, symptoms of the *acute illness phase* usually resolve over 2–8 weeks. During the next *latent phase*, the patient may have mild cough and wheezing, or may be totally asymptomatic. The patient may then develop a *delayed illness phase,* characterized by the sudden onset of fever, chills, cough, dyspnea, and generalized lung crackles [67, 68]. Lung biopsies in this delayed illness phase have shown proximal bronchiolitis obliterans without organizing pneumonia [67, 68]. The bronchioles are typically packed with inflammatory exudate and fibrin that may obliterate the entire lumen. If extensive, it may cause life-threatening hypoxemia. Symptom severity in the *acute illness phase* does not always correlate with the severity of bronchiolitis obliterans in the *delayed illness phase*.

Sulfur Dioxide

Sulfur dioxide (SO_2) is a colorless, dense, irritating gas that is highly water soluble. It has a strong, pungent, odor. SO_2 is a common atmospheric pollutant from the combustion of coal and gasoline. It is used in a variety of industrial processes, such as bleaching, refrigeration, and paper manufacturing [69]. Upon contact with water in the mucous membranes SO_2 forms sulfuric acid (H_2SO_4). As a highly soluble gas, the predominant effects of SO_2 exposure are irritation of the eyes, nose, mucous membranes, pharynx, and upper respiratory tract. High dose exposure doses (>10 ppm) can penetrate into the lower airway causing bronchospasm with cough, wheeze, dyspnea, and chest pain. Symptom severity increases with exposure doses. Individuals with preexisting asthma or chronic obstructive lung disease are more likely to develop severe exacerbations [69]. These include RADS, asthma, and even bronchiolitis obliterans [69, 70].

Smoke

Smoke is a toxic, irritant mixture of gases, vapors, fumes, liquid droplets, and carbonaceous particles generated by the incomplete combustion or pyrolysis of multiple substances at high temperatures. Common combustible materials in a fire include wood, paper, plastics, polyurethane, paints, and other polymers present in carpeting and upholstery. Toxic gases are released during combustion and pyrolysis. These gases include both asphyxiants and irritants. CO and CN are common asphyxiants found in smoke. Aldehydes, acrolein, NO_2, SO_2, and HCl are common irritants found in smoke. Particulates present in smoke adsorb these irritant chemicals to their surface, which can concentrate the chemicals and this increases damage to the respiratory tract upon inhalation.

Approximately 80% of all fire-associated deaths are attributed to inhalation injury [71]. Inhalation injury is a greater influence in determining burn mortality than even burn size or age [72]. Patients being treated in burn centers have a mortality rate of 29% in the presence of inhalation injury, in comparison with a mortality rate of 2% in its absence [73].

Heat injury from hot gases and steam is usually limited to the upper respiratory tract as heat rapidly dissipates across the upper airways [74]. Smoke particles greater than 10 μm in diameter also contribute to upper airway injury (rhinosinusitis, pharyngitis, laryngitis, and upper airway edematous obstruction), as they do not penetrate into the lower airways unless present at high concentrations. Subglottic or supraglottic edema following smoke inhalation can lead to significant upper airway obstruction. Upper airway obstruction occurs in up to 30% of burn patients and may occur as early as 4 h or as late as 24 h after exposure [75]. The production of upper airway edema can be due to direct mucosal damage and ulceration from heat and superheated steam, the release of inflammatory mediators from the damaged mucosa, and the production of oxygen free radicals from toxic chemicals on the surface of smoke particles. Acute upper airway edema following smoke inhalation usually resolves within 3–4 days. Rarely, thermal injury can produce circumferential, constricting eschars or scarring of the upper airway after the acute edema resolves. Such eschars can produce chronic upper airway obstruction.

In the large to medium size airways of the chest, tracheobronchitis can develop as a result of smoke inhalation. Heat injury is rare [74]. Severe cough and chest tightness with or without bronchospasm are common presenting symptoms. Tracheobronchitis can be due to irritant chemical and/or particulate injury, the release of inflammatory mediators from the damaged mucosa, and the production of oxygen-free radicals from toxic chemicals on the surface of smoke particles.

Particles less than 3 μm in diameter travel to the distal portions of the respiratory tract and can cause small airways and alveolar injury. Lower airway penetration by small smoke particulates can cause irritation, inflammation, and bronchospasm. Individuals with preexisting asthma or chronic obstructive pulmonary disease may experience exacerbations, but bronchospasm can also occur in individuals with no prior history of airway disease. Small smoke particles can also cause alveolar-capillary injury in the lung parenchyma by direct oxidative damage from adsorbed irritants and by oxygen-free radicals and inflammatory mediators released by neutrophils that migrate to areas of irritant damage. Pulmonary edema can occur as a consequence of alveolar-capillary injury and may occur hours to days after smoke inhalation. Although pulmonary edema occurs in far less than 10% of smoke inhalation victims, it has a high mortality rate [76].

Airway injury, whether it is tracheobronchitis or small airway bronchoconstriction or bronchiolitis, can cause sloughing of necrotic tissue into the lower airways that can lead to mucous plugging, bronchial obstruction, atelectasis, hyperinflation, and altered mucocilliary clearance. Secondary bacterial pneumonia can develop in obstructed lung segments or as the result of alveolar damage adversely affecting local immunodefenses.

Most deaths from smoke inhalation result from asphyxiation due to CO or CN in the inhaled smoke [10, 33–35]. CO intoxication is responsible for 80% of smoke inhalation fatalities and approximately one fourth of these occur in victims with underlying cardiac or pulmonary disease [6]. Far less often, it may be the result of NO_2 toxicity, a potent irritant that can cause the development of methemoglobinemia, which can further decrease the already impaired oxygen carrying capacity of hemoglobin caused by carboxyhemoglobinemia. Coexisting CN intoxication needs to be considered in all smoke inhalation victims with CO intoxication, especially those with clinical evidence of altered neurologic or cardiac status. In a study from Paris, a clear association was found between blood CN levels and % carboxyhemoglobin levels [33]. This association was strongest in patients with metabolic acidosis and elevated lactate levels [33]. In a study from the Dallas County Fire Department, a CN blood level above 1.0 mg/L was a strong predictor of death but the association between CO and CN levels was not strong [76]. Of the 144 patients that reached the emergency room alive, 12 had blood cyanide concentrations exceeding 1.0 mg/L and 8 of the 12 subsequently died. In these 12 patients, the relationship between % carboxyhemoglobin levels and CN blood levels was poor [76].

General Considerations in the Diagnosis and Treatment of Irritant Toxic Gases and Smoke Inhalation

Exposure duration is based not only on exposure time but also on the patient's minute ventilation during that time. Chemical analyses of material at the site of exposure, if available, can be particularly helpful in identifying the offending toxicant and estimating its exposure concentration. The relative solubility of a toxic gas can be helpful in determining the areas of the respiratory tract where irritant injuries are most likely to occur and obviously patients with preexisting pulmonary disease are most at risk. When the irritant toxic gases are in the setting of smoke inhalation, the exposure will be to multiple gases and particulates. Facial burns, singed eyebrows, soot in the upper airway, and carbonaceous sputum make smoke inhalation highly likely.

The management of acute inhalational injury from toxic irritants or smoke is at first supportive. All contaminated clothing is removed in order to prevent further inhalation and percutaneous absorption of the toxic substance. Surface (skin) burns are treated. The eyes are thoroughly flushed with sterile normal saline as soon as possible. Careful attention to the eyes is important as cataracts can occur following heavy exposures. Humidified oxygen is given by face mask. Not everyone exposed to smoke warrants hospital admission. Victims with mild inhalation exposures may be treated and released if they: (1) are asymptomatic with normal mental status and absent of confusion; (2) demonstrate no burns, carbon material, or edema in the upper airway; (3) have a normal pulmonary exam without signs of upper or lower respiratory distress, stridor, or wheeze, (4) have a normal cardiac exam, (5) show hemodynamic stability, and (6) reveal normal readings on pulse oximetry and

noninvasive carboxyhemoglobin testing. Upon release, patients should be advised to seek medical attention if symptoms occur or reoccur as the clinical manifestations of inhalation injury may take 4–24 h to develop [76]. It is for this reason that borderline patients or patients with significant comorbidity should be observed rather than released whenever possible.

The carboxyhemoglobin level, a measure of CO intoxication, should be obtained in all patients with suspected exposure to smoke, fires, or other sources of combustion. If high levels of carboxyhemoglobin, methemoglobin, or CN exist, the arterial oxygen tension (Pao_2) is not useful in assessing the adequacy of oxygen transport or tissue oxygenation. Arterial oxygen saturation should be measured by CO-oximetry because pulse oximetry and the calculation of Sao_2 from the Pao_2 will overestimate the actual oxygen saturation of hemoglobin.

All individuals with known or suspected inhalation injury should be given 100% humidified oxygen as soon as possible. This will help to improve the oxygen carrying capacity of hemoglobin when high levels of carboxyhemoglobin or methemoglobin are present. High levels of methemoglobin are unusual but, if present, can be treated with intravenous methylene blue. The fraction of inspired oxygen can be titrated down to maintain a Pao_2 greater than 60 mmHg once carboxyhemoglobin and methemoglobin levels have returned to normal. When available, HBOT should be considered for the treatment of CO intoxication according to the criteria for previously delineated in the section in this chapter. HBOT has been used to treat patients with extreme levels of CO poisoning (equal or greater than 25% carboxyhemoglobin) or end-organ sensitivity to CO at mildly elevated levels. Examples of this might include neurologic abnormalities or hemodynamic instability that was felt to be caused by CO poisoning.

Severely ill smoke inhalation patients presenting with seizures, coma, hemodynamic instability, and/or severe lactic acidosis should be suspected of having both CO and CN intoxication [33–35, 77]. Blood CN levels can be measured, but results cannot be obtained in time to make therapeutic decisions and therefore the decision to treat for CN toxicity should be based on the exposure characteristics and clinical presentation. The New York Fire Department protocol is to intubate such patients, provide hemodynamic support as needed, empirically treat for CN poisoning with hydroxycobalamin and, if noninvasive carboxyhemoglobin levels are elevated, transport to an HBOT center. In addition, all smoke inhalation victims found in cardiac arrest receive hydroxycobalamin during cardiac resuscitation.

When CN poisoning is suspected, treatment with hydroxycobalamin is preferable to sodium thiosulfate because of its rapid onset of action. Inhaled amyl nitrite and intravenous sodium nitrite should be avoided because they generate methemoglobin that can further impair the oxygen carrying capacity of blood hemoglobin if high levels of carboxyhemoglobin or methemoglobin are already present. The Paris Fire Brigade routinely administers hydroxycobalamin to smoke inhalation patients and published their experience in 2006 [39]. Of the 29 patients in cardiac arrest, 18 (62%) recovered with cardiac resuscitation and hydroxycobalamin treatment. The average time between hydroxycobalamin administration and recovery of spontaneous cardiac activity was 19 min. In 15 hemodynamically unstable patients not in

cardiac arrest, 12 (80%) showed hemodynamic improvement (BP >90 mmHg) after hydroxycobalamin. The average time for hemodynamic improvement was 49 min from the start of hydroxycobalamin infusion and 29 min from the end of hydroxycobalamin infusion. In a second study, 28 of 42 patients (67%) admitted to the ICU with smoke inhalation and confirmed CN poisoning, survived after hydroxycobalamin administration [40].

Upper airway injury from irritant toxic gases or smoke inhalation should be suspected when there is hoarseness, sore throats, carbonaceous material in the pharynx, and stridor. Such patients are at high risk of developing progressive laryngeal edema with complete obstruction of the upper airway. Smoke inhalation further adds to this risk due to heat and particulate matter exposure. Patients with laryngeal edema can be extremely difficult to intubate and may require emergency tracheostomy. However, not all patients require intubation [78]. Prompt inspection of the larynx with a laryngoscope is imperative [73]. Immediate intubation is usual when there is evidence of significant upper airway edema or blisters. All patients with upper airway edema are treated with nebulized racemic epinephrine and systemic corticosteroids. If edema is minimal and early intubation is not required, airflow can usually be maintained with positive pressure breathing administered by the use of continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP). An inhaled mixture of helium and oxygen can also improve upper airway airflow by reducing turbulence as a result of its low density. If it is decided that immediate or early intubation is not necessary, patients with upper airway edema should be admitted to the hospital and closely monitored for signs of edema progression and the need for emergent intubation at a later time over the next 24–48 h [78].

Lower airway involvement from irritant gas or smoke inhalation is suspected when there is dyspnea, wheezing, rales and/or pulmonary congestion. Hypoxia and bilateral infiltrates on chest imaging may develop over the next 24–48 h. Additional diagnostic evidence can be provided by laryngoscopic or bronchoscopic demonstration of edema, hemorrhage, or carbonaceous material distal to the vocal cords. Inhalation injury to the smaller airways and lung parenchyma can be confirmed by Xenon 133 ventilation scanning or non-contrast chest CT scans [79–81]. However, the positive predictive value of Xenon 133 ventilation scans and non-contrast chest CT scans in determining the need for intubation, determining the need for aggressive treatment, or assessing prognosis has not been determined [79–81].

Acute bronchospasm, irritant asthma, or RADS [82–85] should be treated with β_2 agonists. Ipratropium can be added if significant improvement is not obtained with a β_2 agonist alone. In the presence of significant burn injuries, treatment with systemic corticosteroids is usually contraindicated as their use is associated with increased mortality from sepsis [86, 87]. Systemic corticosteroids should be reserved for severe upper airway obstruction, severe bronchospasm resistant to bronchodilator therapy and failed extubation due to stridor or bronchospasm [76, 87]. Low-dose inhaled corticosteroids have not been studied in large case series, but it is unlikely that they would negatively impact mortality in burn patients. Animal studies have shown that inhaled corticosteroids improve oxygenation and attenuate the development of acute lung injury following chlorine exposure [88, 89]. Although inhaled

corticosteroids are often given following chlorine and phosgene inhalation, there are no controlled clinical trials regarding their efficacy. Chest physiotherapy and frequent suctioning may be helpful in patients with mucus plugs and thick secretions. Intubation may be necessary if bronchial secretions are excessive and frequent bronchoscopic suctioning may be needed.

Non-cardiogenic pulmonary edema from acute lung injury (ARDS) is far less common than airway injury, but should be suspected in patients with worsening oxygenation and increasing dyspnea. A chest radiograph should be obtained if signs of respiratory distress, abnormal breath sounds, or worsening hypoxemia are noted. Pulmonary edema or ARDS from inhalation injury typically presents as scattered, nodular alveolar infiltrates on chest radiographs, although large, diffuse, confluent infiltrates may occur as the illness progresses. Careful attention to fluid and electrolyte balance is essential, especially if surface burns are present. If gas exchange abnormalities are severe, noninvasive positive pressure ventilation with CPAP or BiPAP may help to support adequate oxygenation. If oxygenation continues to be inadequate or secretions are burdensome, intubation and mechanical ventilation are required. Nasotracheal intubation should be avoided because of the severe nasal inflammation that typically occurs following the inhalation of chemical irritants and because the smaller endotracheal tube diameters needed for nasotracheal intubation do not allow for the repeated bronchoscopic suctioning that may be needed if secretions become a problem. PEEP in the range of 5–10 cm H_2O may help to improve oxygenation in mechanically ventilated patients [90–92]. The use of systemic corticosteroids for the treatment of pulmonary edema or ARDS following toxic irritant inhalation remains controversial [93]. Again, there are no controlled clinical trials evaluating the efficacy of corticosteroid treatment in such patients. Most experts believe that corticosteroids are not useful as the pulmonary edema or ARDS typically resolves in 48–72 h after inhalation exposure, with most patients surviving if appropriate supportive treatment is given. The efficacy of corticosteroids in preventing the development of bronchiolitis obliterans or pulmonary fibrosis in the few patients who develop these problems has not been determined. Experimental studies suggest that treatment to block inflammatory mediators and free radicals may be effective in mitigating acute lung injury in smoke inhalation victims [94–96]. Controlled clinical trials of the efficacy of these agents in smoke inhalation patients have not been conducted.

Secondary bacterial pneumonia can occur as a complication of irritant-induced airway or lung injury [97]. There is no evidence that the administration of prophylactic antibiotics reduces the incidence of secondary bacterial pneumonia.

Long-Term Complications of Acute Inhalation Injury

Although most patients exposed to irritant gases or smoke will recover completely, others may develop chronic, long-term sequelae. The most common long-term complications are listed in Table 10.4. Some of these disorders may become evident

Table 10.4 Long-term effects of acute inhalation injury

Complete resolution of symptoms
Sinusitis/Rhinitis
Gastroesophageal reflux
Asthma
Reactive airways dysfunction syndrome
Chronic bronchitis or chronic obstructive pulmonary disease
Bronchiectasis
Bronchiolitis
Bronchiolitis obliterans or constrictive bronchiolitis
Bronchostenosis
Restrictive interstitial fibrosis

in the days or weeks following acute exposure, whereas others may take months, or even years, before clinical symptoms and signs become evident. Therefore, all patients with acute inhalational injury require medical follow-up for the potential development of these disorders, even if they are initially asymptomatic after resolution of acute signs and symptoms.

Some individuals may develop a chronic cough syndrome, dyspnea or wheezing following acute inhalation injury. Pulmonary function tests, chest radiographs, and high resolution CT scans of the chest can be helpful in determining the etiology of chronic cough in such patients. When chest radiographs and chest CT scans are normal, the chronic cough is usually due to asthma, RADS, bronchitis, rhinosinusitis, and/or gastroesophageal reflux [97, 98]. Such patients could also have RADS or irritant-induced asthma. The diagnostic evaluation of such patients should be guided by a careful history and physical examination. RADS is characterized by immediate and persistent, nonspecific airway hyperreactivity following inhalation of a toxic substance in individuals with no prior history of cigarette smoking, allergen, or airway disease [99]. Irritant-induced asthma is the more proper terminology if symptoms were not immediate, or if there is a history of prior allergies, pulmonary disease, or smoking. When pulmonary function tests are normal, bronchial challenge testing (methacholine, histamine, mannitol, cold air, exercise) may be performed to evaluate airway hyperreactivity in patients suspected of having RADS or irritant-induced asthma. Transient, self-limited bronchial hyperreactivity may occur in the weeks following irritant gas or smoke exposures, so the detection of early bronchial hyperreactivity may not always be predictive of RADS [82–85]. The evaluation of firefighters with heavy exposure to dust and irritant gases during the first days after the World Trade Center collapse showed that bronchial hyperreactivity demonstrated by methacholine challenge testing at 1 or 3 months postexposure was predictive of persistent airway hyperreactivity and RADS [85]. It can take months or years for the symptoms of RADS to resolve, and some patients may never have complete resolution. Treatment with an inhaled bronchodilator should be considered if a significant bronchodilator response is found. Even in the absence of a documented bronchodilator response, a trial of bronchodilator therapy should be considered if there is a history of symptoms with exercise, exposure to irritants or a

change in temperature or humidity. Inhaled corticosteroids are used for symptom control. Early treatment with inhaled corticosteroids in asymptomatic patients has been attempted to prevent progression of symptoms with mixed results [100]. Additional studies are needed.

If symptoms persist, serial measurements of spirometry, lung volumes, and diffusion capacity should be assessed to determine if there is accelerated decline in lung function, hyperinflation, bronchiolitis obliterans, emphysema, or pulmonary fibrosis. A study of over 12,000 firefighters and EMS workers exposed to dust and gases from the September 11, 2001, attack on the World Trade Center, found that the decline in lung function in the first 6–12 months after the attack was 12 times the expected annual decline. Even more important is the fact that this decline persisted for the next 6 years in the majority of those exposed [101]. Another study of firefighters exposed to World Trade Center dust and gases demonstrated that interstitial pulmonary fibrosis was exceedingly rare and that airway obstruction was the probable cause of persistent lung injury [102].

Bronchiolitis obliterans or constrictive bronchiolitis is a rare but serious complication following the inhalation of toxic gases, particularly NO_2, other oxides of nitrogen, SO_2, mustard gas, and/or smoke [103–106]. Bronchiolitis obliterans can take two forms following acute inhalation injury. The first form is manifested by the acute onset of fever, chills, cough, dyspnea, and generalized lung crackles that develop 2–8 weeks after acute exposure to an offending gas such as NO_2. The second form of bronchiolitis obliterans occurs months to several years later. Patients have persistent cough and dyspnea often with an obstructive or mixed obstructive/restrictive impairment on pulmonary function tests that does not respond to inhaled corticosteroids or bronchodilators [104]. Chest radiographs may appear normal, but high-resolution CT scans of the chest often show areas of hyperinflation and air-trapping. Lung biopsy may be necessary to make a definitive diagnosis and typically shows a pure constrictive bronchiolitis. This form of bronchiolitis obliterans is usually not responsive to corticosteroid therapy, and the prognosis for improvement is poor.

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Chapter 11
Hard Metal Lung Disease

Toshinori Takada and Hiroshi Moriyama

Abstract Hard metal lung disease is an occupational interstitial lung disease that affects people exposed to dust of tungsten carbide, a hard metal. The culprit is likely the cobalt used as a binder when tungsten and carbon are heated and combined. The disease can occur in workers engaged in the manufacture, utilization, or maintenance of tools composed of hard metal. The frequency of hard metal lung disease is usually less than 1% in those workers. Hard metal lung disease is diagnosed on the basis of occupational history, high-resolution computed tomography (HRCT) appearance of interstitial lung disease, bronchoalveolar lavage, and/or surgical lung biopsy. HRCT findings of hard metal lung disease may consist of bilateral ground-glass opacities, areas of consolidation, irregular linear densities, extensive reticular infiltrates, and traction bronchiectasis. Diffuse centriolobular micronodular opacities are characteristic. The pathologic findings of hard metal lung disease are a pattern of giant cell interstitial pneumonia (GIP). Features of GIP are bronchiolocentric fibrosing interstitial pneumonia with bronchiolar and peribronchiolar fibrosis and increased macrophages in the airspaces associated with multinucleated giant cells. Multinucleated giant cells in bronchoalveolar lavage (BAL) or lung specimens are diagnostic for hard metal lung disease, but the absence of the cells does not exclude the possibility of the disease. Elemental analysis of BAL or lung specimens shows the presence of increased amount of tungsten and/or cobalt. Hard metal lung disease may improve after removal from exposure and often responds to corticosteroids therapy; however, fatally progressive cases have also been documented. Prevention through a comprehensive respiratory protection by exposure avoidance and use of personal protective equipment is needed.

Keywords Hard metal lung disease • Giant cell interstitial pneumonia • Tungsten carbide • Cobalt • Electron probe microanalyzer

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Introduction

Hard metal was first developed in Germany in the early twentieth century. Several decades later, case reports with chest radiographic abnormalities consistent with pneumoconiosis in hard metal workers started to appear in the literature. Hard metal lung disease is now known as an occupational interstitial lung disease that affects primarily workers exposed to dust of tungsten carbide, a hard metal. The pathologic findings of hard metal lung disease are predominantly those of interstitial pneumonia and fibrosis with prominent multinucleated giant cells, resulting in a pattern of giant cell interstitial pneumonia (GIP) [1–3]. Liebow originally classified GIP as one of the idiopathic interstitial pneumonias [4], but it is now recognized that GIP is pathognomonic for hard metal lung disease [5]. Elemental analysis of bronchoalveolar lavage (BAL) or lung tissue reveals the presence of tungsten and/or cobalt that provides definitive diagnosis of the disease.

Epidemiology

The exact prevalence of hard metal lung disease is unknown, but is likely low. A cross-sectional study of 1,039 tungsten carbide production workers revealed that work-related wheeze occurred in 113 participants (10.9%) and interstitial lung disease in only 7 (0.7%) [6]. These findings suggest that only a small percentage of hard metal industry workers develop interstitial lung disease caused by hard metal exposure. Although the occurrence of hard metal lung disease in tungsten carbide workers is associated with elevated peak air concentrations of cobalt in excess of 500 μg/m^3, some cases have occurred following exposures of less than 50 μg/m^3 [7]. Individuals with increased susceptibility may develop hard metal lung disease after relatively short and low levels of exposure.

Exposure to Hard Metal

Hard metal, or tungsten carbide, is a synthetic compound that is produced by combining tungsten and carbon with cobalt used as a binder during the process. The proportion of cobalt varies between 5% and 25% by weight, depending on the hardness of the product. It has hardness nearly that of diamond and is used to make machine parts that require high temperature resistance, or to make tools used for drilling, cutting, machining, or grinding. The main occupational sources of exposure of hard metal consist of various stages in the production of hard metals, maintenance and resharpening of hard metal tools and blades, and the use of hard metal tools [8]. The component of hard metal that is responsible for the disease is most likely colbalt not tungsten. That the cobalt is the offending agent came from several lines of evidence. In animal studies, instillation of tungsten mixed with cobalt

produced toxic effects in the lung while tungsten alone did not [9, 10]. In diamond cutting industry, diamond tools are also used to cut stones, marble, glass, and to grind or polish various materials. Employees developed respiratory symptoms after working with diamond cutting disks made from the mixture of cobalt powder and microdiamonds. Workers in the manufacturing of diamond tools and those who use high-speed cobalt diamond disks in diamond polishing could develop the pathology of GIP similar to hard metal workers [11–13]. These diamond tools do not contain "hard metal" or tungsten.

Patients with hard metal lung disease usually have a mean exposure duration of more than 10 years, ranging from 2.5 to 30 [14]. Hard metal lung disease may also occur after a shorter duration of exposure, which suggests that host susceptibility factors are also important in determining the development and the severity of the disease [15]. History of exposure to hard metal dust, however, may not be apparent in some cases. Office clerks working in a room next to a poorly air-conditioned hard metal factory may be exposed to hard metal dusts and develop hard metal lung disease. Some patients are unaware of such exposures, and others may have had no history of exposure. A case report from India demonstrated an office sweeper with GIP but no history of hard metal exposure [16]. Conversely, a 15-year-old boy with GIP was highly suspected of having been exposed to hard metal because both of his parents had occupational exposure to hard metal; however, a thorough metal analysis of his lung tissue was negative for tungsten or cobalt [17].

Clinical Presentation

Patients exposed to hard metal may develop three types of reactions: occupational asthma, a syndrome resembling hypersensitivity pneumonitis, and interstitial lung disease, which is generally recognized as hard metal lung disease [18]. The clinical presentation of hard metal lung disease is variable and there is usually no relationship between disease occurrence and the length of occupational exposure. Some patients develop acute disease with after relatively short exposure with rapidly progressive dyspnea. Others present more insidiously usually after long exposure with a radiological abnormality during routine screening.

Signs and Symptoms

In a typical case with hard metal lung disease, respiratory symptoms including dry cough and shortness of breath will appear within several months to years after exposure to hard metal. These symptoms may improve on holidays and exacerbate during workdays, similar to hypersensitivity pneumonia in some cases. Physical examination may show fine crackles during chest auscultation [19, 20]. In advanced

cases, clubbed fingers and weight loss are seen [1]. Patients with hard metal lung disease are sometimes complicated by pneumothorax [19, 21, 22], especially in advanced cases who developed honeycombing changes and multiple cysts.

Laboratory Tests

There are no specific blood tests for diagnosing patients with hard metal lung disease. The blood tests are usually performed to differentiate hypersensitivity pneumonitis, sarcoidosis, or neoplastic lung disease, or exclude secondary interstitial lung diseases, such as those associated with collagen vascular diseases. Patch testing, a method used to determine if a specific substance causes allergic inflammation of the skin, may be used to detect cobalt allergy, which is frequently accompanied by sensitivity to nickel [23, 24]. Three of four patients with hard metal lung disease were patch tested and were found to be positive for cobalt during the surveillance of Japanese hard metal workers (unpublished data). Other noninvasive methods such as urinary and blood concentrations of cobalt may also be used to identify the body burden of cobalt [25, 26].

Pulmonary Function

Pulmonary function tests typically show restrictive lung defect characterized by reduced total lung capacity, vital capacity, and lung diffusing capacity [17, 20]. In the early stages of the disease, the restrictive changes may improve after cessation of exposure and recur on returning to the workplace. In the advanced stages with pulmonary fibrosis, restrictive lung defects are frequently accompanied by impaired gas exchange with hypoxemia during exercises, or even at rest. Obstructive defect shown by a decrease in FEV1/FVC may occur at end stage when cystic changes predominate.

Chest Imaging

There are no pathognomonic radiographic features of hard metal lung disease. Although a patient with significant clinical and physiological impairment may sometimes have a normal chest radiograph, the chest radiograph typically shows a diffuse micronodular and reticular pattern predominantly in the lower lung zones (Fig. 11.1a). There are also nodular or diffuse reticulonodular infiltrates, and/or ground-glass opacities. In advanced disease, the lung volume decreases and small cystic lesions i.e. honeycombing may develop.

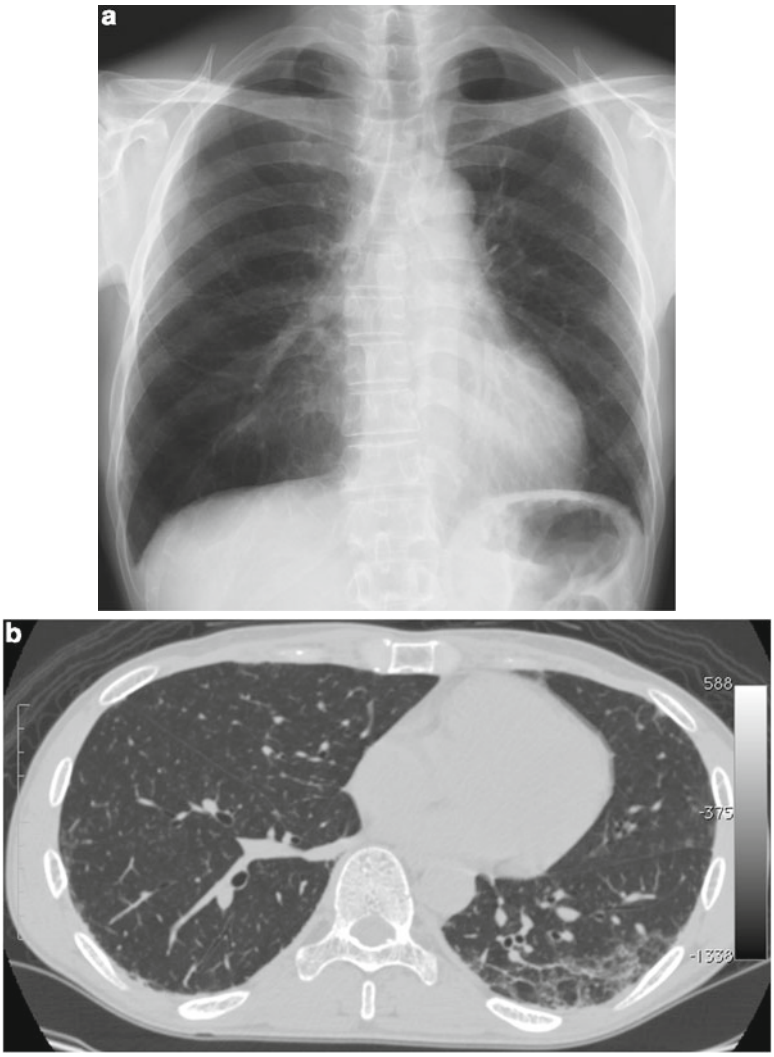

Fig. 11.1 A 53-year-old Japanese man presented with dry cough and exertional dyspnea. He had a history of exposure to hard metal for 30 months. A chest radiograph demonstrates fine reticular opacities mainly in the left lower lung with mild volume reduction (**a**). HRTC demonstrates diffuse centriolobular micronodular opacities and irregular linear opacities in the subpleural zone of the left lower lobe (**b**).

High-resolution computed tomography (HRCT) has become an essential diagnostic tool in diffuse parenchymal lung disease, in particular interstitial lung disease. Figure 11.1b shows the characteristic radiologic appearance of HRCT in a mild case with hard metal lung disease; it shows diffuse centriolobular micronodular opacities in the middle and lower lung fields and subpleural curvilinear densities

with ground-glass attenuation in the left lower lobe. Centriolobular micronodular opacities pathologically correspond to centrilobular fibrosis and giant cell accumulation within the alveolar space. HRCT findings of hard metal lung disease may also consist of areas of consolidation, irregular linear opacities, extensive reticular opacities, and traction bronchiectasis [27, 28].

Bronchoscopy and BAL

BAL findings from case series and case reports of patients with hard metal lung disease show increased total cell counts, increased lymphocytes and eosinophils, and decreased CD4/CD8 ratio [1, 17, 20, 29]. Reduced CD4/8 ratio suggests that immunologic pathogenesis of the lung disease may be similar to that of hypersensitivity pneumonitis [30]. The presence of bizarre multinucleated giant cells in BAL is diagnostic for hard metal lung disease [31]. Elemental analysis of macrophages in BAL could detect inorganic dust particles and reveal the increased amount of tungsten [32]. Lung biopsy usually is not needed if these BAL findings are present.

Pathology

The histologic pattern of GIP is characteristic of hard metal lung disease [5, 33]. Transbronchial biopsies (TBBs) are too small for the pathologists to make an accurate pathologic diagnosis of GIP. Features of GIP are bronchiolocentric fibrosing interstitial pneumonia with bronchiolar and peribronchiolar fibrosis and increased macrophages in the airspaces associated with multinucleated giant cells (Fig. 11.2). The characteristic distribution of fibrosis in GIP suggests that the inflammation in the centrilobular area is initiated by hard metal detected by elemental analysis. Other less characteristic cases may resemble usual interstitial pneumonia or desquamative interstitial pneumonia with or without honeycombing.

Multinucleated giant cells are morphologically classified into Langhans-type cells and foreign body-type cells. Langhans-type cells showing a circular peripheral arrangement of nuclei are often seen in many infectious granulomatous disorders or in unknown pathological inflammatory granulomatous disorders such as sarcoidosis. Foreign-body-type cells, which have the nuclei scattered in an irregular fashion throughout the cell, are characteristic in foreign body granulomas. Multinucleated giant cells in GIP do not resemble either Langhans-type cells or foreign-body-type cells. They distinctively show cannibalism containing phagocyted cellular material (Fig. 11.2b). The phagocytized cells are mostly macrophages or neutrophils. Giant cells are also found in other diseases such as sarcoidosis and viral pneumonia, especially pneumonia due to measles. GIP by measles is differentiated from hard metal

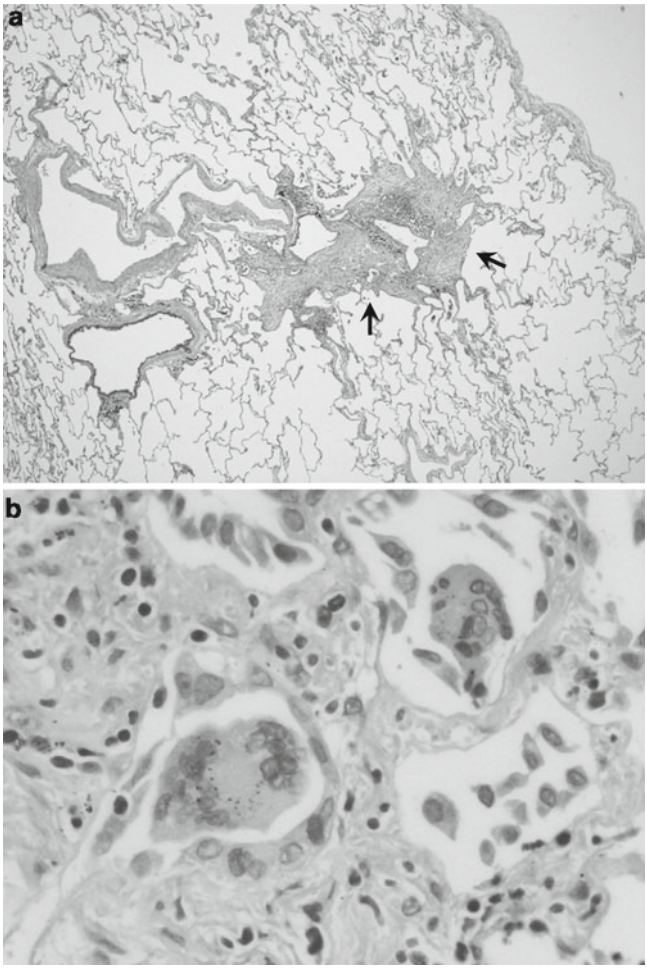

Fig. 11.2 Surgical lung biopsy specimens demonstrating giant cell interstitial pneumonia (GIP). Low magnification of lung biopsy from a 53-year-old Japanese hard metal manufacturer shows centrilobular inflammation and fibrosing lesions (*arrows*) (**a**, ×4). Higher magnification shows irregular multinuclear giant cells in the alveolar spaces (**b**, ×80).

lung disease by the presence of interstitial edema, pneumocyte hyperplasia, and hyaline membranes characteristic of diffuse alveolar damage [34]. Giant cells in the granuloma of sarcoidosis are conglomeration of epithelioid cells sharing the same cytoplasm and having multiple nuclei. They may contain cytoplasmic inclusions such as asteroid bodies and Schaumann bodies [35] and are morphologically different from those in hard metal lung disease.

Table 11.1 Techniques of elemental analysis of human tissues

Liquid analysis
Atomic absorption spectrometry
Plasma optical emission mass spectrometry
Ionic-coupled plasma emission spectrometry
Solid analysis
EPMA-EDS
EPMA-WDS

EPMA electron probe microanalyzer; *EDS* energy dispersive spectrometer; *WDS* wave length dispersive spectrometer

Elemental Analysis

Various techniques of elemental analysis for detection of hard metal elements have been described (Table 11.1). Liquid analysis includes atomic absorption spectrometry, plasma optical emission mass spectrometry, and ionic-coupled plasma emission spectrometry [16, 28]. These techniques can be used to detect elements in dissolved tissue solution but cannot correlate the anatomical relationship between elements and the characteristic centrilobular fibrosis with giant cell accumulation within alveolar space in GIP because the lung architecture is generally destroyed by digestion or ashing.

In contrast, solid analysis uses thick or thin section of specimens without tissue destruction. It has been mainly used to identify the constituents of hard metal in the lung tissue. Electron probe microanalyzers (EPMA) irradiate specimens with a finely focused electron beam. When combined with energy dispersive spectrometers (EDS), EPMA can simultaneously analyze all elements and map chemical elements in lung tissue of hard metal lung disease with very high resolution [2, 5, 36]. Using this technique (EPMA-EDS), Abraham et al. reported that 30 of the 31 cases with GIP were amongst the 50 cases with the highest tungsten concentrations. In addition, the top 27 cases all displayed GIP and the 30 GIP cases had been employed in the tungsten carbide industry [5].

EPMA with a wavelength dispersive spectrometer (WDS) also has been widely used in the field of material sciences to obtain element distribution in small samples with a spatial resolution in the order of 1 μm. WDS is almost ten times more sensitive than EDS for all elements under optimized operating conditions [37]. When EPMA-WDS is applied to a tissue section, however, intense beam to detect trace amount of elements may also burn the tissue sample because of high temperature. Watanabe et al. has developed an improved EPMA-WDS technique that can be used to analyze metal elements in tissue sections of 2-μm thickness [38].

Moriyama et al., applying EPMA-WDS to biopsy lung tissue of hard metal lung disease, demonstrated that tungsten was distributed in a relatively high concentration almost throughout the peribronchiolar fibrosis in the centrilobular lesion. Qualitative analysis of a selected area (10×10 μm area) in a fibrosing lesion of GIP showed the presence of Al, Si, Ti, Cr, Fe, and Ta, in addition to tungsten.

Cobalt, which is always present in hard metal and is thought to be critical in the pathogenesis of GIP, is not always detectable because biosoluble cobalt rapidly disappears from the lung. In patients with hard metal lung disease, cobalt is only detected in approximately 10% of lung tissue samples by EPMA-EDS [5] and in 24% by the more sensitive EPMA-WDS [14]. Lung tissues from TBBs may also be used for elemental analysis. The distribution of mineral dust in the lung is usually uneven [39]. TBBs usually contain the peribronchial connective tissues, which are a common repository for inhaled dust [40]. Thus, if TBBs are used for elemental analysis, detection of tungsten or cobalt may be falsely negative due to the smaller samples and uneven distribution of the deposited dust. Larger surgical lung biopsy samples are preferred for exact mapping of hard metal elements in lung tissue.

Readers interested in elemental analysis of lung tissue by EPMA-WDS are referred to the following web site for more information: http://www.med.niigata-u.ac.jp/in2/.

Diagnostic Evaluation

The following four elements are required for the diagnosis of hard metal lung disease (see Fig. 11.3):

1. A history of hard metal exposure; in particular, engagement in hard metal industry. As with any occupational disease, a comprehensive and detailed work history is a key element for the diagnosis. Note that history of exposure to hard metal dust is sometimes not apparent.
2. Chest HRCT showing opacities consistent with hard metal lung disease; in particular, centriolobular micronodular opacities.
3. Giant cells in BAL and/or a pathological diagnosis of GIP in surgical lung biopsy. Multinucleated giant cells in BAL or lung specimens are diagnostic for hard metal lung disease, but the absence of the cells does not exclude the possibility of the disease.
4. Tungsten and/or cobalt detected by elemental analysis in giant cells or lung specimens. Note that cobalt is only detected in some lung tissue samples because of its biosolubility.

For the differential diagnosis, all other types of interstitial pneumonia, in particular, hypersensitivity pneumonitis, sarcoidosis, neoplastic lung disease, or secondary interstitial lung disease such as collagen vascular disease associated lung fibrosis should be excluded. Elemental analysis of BAL or lung specimens shows the presence of increased amount of tungsten and/or cobalt for a definite diagnosis of hard metal lung disease. Although the finding of GIP is almost pathognomonic of hard metal lung disease, Moriyama et al. reported two patients whose biopsies exhibited features of GIP but no tungsten or cobalt was detected, and neither had a history of work in the hard metal industry [14]. Screening of lung tissue from patients with suspected occupational lung diseases by EPMA-WDS sometimes yields elements

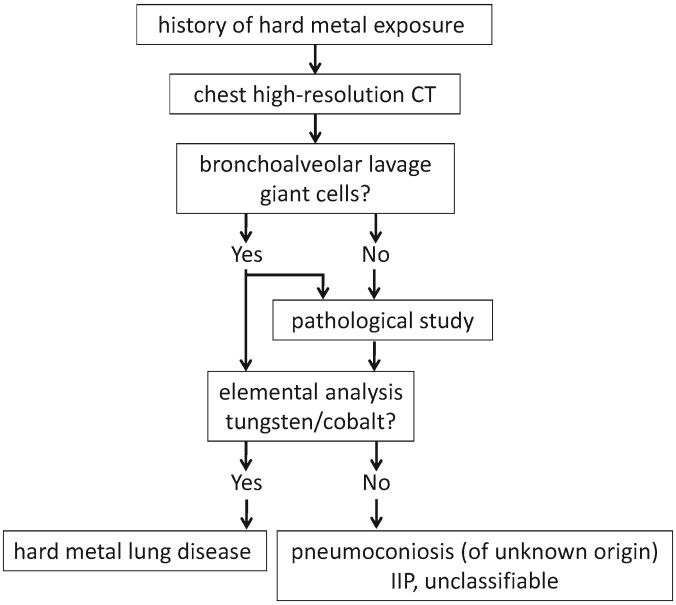

Fig. 11.3 Proposed diagnostic algorithm for hard metal lung disease. A patient with respiratory symptoms with occupational history in hard metal industry should proceed to chest HRCT. If interstitial lung disease is detected by HRCT, the patient should be further investigated by BAL and/or surgical lung biopsy. Giant cells in BAL or giant cell interstitial pneumonia are pathognomonic for hard metal lung disease. Hard metal elements, tungsten and/or cobalt, detected by elemental analysis are the definitive findings for diagnosis of the disease. *IIP* idiopathic interstitial pneumonia.

that have not been thought to cause lung injury, including indium, vanadium, and niobium, etc. Extrinsic elements that are difficult to detect with current techniques may cause non-hard metal lung disease or "idiopathic" GIP [41].

Treatment and Prognosis

Hard metal lung disease may improve with only removal from exposure and often responds to corticosteroid therapy. Accurate diagnosis is therefore essential to patient management. However, fatally progressive cases have also been documented [42].

Exposure Cessation

Hard metal lung disease progresses with continuation of the exposure. Thus, patients with the disease should be removed from further exposure to hard metal dust.

The complete cessation of exposure may bring improvement and even complete remission in the early forms of the disease. Interruption of the exposure by improved hygiene at work and exhaust ventilation produced good symptomatic and clinical improvement in diamond polisher's lung [11]. However, the disease may recur in subjects who return to work after being successfully treated by removal from exposure and corticosteroid therapy. Furthermore, the continued exposure can cause rapid progression of the disease and fatal outcome in the subjects [22, 42]. Twelve of 19 cases with hard metal lung disease surveyed in Japan were removed from further exposure by job change, retirement, and reshuffle at workplace, and four cases improved by only exposure cessation (unpublished data). Two cases managed only by strict wearing of protective mask or working in areas with better exhaust ventilation without job change did not show improvement. This suggests that complete removal from exposure is necessary for clinical improvement.

Medical Treatment

Although no controlled studies exist, corticosteroid therapy is reported to produce clinical, functional, and radiologic improvement [1, 2, 11, 43, 44]. In our institute, 13 of 19 cases with hard metal lung disease in Japan were initially treated by oral prednisolone 40–60 mg/day and one third also treated by intravenous methylprednisolone (1 g/day for 3 days) (unpublished data). Most improved and only three cases died of respiratory failure. Exposure cessation and glucocorticoids may not be sufficient in some cases and, in this situation, addition of a second agent should be considered.

A second immunosuppressive agent may be added to glucocorticoid therapy for either its glucocorticoid-sparing effect or progressive lung disease not responsive to corticosteroid therapy alone. The choice of a specific agent is dependent on the experience of the treating clinician, but cyclophosphamide, azathioprine, or cyclosporin was most commonly used [45]. One case report showed that a 31-year-old woman with severe pulmonary fibrosis secondary to hard metal disease was treated with glucocorticoid and cyclophosphamide, which resulted in stabilization of her pulmonary function. She underwent a successful term pregnancy subsequently [46].

Lung Transplantation

Lung transplantation has been used as the last resort for patients with hard metal lung disease [22, 47]. There is also a report that documented recurrence of the disease in the transplanted lung [47]. Although autopsy confirmed the presence of numerous giant cells characteristic of GIP with associated fibrosis throughout the transplanted lung, there was no evidence of tungsten particles in the transplanted lungs in that case, indicating GIP might develop in the transplanted lung via immune mechanisms.

Prevention

Hard metal lung disease is a preventable disease. Primary prevention is through exposure control by better industrial hygiene practices, i.e., mask wearing and maintenance of better exhaust ventilation and workplace monitoring. The current Occupational Safety and Health Administration (OSHA) permissible exposure limit (PEL) for cobalt is 0.1 mg/m^3 of air as an 8 h time weighted average (TWA) concentration, but this may be still too high as hard metal lung disease has been reported in workers exposed to very low level of cobalt dust [26]. Regular chest radiographs and spirometry screening may be useful in identification of early disease, especially in employees working in poor hygiene conditions. Patch test for cobalt may also be useful in detecting the disease at an earlier stage.

Summary and Recommendations

1. Workers in hard metal manufacture, maintenance of hard metal tools, and diamond tooling are exposed to hard metal elements, in particular, cobalt, and thus are at risk for developing hard metal lung disease.
2. Hard metal lung disease appears 2.5–30 years after exposure, but history of exposure to hard metal dust may be obscure.
3. The diagnosis of hard metal lung disease is usually based on a good exposure history, giant cells in BAL and/or a pathological diagnosis of GIP in surgical lung biopsy. The presence of increased amount of tungsten by elemental analysis confirms diagnosis.
4. Complete cessation of exposure with or without corticosteroids is the most acceptable treatment for hard metal lung disease. Prevention through a comprehensive exposure control strategy in the workplace by the use of personal protective equipment and better ventilation systems should decrease the prevalence of hard metal lung disease.

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Chapter 12
Beryllium Disease

John Ferguson, Margaret M. Mroz, and Lisa A. Maier

Abstract Exposure to beryllium remains a significant occupational hazard, clinically resulting in berylliosis, or chronic beryllium disease (CBD). This scarring lung disease is an interstitial lung disease characterized by granulomatous inflammation that affects 2–10% of those exposed. Serving as a model for other granulomatous disease, CBD provides an example of an exposure-related disease that results from an environmental–genetic interaction. The development of CBD requires both a genetic predisposition, namely a major histocompatibility complex (MHC Class II) allele of HLA-DPB1 with a glutamic acid at amino acid position 69 (glu69), as well as exposure to beryllium.

The precursor to CBD, beryllium sensitization (BeS), is defined by the demonstration of a beryllium-specific cell-mediated immunity using the beryllium lymphocyte proliferation test (BeLPT), a test which provides clinicians the ability to differentiate CBD from similar granulomatous diseases. CBD is characterized by the presence of sensitized T-lymphocytes with Th1 cytokine production. Like many granulomatous diseases, CBD has a variable course, and although immunosuppressive drugs may be beneficial in some individuals, the disease has no cure. Thus, the focus on decreasing the prevalence of CBD relies on improving prevention in the workplace. This chapter will outline the potential for workplace exposure to beryllium as well as the immunopathogenesis, clinical manifestations, diagnosis, and current treatment of BeS and CBD.

Keywords Chronic beryllium disease • Berylliosis • CBD • Beryllium sensitization • BeS • Beryllium lymphocyte proliferation test • BeLPT

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Historical Background

Beryllium is a hard, brittle, gray-white alkaline natural metal extracted throughout the world [1]. The physiochemical properties of beryllium that led to its use in industrial applications include its light weight, corrosion resistance, high strength-to-weight ratio, high thermal conductivity, and low electrical conductivity. Its high melting point of over 1,200 °C and low atomic weight of 9.012 make it a valuable resource. First discovered in France in 1798 [2], beryllium was not used commercially in the USA, Europe, or Asia until the 1930s when it was first introduced into nuclear weapons applications and fluorescent lighting. Acute pulmonary toxicity due to beryllium was first described in medical literature in 1933 by Weber, followed by multiple case reports in Europe and the USA [3–6]. In 1945, 170 cases of beryllium poisoning, ranging from dermatitis to acute lung effects such as chemical pneumonitis were reported among three cohorts in the USA involved in beryllium extraction and manufacturing [6]. In 1946, an epidemic of "sarcoid-like" lung disease was described among fluorescent light workers related to the use of beryllium phosphors. Exposures to compounds other than beryllium were initially thought to be the cause of the pulmonary toxicity [7]. Because of beryllium's unique properties and applications, skeptics of beryllium toxicity professed in a Lancet review: "To charge such an admirable metal with having poisonous properties is about as distasteful as accusing a trusted butler of stealing the family plate" [8]. It soon became clear however, that exposure to beryllium itself was the cause of its associated health effects [7]. Ultimately, the use of beryllium in fluorescent lighting was discontinued. However, beryllium continued to be used in the nuclear weapons industry resulting in additional case reports of beryllium poisoning [9–14]. CBD was also diagnosed among individuals living around beryllium plants and family members of beryllium workers. Because CBD occurred at both high and low levels of exposure it was hypothesized that the disease was immunologically mediated. This eventually led to the establishment of the current beryllium exposure limit of 2 $\mu g/m^3$.

Exposure to Beryllium

With the reduction in exposure due to an established exposure limit, cases of acute beryllium disease diminished. However, exposure to beryllium continues today in many manufacturing industries including computers, aerospace, nuclear systems, ceramics, automotive systems, telecommunications, nuclear weapons, foundries, and dental alloys. One million individuals or more have been exposed in the USA alone [15], of whom it is estimated that over 134,000 are currently working [16]. Despite improved industry standards for worker protection, many individuals continue to develop BeS and CBD [17, 18], at low or incidental exposure levels, including those in administrative positions or security [19–24]. Estimates from various studies have shown that CBD still occurs in approximately 2–10% of exposed workers [17, 25–30].

There are several forms of beryllium, including beryllium sulfate and beryllium oxide, as well as compounds that include copper alloys. Chemical properties may play a role in the pathogenesis of disease. *Beryllium oxide* remains in the lung for an extended period of time compared to the more soluble salts [31]. It also may cause a more immunogenic response when fired at lower temperatures than at high temperatures. Dissolution rates also seem to be an important factor in provoking the immune response [32].

The current OSHA limit for exposure is 2 μg/m^3 as an 8 h time-weighted average, but case reports have noted BeS and CBD at average exposure levels estimated to be as low as 0.02 μg/m^3 [33–36]. Machining of beryllium has been shown to be a risk factor for BeS and CBD, producing inhalable particles [37, 38]. Particles less than 2.5 μm are more likely to deposit into the lower lung parenchyma rather than the upper airway leading to CBD [39–41]. Processes such as melting, casting, grinding, drilling, extracting, or smelting of beryllium tend to produce these smaller particles [39]. Individuals with minimal exposure have developed sensitization and disease, including residents of neighborhoods surrounding beryllium factories [34, 42]. However, recent studies have shown higher prevalence of disease associated with higher measures of exposure.

In addition to inhalation exposure, skin contact is another important source of exposure that may lead to sensitization and granulomatous dermatitis [43–45]. Thus, preventive measures should include covering the skin in addition to preventing respiratory exposures.

Immunopathogenesis of CBD

The pathogenesis of chronic beryllium disease is characterized by accumulation of CD4+ T-lymphocytes within tissue, primarily the lung and skin [28]. The importance of the CD4+ lymphocyte and MHC II regulation have been confirmed by animal models, showing a lack of humeral immunity and a variable response predetermined by genetics [31, 46–48]. The activation and migration of these T-lymphocytes requires a complex interaction between antigen-presenting cells (macrophages and dendritic cells) and T-lymphocytes, leading to an effector memory cell phenotype and chronic inflammation. This process can be simplified into three steps (Fig. 12.1):

1. Beryllium binding to antigen-presenting cells (APCs)
2. Presentation of beryllium to CD4+ T-lymphocytes and Th1 cytokine release
3. Tissue infiltration of T-lymphocytes with ongoing inflammation and granuloma formation

Following an exposure, antigen-presenting cells bind to beryllium through a complex interaction, which has not yet been fully characterized. The biological structure of the MHC II complexes that attach to the antigen-presenting cells determines the individual's ability to present it to lymphocytes [49]. The structure of the HLA-DP2 has recently been crystallized, with the peptide-binding groove demonstrating four

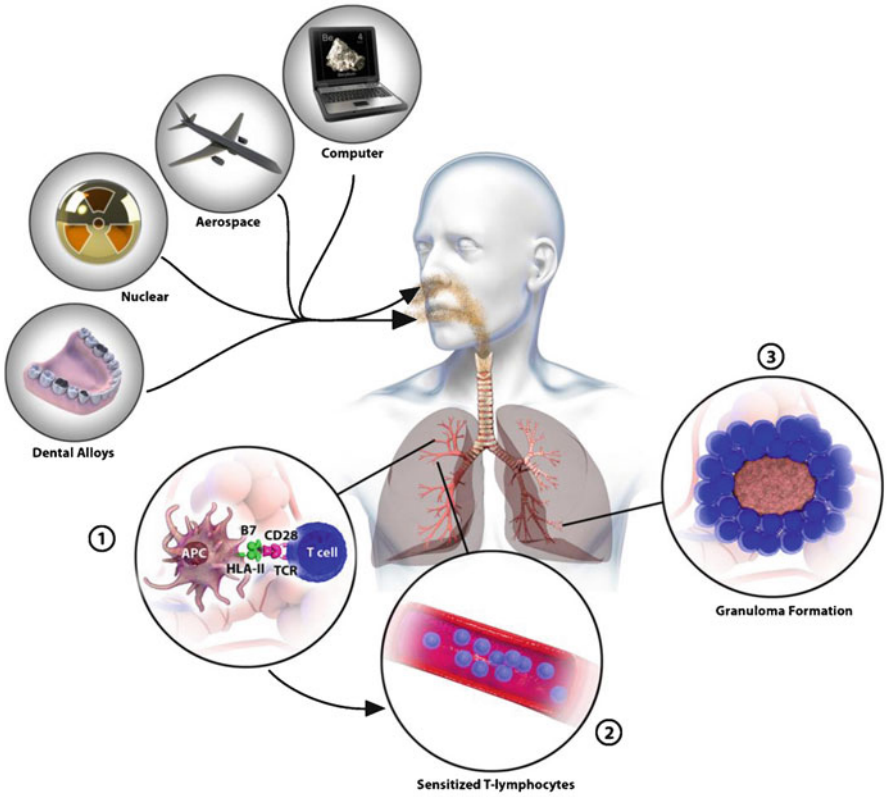

Fig. 12.1 Exposure pathways and pathogenesis of CBD. Respiratory exposure to beryllium occurs through various manufacturing processes, including ceramics, aerospace, and nuclear weapons. Inhaled Be particles are presented to CD4 T-lymphocytes by alveolar macrophages through the MHC class II–T-cell receptor complex, requiring B7-CD28 costimulation. Sensitized T-lymphocytes may be detected in peripheral blood with the use of the BeLPT. Following T-lymphocytes sensitization, granuloma formation may occur within the lung through an increase in cytokine production, leading to the diagnosis of CBD.

distinct pockets. When associated with the HLA-DPB1*0201 allele, these pockets are large, hydrophobic, and wide, able to accommodate a beryllium-containing complex. Multiple polymorphisms of the MHC II class exist, resulting in a negatively charged environment for the positively charged beryllium antigen, leading to effective antigen presentation and sensitization [50]. The precise antigenic form of beryllium presented by the MHC II molecule is uncertain [51–53]. Proposed models of interaction include a direct binding to MHC II, peptide-mediated binding to MHC, or indirect binding through cryptic peptides [54]. Whether antigen processing occurs in presentation of beryllium or how beryllium enters the cell has also not yet been defined.

Following antigen binding to the MHC II complex, beryllium is presented to CD4+ T-lymphocytes. The importance of T-cells in the development of CBD has

been noted with in vivo patch testing. Patch testing with beryllium sulfate leads to T-cell infiltration of the dermis and subsequent granuloma formation [55, 56]. In addition, following skin patch testing, the presence of an oligoclonal T-cell population was noted in the lung, blood, and skin, further validating the importance of a specific T-cell subset in granulomatous inflammation [57, 58]. Beryllium presentation to CD4+ T-cells leads to a memory-type Be-specific CD4+ T cell phenotype, manifested by a Th1 cytokine production that includes IL-2, IL-6, IFN-γ, and TNF-α [59], in part through a transcription-dependent mechanism [60]. This type of response enhances cell-mediated immune responses such as delayed-type hypersensitivity reactions [54, 57]. CBD T cells have further shown an effector-type phenotype [49, 61, 62]. Unlike sarcoidosis, both CD8 cells and Th2 cells that secrete IL-4, IL-5, IL-10, and IL-13 are generally absent. Activation of T-cells typically requires HLA-TCR binding, but also requires costimulation through the antigen-presenting cell B7 and T-lymphocyte CD28 interaction. In chronic beryllium disease, however, T-cells transition to functional independence from central memory CD28 dependence [63]. The T helper 1 cytokines promote macrophage accumulation, and are suspected to lead to the development of granulomatous inflammation [62].

IFN-γ and TNF-α production likely leads to tissue damage and granuloma formation [64–68]. Normal down regulatory mechanisms may be absent to reduce Be-stimulated inflammation as decreased expression of FoxP3 T-regulatory cells have been shown in CBD patients when compared with beryllium-sensitized subjects, while such cells were inversely correlated with disease severity [69].

Genetics of CBD

Since not all exposed developed BeS or CBD, it was promptly postulated that a genetic predisposition was required. Familial cases were noted between twins and in parents and children, indicating the importance of a genetic predisposition [70, 71]. Alleles of the HLA-DPB1 gene on chromosome 6, with a glutamic acid residue at position 69 (E69) were found to be highly associated with BeS and CBD [72]. The Glu69 allele is present in 73–95% of CBD patients, compared to 30–48% in exposed controls according to various reports [73–77]. E69 also appears to play a functional role, as monoclonal antibodies against HLA-DP inhibit cell proliferation in E69 positive individuals. However, BeS and CBD may develop in individuals without E69, and it appears that HLA-DRB1 with a glutamic acid at position 71 also may present antigen and serve as a risk factor. Recent studies have shown that beryllium exposure in combination with HLA-DPB1 E69 genotype is important in determining the risk for BeS and CBD [78] and that the odds of BeS and CBD appear to be greater among carriers of the non-*02 HLA-DPB1 E69 alleles and among HLA-DPB1 E69 homozygotes [78]. Screening for this genetic susceptibility in workers is problematic due to the low positive predictive value of glu69 for CBD. Additional markers are likely important in the development of severe disease [79].

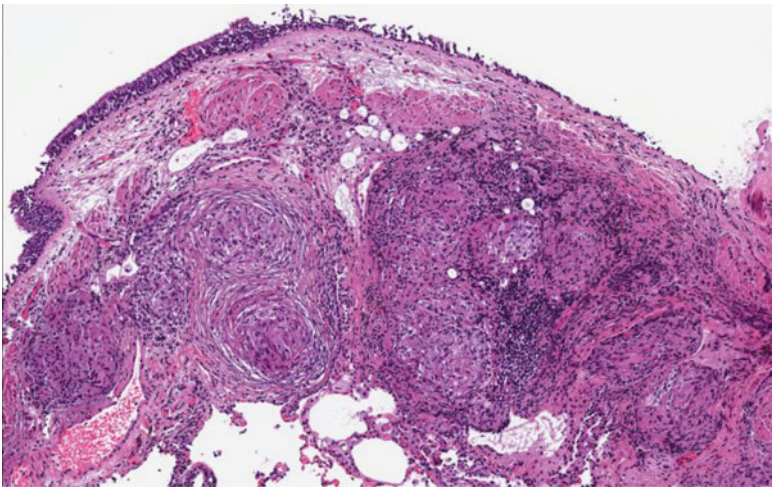

Fig. 12.2 Transbronchial biopsies obtained from an individual with CBD. These typically demonstrate well-formed peribronchovascular granulomas in the interstitium and/or airways. Interstitial fibrosis may form later in the course of the disease.

Histopathophysiology

The classic pathologic progression of beryllium disease is thought to occur in four phases: nonspecific inflammatory responses, then foamy macrophages with peribronchial lymphoid proliferation, next granuloma formation, and finally interstitial fibrosis [28, 80, 81].

The noncaseating granulomas in CBD are composed of macrophages surrounded by T-lymphocytes (Fig. 12.2). From a clinical standpoint, CBD must be distinguished from other granulomatous disease such as sarcoidosis, fungal infections, mycobacterial infections, and hypersensitivity pneumonitis, although the pathology is virtually the same. While beryllium metal can be identified within granulomas by ion mass spectroscopy [82], but not by light microscopy, detection of beryllium in the lung is not used for clinical diagnosis.

Ultimately, the BeLPT must be used to differentiate CBD from other granulomatous lung diseases.

Clinical Characteristics

Acute Beryllium Disease

High levels of exposure to beryllium can lead to lower airway involvement manifesting as bronchiolitis, pulmonary edema, and pneumonitis known as acute beryllium disease. In addition, upper airway involvement with URI-like symptoms may

also result. The symptoms of acute pulmonary toxicity frequently resolve after removal from beryllium exposure and following a short course of systemic glucocorticoids, similar to HP. The distinction between acute disease and CBD may be complex, as some cases of acute toxicity have behaved as a delayed hypersensitivity reaction, much like CBD, leading to the hypothesis that these may be within a spectrum of disease [83]. In addition, individuals with acute disease have gone on to develop CBD, often years after removal from exposure. Due to improved industry standards starting in the 1940s and 1950s, acute beryllium toxicity is uncommon, and will rarely be seen [84].

Beryllium Sensitization and the BeLPT

The demonstration of a beryllium-specific cell-mediated immure response with the BeLPT defines beryllium sensitization [63]. In this test, cells are stimulated with beryllium, and the proliferation of lymphocytes is measured by incorporation of tritiated thymidine [85]. Results are expressed as a stimulation index (SI), which is the ratio of the counts per minute of radioactivity in cells stimulated with beryllium salts divided by the counts per minute for unstimulated cells. The test is set up using three different concentrations of beryllium on two separate days of incubation. A test is considered abnormal if two or more of the six stimulation indices exceed the normal range. The blood test is highly specific (0.969), with a sensitivity of 0.683, so repeat testing should be performed to confirm an abnormal result. Further clinical evaluation is needed to diagnose CBD, although the BeLPT is useful in differentiating CBD from other granulomatous disease such as sarcoidosis.

Individuals with beryllium sensitization are asymptomatic with normal imaging and normal pulmonary physiology. Screening exposed populations with the peripheral blood BeLPT often detects CBD that is either already present on initial clinical evaluation or sensitization that progresses to CBD upon follow-up clinical evaluation [86]. As a result, it is important to continue to monitor individuals with BeS for progression from BeS to CBD. Clinically, individuals with BeS should be evaluated approximately every couple of years, usually with a chest radiograph and pulmonary function testing to assess disease progression. Bronchoscopy may be considered depending on the results of these tests.

Chronic Beryllium Disease

Clinical Signs and Symptoms

Clinical symptoms of chronic beryllium disease are nonspecific, but may include cough, dyspnea, fatigue, night sweats, weight loss, and anorexia. The presentation may be sudden after an acute stressor but typically develops slowly with dyspnea, cough, and constitutional symptoms. The latency until exposure varies between

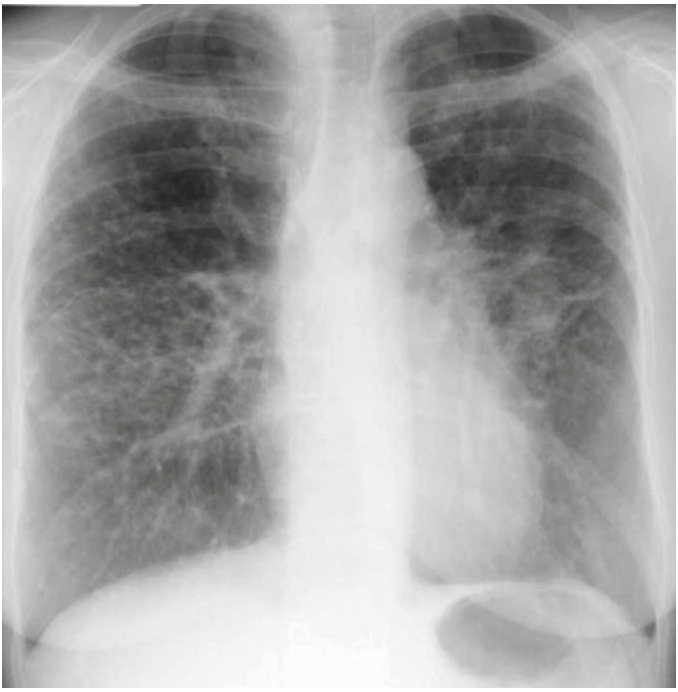

Fig. 12.3 Posterior lateral chest radiograph in CBD. Chest radiography demonstrates mid-upper-lung interstitial markings with variable fibrosis, in individuals with CBD.

6 and 40 years from the first exposure, with no clear relationship to the duration of exposure, and an estimated mean of 10 years [87]. However, CBD has also developed within 3 months of the first exposure. Individuals often lack clinical symptoms, but rather are recognized based on workplace screening, using the BeLPT or occasionally radiographic abnormalities. Chronic beryllium disease symptoms, pulmonary function physiology, and radiographic findings are similar between CBD and other granulomatous lung diseases such as sarcoidosis [88, 89].

Physical examination findings are predominantly manifested as dry bibasilar rales but can often be normal [90]. Symptoms of pulmonary hypertension or cor pulmonale may be present with advanced disease [91, 92]. The physical examination may reveal hepatomegaly, splenomegaly, uveitis, or skin manifestations of chronic beryllium disease.

Imaging

Imaging may be normal when CBD is diagnosed through medical screening using the BeLPT. Classically, progression of granulomatous inflammation manifests as mid-upper-lung interstitial lesions, honeycombing, pleural irregularities, and often hilar adenopathy [93] (Figs. 12.3 and 12.4). Radiographic differential diagnoses

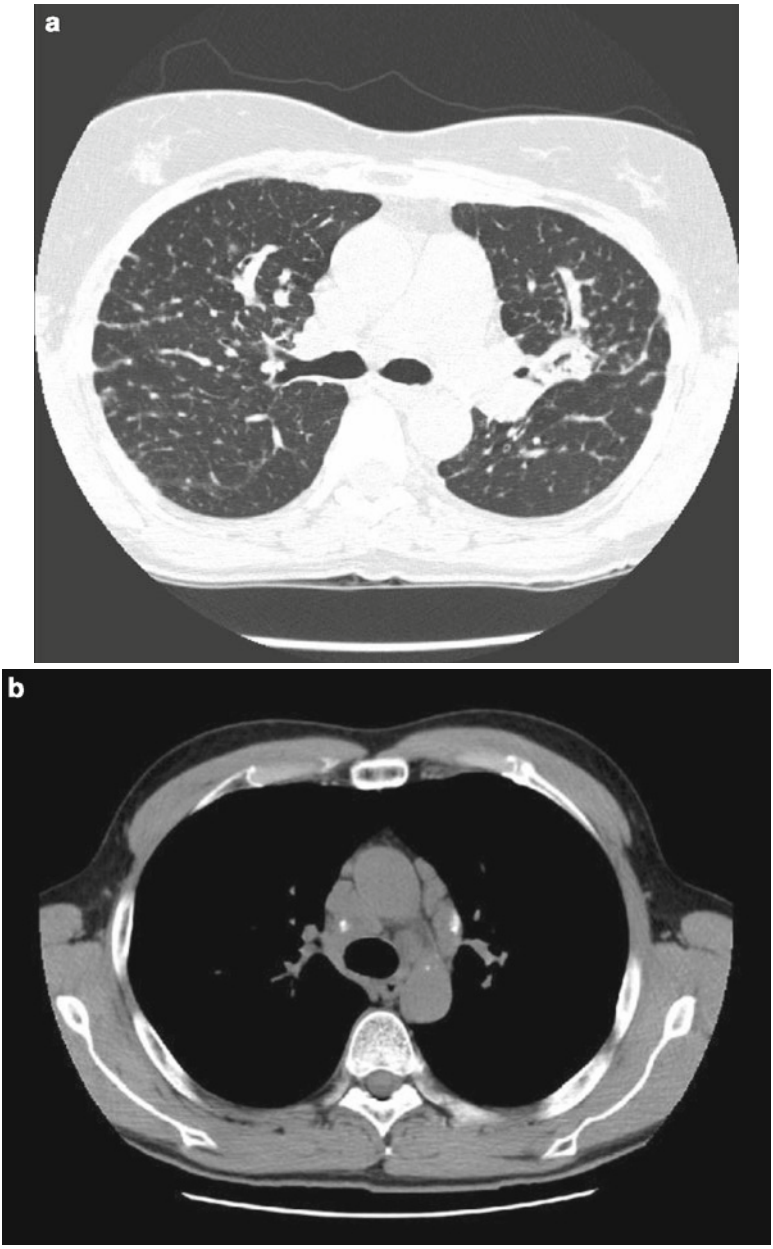

Fig. 12.4 High-resolution chest CT. (**a**) HRCT may demonstrate classical findings of multiple nodules tracking the bronchovascular bundle, with coalescence of nodules forming conglomerate masses, along with evidence of fibrosis noted on lung windows and (**b**) on mediastinal windows calcified or noncalcified hilar adenopathy may be apparent.

include sarcoidosis, silicosis, and chronic hypersensitivity pneumonitis. The chest x-ray (CXR) is insensitive in detecting abnormalities in CBD, and often a high-resolution computed tomography (HRCT) is required. In one case series, the HRCT revealed abnormalities in 89% of patients, but CXR in only 54% of patients [94]. CT scans often reveal parenchymal nodules along the bronchovascular bundles or interlobular septa along with septal thickening [93, 94] (Fig. 12.4a, b). On both CXR and HRCT, subpleural pseudoplaques may be seen. Bronchial wall thickening occurs in 46% of patients likely due to peribronchial accumulation of granulomas [93]. With advanced disease, honeycombing and pulmonary fibrosis may occur. Unlike sarcoidosis, hilar adenopathy is much less common in CBD [93–95].

Pulmonary Function Testing and Exercise Physiology

Pulmonary function testing *(*PFT*)* in CBD may manifest as a restrictive physiology with TLC <80% and supernormal flows, with airflow limitation, or with isolated decreased diffusion of carbon monoxide (DLCO). The DLCO may be reduced out of proportion to the degree of restriction and arterial hypoxemia is often present in individuals with CBD [95]. Obstruction, in fact, can be seen nearly as frequently as restriction [96, 97]. Neither obstructive nor restrictive physiology should conclusively rule in or rule out the diagnosis of CBD, but full PFTs with DLCO should be followed over time for changes in spirometry or gas exchange. A decrease in DLCO in the absence of radiographic infiltrates may be an early marker of progression of disease [98].

Exercise physiology derangements in CBD include a rise in dead space (V_d/V_t), and a reduced exercise capacity. In addition, decreased oxygen consumption (VO_2), a widening of the alveolar–arterial oxygen gradient, oxygen desaturation, and ventilation limitation are common abnormalities seen in CBD. Exercise tolerance proves to be a sensitive marker of CBD progression, even when lung volumes, spirometry, and diffusing capacity are normal [99].

Laboratory Testing

Just as with other granulomatous lung diseases, nonspecific lab tests occur including elevated levels of immunoglobulins, hypercalcemia, and abnormal hepatic enzymes. These may be normal as well [100]. While serum angiotensin-converting enzyme (ACE) levels may be elevated, such findings have a weak correlation to the extent of granulomatous inflammation, are nonspecific, and accordingly have a limited role in the diagnosis [100].

Bronchoalveolar Lavage

In individuals with CBD, bronchoalveolar lavage (BAL) white cells may be elevated compared to healthy subjects. The most common finding in CBD is a lymphocytic

alveolitis similar to other granulomatous disease [87]. The lymphocytes are predominantly T-cells, although this is not used for diagnosis. The BAL BeLPT is usually abnormal in CBD subjects, but in some individuals granulomas are present even when the lymphocyte count and the BAL BeLPT are normal.

Progression from BeS to CBD

The presence of noncaseating granulomas distinguishes CBD from BeS. To confirm the suspicion of CBD transbronchial biopsies are usually obtained. Eight to twelve biopsies from the most directly involved radiographic regions are recommended. If the biopsies are nondiagnostic, repeat transbronchial biopsies can be performed. If the diagnosis remains uncertain, a surgical lung biopsy may be considered, along with cultures for fungus and AFB. The presence of lymphocytosis by BAL and a positive lavage BeLPT, with high clinical suspicion and radiographic findings may suffice to confirm the diagnosis.

Diagnostic Evaluation

A thorough history with emphasis on specific occupational and environmental exposures should be performed to assess the likelihood of exposures to beryllium at any point in the patient's lifetime. The first exposure to beryllium and the duration of the exposure should be noted, as well as the amount of exposure on the job, although the duration and exposure time is not clearly linked to the development or severity of disease [101]. Currently, the diagnosis of CBD requires the demonstration of sensitization to beryllium. Up to 6% of chronic beryllium disease cases have been misdiagnosed as sarcoidosis, and all individuals suspected of beryllium exposure should be offered the BeLPT [102].

Individuals with BeS and/or clinical signs and symptoms consistent with CBD should undergo testing to confirm the diagnosis, including a BeLPT, chest radiography, pulmonary function testing, exercise physiology, and BAL with transbronchial biopsy. Many of these tests are used to assess the physiologic impairment if CBD is present and/or to establish a baseline for future follow-up. The BAL and biopsy are usually used to confirm granulomatous inflammation and rule out fungal infections and mycobacterial infections (Table 12.1).

Beryllium patch testing may find utility as an alternative to the BeLPT. This is typically reserved for individuals with a high clinical suspicion and should be approached with caution, as this can exacerbate symptoms [103, 104].

Alternative and experimental tests are under ongoing investigation [105–107]. Induced sputum (IS) with flow cytometry has been proposed as an alternative to transbronchial biopsies. The ELISPOT assay for IFN-γ has shown potential as an alternative to the BeLPT and possibly to limit the number of individuals undergoing bronchoscopy.

Table 12.1 Differential diagnosis of granulomatous lung disease

Differential diagnosis	Examples
Metal exposures	CBD, Silicosis, Zirconium, Titanium
Environmental exposures	Hypersensitivity pneumonitis
Idiopathic/immunologic	Sarcoidosis, Wegener's, Churg–Strauss
Viral	Measles
Fungal	Histoplasmosis, coccidiomycosis, blastomycosis
Bacterial	Brucellosis, *Chlamydia*, leprosy, tuberculosis, nontuberculous mycobacterium

Clinical Course

Beryllium sensitization progresses to CBD, and has been estimated to occur at a rate of approximately 6–8% per year [22]. The clinical course of CBD can be variable. Historically, approximately one third of individuals with CBD developed a progressive decline in lung function to end-stage lung disease. Recent studies have been more limited, although two are worthy of mentioning. In a study of ten CBD patients, three completely remitted in a year, one improved, five developed persistent disease, and one died of cor pulmonale. Three of the five individuals with persistent disease developed additional complications, including cavitary lung lesions, pneumothoraces, and recurrent infections [108]. The factors that determine the clinical course are not completely understood. To help define CBD progression in those identified with the BeLPT in workplace screening, another study compared never-smoker CBD cases ($n=81$) to never-smoking BeS patients ($n=83$) [109]. While CBD and BeS cases did not differ significantly in exposure time or physiology at baseline, CBD patients were more likely to have machined beryllium. At 30 years from first exposure, measures of gas exchange and lung function were significantly worse for CBD subjects, and machinists demonstrated faster disease progression. Of CBD cases, almost 20% developed clinical abnormalities requiring oral immunosuppressive therapy within an average of 1.4 years after initial diagnosis or an average of 22.8 years after first exposure. Thus, the type and duration of exposure along with genetic factors may affect CBD clinical course. Recognizing, following, and treating beryllium disease is crucial as it can progress to a debilitating and even fatal disease. Clinical monitoring parameters are summarized in Table 12.2.

Carcinogenesis of Beryllium

Early studies suggested that beryllium exposure may cause lung adenocarcinoma and bronchoalveolar cell carcinoma [110]. Subsequent studies confirmed an increased risk of lung cancer in humans, with standard mortality ratios (SMR) of 1.22–2.32 [111–114].

Table 12.2 Clinical monitoring parameters for CBD

Pulmonary function tests
Arterial blood gas
High-resolution CT of the chest
6 min walk test (or CPET)
Echocardiogram
Cardiopulmonary exercise test

Dissenting opinions on the role of beryllium in the development of cancer have focused on confounding factors, including the processing of beryllium through other sulfuric exposures, smoking effects, and the borderline statistical significance of the SMRs [90, 115]. A meta-analysis of 33 animal and 17 epidemiological studies did determine that the evidence is limited due to an inadequate smoking history and a lack of well-characterized exposure [116]. More recently, a study examined 9,199 workers from 7 beryllium processing plants followed for mortality from 1940 to 2005. Lung cancer was significantly elevated by 17% overall compared to the US population and those with the highest cumulative exposure controlling for both cigarette smoking and exposure to other lung carcinogens [117]. As a result of these and other human and animal studies, beryllium remains listed as a likely carcinogen in the lung [118, 119].

Treatment

The first step in treatment of CBD, like most occupational hazards, is removal from the exposure, although evidence that symptoms will improve is limited. The decision to initiate therapy must be individualized to each patient based on many factors, although primarily focused on evidence of lung function abnormalities and change in lung function over time. Treatment may also be influenced by evidence of pulmonary hypertension, evidence of impairment in quality of life, or progressive gas exchange abnormalities. Once the decision is made to begin therapy, baseline testing should be obtained, including full pulmonary function tests along with other clinically relevant monitoring parameters. These same parameters should be monitored to assess efficacy of therapy.

Corticosteroids remain the mainstay of treatment of chronic beryllium disease. The suspected mechanism of the steroid effect is through suppression of the hypersensitivity reaction and prevention of the development of fibrosis [120]. Corticosteroids have demonstrated a favorable clinical response in most CBD patients, as demonstrated by dyspnea scores, and lung function, although randomized controlled studies have not been performed, and likely will not. The initial recommended dose is a prednisone equivalent of approximately 40 mg daily or every other day. There has been no proven benefit to higher doses. After 3–6 months of the initial dose, the steroid dose may be gradually decreased to the lowest dose possible every 3–6 months, while monitoring lung function closely for signs of relapse. Relapses commonly occur after cessation of steroids [121], and with the rare

exception, lifelong steroid therapy at the lowest dose possible to prevent recurrent symptoms is usually needed. Despite treatment with corticosteroids, worsening pulmonary fibrosis may occur, often after a short-lived initial improvement in physiology [122]. In addition, corticosteroids may not be helpful once the patient develops fibrosis [95]. There is no current evidence to suggest early steroid therapy prevents the progression of BeS to CBD.

Steroid-sparing agents, much like those used in sarcoidosis, can be used for those who develop prednisone intolerance. There has been limited experience with methotrexate, azathioprine, and mycophenolate mofetil.

Standard adjunctive therapies for chronic lung disease should be added, including prevention of pulmonary hypertension, prophylaxis against opportunistic infections, and prevention of osteoporosis. Supplemental oxygenation should be used for hypoxemia, along with treatment of pulmonary hypertension and cor pulmonale. Lastly, lung transplantation should be considered for progressive disease in appropriate candidates.

Summary

Despite recent advances in workplace prevention and a better understanding of the immunologic pathogenesis, new cases of chronic beryllium disease continue to occur. CBD may be recognized early through the use of the BeLPT. Treatment remains limited primarily to the use of glucocorticoids, but may help prevent the progression of disease in symptomatic individuals.

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Chapter 13
Occupational Lung Cancer

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Abstract The lungs are the most common site for primary cancers in humans. This chapter focuses on examining occupational cancers in the parenchyma of the lungs, and starts with a historical review on the identification of lung carcinogens in various occupational groups. Occupational lung cancer linked to radon was first described in 1879. Various occupational exposures were subsequently found to increase the risk of lung cancer. Of the 107 agents classified by the International Agency for Research on Cancer (IARC) as Group 1 (confirmed human) carcinogens, 26 are regarded as carcinogens for lung cancers, and all except two mainly involve occupational exposures. Exposure to occupational carcinogens is an important determinant of lung cancer death and disability globally. Estimates on the contribution of occupational cancers to the population disease burden of lung cancer (population attributable fractions) ranged from 0.6 to 40%, depending on the population or geographical location, which might be explained by the different mix of industries and exposures. When examining the possible etiologic associations between occupational exposures and lung cancer, the effect of smoking should be carefully examined, as smoking is the most important cause for lung cancer in most countries, and exposures to occupational lung carcinogens not infrequently coexist with smoking. Smoking can act as a confounder or can modify the effects of occupational lung carcinogens. Lung cancers are irreversible and self-propagating, usually with poor prognosis, and hence should best be prevented. For occupational cancer, primary prevention is most relevant and has been found to be very successful in the past. Removing the agent, through elimination or substitution of known carcinogens, is most effective. Exposure can also be reduced through engineering and administrative means by modification of the plant, the working environment or the work process.

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Introduction

The lungs are the most common site for primary cancers in many parts of the world, as they are the organs with the largest surface areas having nonstop contact with the outside environment. Workers can withhold eating and drinking during work, but cannot stop breathing at work. Hence, whatever contaminants present in the air of the working environment can continue to act on the respiratory tract unless adequate respiratory protections are in place. Cancers occurring in the lungs are a heterogeneous group of malignancies with different histological characteristics, responses to treatments, and prognosis. These malignancies can have very different etiologies or risk factors as well.

This chapter focuses on examining occupational cancers in the parenchyma of the lungs, as pleural malignancies have been covered in other chapters (c.f. asbestos). Parenchymal lung cancers are frequently classified broadly into small cell lung cancer and nonsmall cell lung cancers (NSCLC), with the major histological subtypes of squamous cell carcinoma (SCC), adenocarcinoma (ADC), and large cell carcinoma (LCC) in the latter group [1].

Some Historical Aspects

The first description of occupational lung cancer was reported by Harting and Hesse in 1879 [2]. They described autopsy findings that documented pulmonary malignancy in miners in the Erz Mountains of Eastern Europe. The malignancy was subsequently shown to be primary carcinoma of the lung [3]. The finding of high levels of radon in mines in the region and in the nearby mines of Joachimsthal in Czechoslovakia where miners also had high lung cancer rates, led to the hypothesis that radon was the cause of the lung cancers [4–6].

The next report of lung cancer related to occupational exposure came more than half a century later in 1935. Pfeil reported two cases of pulmonary carcinoma in men who worked in the chrome industry in Germany. The first case occurred in 1911 in a large chromium manufacturing plant in Germany presenting with coughing and reddish expectoration. The patient also suffered from fractured ribs and was diagnosed as having a lung tumor. Postmortem examination confirmed the diagnosis of primary pulmonary carcinoma with metastases. In the following year, Pfeil treated a second patient, who worked in the same chrome plant as the first, for exudative costal pleurisy. This patient was found to have pulmonary carcinoma upon his death. Five more men died from lung cancer in this same chrome plant before 1935 [7]. In the same year of 1935, Lynch and Smith [8] reported that in addition to causing asbestosis, asbestos might also cause lung cancer.

Table 13.1 Reports of occupational exposures linked to lung cancer before 1950

Year	Occupational exposure	Author(s)
1879	Ionizing radiation	Harting and Hesse
1911	Chromium production	Pfeil
1935	Asbestos	Lynch and Smith
1936	Gas production	Kuroda and Kawahata
1939	Nickel	Amor
1948	Arsenic	Hill and Faning

Since then, various occupational exposures have been documented to be associated with increased risk of lung cancer, including gas production [9], nickel [10], arsenic [11] mustard gas [12], and chloromethyl methyl ether [13]. Studies of risk factors for lung cancer in occupational groups have contributed significantly to the understanding of risk factors for lung cancer in general. Table 13.1 shows the identification of occupational exposures linked to lung cancer in the earlier years.

Epidemiology and Contribution to Population Disease Burden

Lung cancer is the most well-studied occupational cancer and previous exposure to occupational carcinogens is an important determinant of lung cancer death and disability globally. Various people have estimated the contribution of occupational cancers to the population disease burden of lung cancer. Studies using job-exposure matrices gave population attributable fractions (PAFs) ranging from 0.6 to 35%, and when a list of recognized carcinogenic exposures was used for the selection of the relevant occupations, the estimates varied between 2.4 and 40% [14] in different populations or geographical locations, due to different industries/exposures. As more and more studies explore the associations between occupational exposure and lung cancer, the PAF will probably continue to increase, especially when tobacco smoking control is in place. On the other hand, it is possible that the PAF for occupational exposures will decrease, as more stringent controls of occupational hazards are implemented.

In 2005, Driscoll et al. [15] estimated that about 10% lung cancer deaths among men (88,000) and 5% of women (14,000) in the world were attributable to exposures to eight occupational lung carcinogens (i.e., arsenic, asbestos, beryllium, cadmium, chromium, diesel exhaust, nickel, silica), which led to an overall 102,000 deaths and 969,000 DALYs worldwide. Using the 14 epidemiological subregions of the World Health Organization (WHO) [16], Driscoll et al. found that lung cancer burden attributable to occupational lung carcinogens varied across different populations and countries, from the lowest PAF of 5% in the WHO subregion A of the Americas with a very low child and adult mortality, to the highest PAF of 14% in the WHO subregion C of Europe where a low child but high adult mortality was observed. The PAF among males varied from 6 to 15% and that among females

varied from 2 to 9%. Even within the same country, such as Italy, the PAF of occupational lung cancers tends to vary in different calendar time periods (4.9% in 2002–2005; 11.9% in 1976–1980), due to the involvement of different industrial activities and occupational exposures [17, 18].

The WHO estimates that roughly 19% of all cancers are attributable to the environment globally, including work settings, and results in 1.3 million deaths every year. Selected occupational lung carcinogens, such as beryllium and silica, were estimated to cause 111,000 lung cancer deaths in 2004, while asbestos caused 59,000 deaths (from mesothelioma) [19].

Occupational Exposures

The identification of occupational carcinogens is very important as recognition can usually lead to effective control. Occupational lung cancer is, to a very large extent, a preventable disease.

In general, occupational carcinogens can be categorized under physical, chemical, and biological agents, but for lung cancer, only the first two categories are of importance. Chemical agents are by far the largest group and can be further subdivided into the following subcategories: polycyclic aromatic hydrocarbons (PAH), dusts and fibers, metals and related substances, alkylating agents and other organic chemicals, and others.

IARC Carcinogens Related to Lung Cancers

Of the 108 agents classified by the IARC as Group 1 (confirmed human) carcinogens, 27 are regarded as carcinogens for lung cancers (Table 13.2) [20–24], and all except two (coal, indoor emissions from household combustion; active tobacco smoking) mainly involve occupational exposures. For Group 2A (probably carcinogenic) carcinogens 6/64 are associated with lung cancer (Table 13.3) [20–24] and all six are occupation related. Unfortunately, specific histological types of lung cancer were not mentioned or specifically examined for all except four agents (see Table 13.2). Only 12 of the 27 Group 1 lung carcinogens and 4 of the 6 Group 2A lung carcinogens refer to specific chemicals or chemical groups with Chemical Abstracts Service (CAS) numbers and the rest relate to mixtures or exposure circumstances.

Apart from the occupational agents/exposures that have been evaluated by IARC, a review of more recent analytic epidemiological studies published since 2001 yielded additional information on other potential occupational carcinogens or exposures that could be linked to lung cancer (Table 13.4) [25–34].

Table 13.2 Agents' link to lung cancer defined as Group1 by IARC in the various monographs

Agent/process (CAS No.)	Monograph no. and histology[a] if specified	Main industries/uses/exposures
Physical agents		
Ionizing radiation (all types)	75, 78, 100D	Radiologists; technologists; nuclear workers; radium-dial painters; plutonium workers; cleanup workers following nuclear accidents; aircraft crew; medical use; nuclear power; industrial uses; military activities; non-uranium mining
Radon-222 and its decay products (010043-92-2)	43,78,100D	Underground mining of gold, iron (hematite), and uranium (Radon is a radioactive gas formed from the isotopic decay of uranium and radium and is naturally found in volcanic rock)
Polyaromatic hydrocarbons (PAHs)	92	
Benzo[a]pyrene (000050-32-8)	92, 100F	Work involving combustion of organic matter; foundries; steel mills; firefighters; vehicle mechanics
Coal, indoor emissions from household combustion	95, 100E	Mainly nonoccupational
Coal gasification	92, 100F	Processing and use of coal and coal-derived products; coal liquefaction; coal gasification; coke production and coke ovens; coal-tar distillation; paving and roofing involving coal-tar pitch; creosote as a wood preservative; foundries aluminum production
Coal-tar pitch (065996-93-2)	35, Suppl 7, 100F	
Coke production	92, 100F	
Mineral oils, untreated and mildly treated	33, Suppl 7, 100F	Production; used as lubricant by metal workers, machinists, engineers; printing industry (ink formulation); used in cosmetics, medicinal and pharmaceutical preparations
Engine exhaust, diesel	46, 105F	Railroad workers; Professional drivers; Dock workers; Mechanics
Soots (as found in occupational exposure of chimney sweeps)	35, Suppl 7, 100F	Chimney sweeps; heating-unit service personnel; brick masons and helpers; building demolition workers; insulators; firefighters; metallurgical workers; work involving burning of organic materials
Tobacco smoking	83 (all types), 100E[b]	Mainly nonoccupational
Tobacco smoke, second-hand	83, 100E	Several occupational situations, such as working in bars, restaurants, offices, etc.

(continued)

Table 13.2 (continued)

Agent/process (CAS No.)	Monograph no. and histology[a] if specified	Main industries/uses/exposures
Dusts and fibers		
Asbestos (all forms) (001332-21-4, 013768-00-8, 012172-73-5, 017068-78-9, 012001-29-5, 012001-28-4, 014567-73-8)	14, Suppl 7 (squamous, small-cell), 100C	Mining and milling; by-product manufacture; insulating; shipyard workers; sheet-metal workers; asbestos cement industry
Silica dust, crystalline in the form of quartz or cristobalite (014808-60-7)	68, 100C	Mines; granite quarrying and processing, crushed stone and related industries, foundries; other metallurgical operations; ceramics, cement and glass industries, construction; sandblasting of metal surfaces; agriculture; miscellaneous operations
Metals and related processes		
Aluminum production	34, Suppl 7, 100F	Aluminum production (The industrial process exposes workers to tar fumes. Aluminum itself is not carcinogenic, but exposure to polycyclic aromatic hydrocarbons generated in primary aluminum production is.)
Arsenic and inorganic arsenic compounds (007440-38-2)	23, Suppl 7 (adeno-, oat-cell), 100C	Nonferrous metal smelting; production, packaging, and use of arsenic-containing pesticides; sheep dip manufacture; wool fiber production; mining and smelting of ores containing arsenic, e.g., copper
Beryllium and beryllium compounds (007440-41-7)	58, 100C	Ceramics; electrical connectors; nonferrous foundries, nonferrous smelters; sandblasting; aerospace; nuclear control equipment; electronics; refractories, beryllium smelting or fabrication; hazardous waste processing; dental equipment and supplies; engineering and scientific equipment; mechanical measuring devices; tool and die making; soldering; welding or flame cutting; metal plating; automotive parts; telecommunication equipment; golf club manufacture
Cadmium and cadmium compounds (007440-43-9)	58, 100C	Smelting and refining of zinc, lead and copper ores; electroplating, manufacture of cadmium alloys and of pigments and plastic stabilizers; production of nickel-cadmium batteries and welding

Chromium (VI) compounds, (018540-29-9)	49, 100C	Chromate production; chrome plating; pigment production and spray painting; steel smelting and welding; cement production and use; chromium ferro-alloy production; wood preservatives; leather tanning; water treatment; photography; lithography; drilling muds; synthetic perfumes; pyrotechnics; corrosion resistance
Iron and steel founding	34, Suppl 7, 100F	Iron and steel foundry (The industrial process exposes workers to tar fumes, and stainless steel production exposes workers to Cr(VI) and to nickel.)
Nickel compounds	49, 100C	Nickel mining and ore comminution; nickel roasting, calcining, smelting and refining; production of stainless steel and nickel alloys; steel foundries; production of nickel-containing batteries; production and use of nickel catalysts; nickel plating; welding; thermal spraying of nickel; production and use of paints; grinding, polishing and buffing of nickel-containing metals; miscellaneous exposure to nickel
Alkylating agents and other organic chemicals		
Bis(chloromethyl) ether and chloromethyl methyl ether (technical grade) (000542-88-1, 000107-30-2)	4, Suppl 7 (small cell), 100F	Production; chemical intermediate; alkylating agent; laboratory reagent; plastic manufacturing; ion-exchange resins and polymers
2,3,7,8-Tetrachlorodibenzo-para-dioxin (TCDD) (001746-01-6)	69, 100F	Production; use of chlorophenols and chlorophenoxy herbicides; waste incineration; PCB production; pulp and paper mills; steel mills
Rubber manufacturing industry	28, Suppl 7, 100F	Back processing, tyre curing, synthetic rubber production and vulcanization
Others		
Painter	47, 98, 100F	Manufacture of paints and related products; construction painting and lacquering; painting, varnishing and lacquering in the wood industry; painting in the metal industry; house painting, vehicle painting, etc.
Acid mists, strong inorganic	54, 100F	Isopropanol manufacture; synthetic ethanol manufacture; pickling and other acid treatment of metals; sulfuric acid manufacture; soap and detergent manufacture; nitric acid manufacture; phosphate fertilizer manufacture; lead battery (accumulator) manufacture
Sulfur mustard (000505-60-2)	9, Suppl 7, 100F	Production; used in research laboratories; military personnel

[a]The histological type was identified based on the summary of relevant IARC monographs

[b]Tobacco smoking increases the risk of all histological types of lung cancer including squamous-cell carcinoma, small-cell carcinoma, adenocarcinoma (including bronchiolar/bronchoalveolar carcinoma), and large-cell carcinoma

Based on data from refs [20–24]

Table 13.3 Agents' link to lung cancer defined as Group 2A by IARC in the various monographs

Agent (CAS No.)/process	Monograph No.	Main industries/uses/exposures
Polyaromatic hydrocarbons		
Dibenz[a,h]anthracene (000053-70-3)	92	Work involving combustion of organic matter; foundries; steel mills; firefighters; vehicle mechanics
Organics		
α-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures) (agents group: 000098-87-3, 000098-07-7, 000100-44-7, 000098-88-4)	29, Suppl 7, 71	Production; dye and pesticide manufacture
Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing (064742-93-4)	103	Roofers, road pavers and mastic asphalt workers
Epichlorohydrin (000106-89-8)	11, Suppl 7, 71	Production and use of resins, glycerine, and propylene-based rubbers; used as a solvent
Nonarsenical insecticides (occupational exposures in spraying and application of Aldicarb, Chlordane, and Heptachlor, DDT and associated compounds, Deltamethrin, Dichlorvos, Fenvalerate, Permethrin)	53	Production; pest control and agricultural workers; flour and grain mill workers
Others		
Hairdresser and barber	57, 99	Occupational exposure as a hairdresser and barber

Based on data from refs [20–24]

The Possible Effects of Smoking on Occupational Lung Cancer: Confounding or Interaction?

Smoking is usually regarded, legitimately, as the most important cause for lung cancer in most countries, especially among males. As exposures to occupational lung carcinogens not infrequently coexist with smoking, the possible effects of smoking on the association between exposures to occupational carcinogens and the risk of lung cancer need to be carefully examined.

In most of the previous occupational epidemiologic studies, smoking was simply treated as a potential confounding factor when the associations between occupational exposures and lung cancer were being examined. There is, however, some evidence that smoking might modify the effects of occupational carcinogens (e.g., asbestos and silica/silicosis) on the risk of lung cancer [35, 36]. On the other hand, such potential interactions have been infrequently examined by formal tests, probably due to

Table 13.4 Potential occupational carcinogens for lung cancer not yet evaluated by IARC

Author	Study design	Carcinogenic agent/process	Effect magnitude
van Barneveld et al. [25]	A historical cohort study	Biology Research Laboratory workers	Significantly increased lung cancer mortality for men working in genetics (RR = 11.3, 95% CI: 2.9–43.7), virology (RR = 8.0, 95% CI: 1.8–35.7) and plant physiology (RR = 6.1, 95% CI: 1.9–18.9) was found
Smailyte et al. [26]	Cohort study in cement workers	Cement dust	Excess risk was found for cancer of the lung (SIR 1.5, 95% CI 1.1–2.1)
Alavanja et al. [27]	The agricultural health study cohort	Pesticides	Two widely used herbicides, metolachlor and pendimethalin (from low to higher exposure categories: odds ratio (OR) = 1.0, 1.6, 1.2, 5.0; p(trend) = 0.0002; and OR = 1.0, 1.6, 2.1, 4.4; p(trend) = 0.003, respectively), and two widely used insecticides, chlorpyrifos and diazinon (OR = 1.0, 1.1, 1.7, 1.9; p(trend) = 0.03; and OR = 1.0, 1.6, 2.7, 3.7; p(trend) = 0.04, respectively), showed some evidence of exposure response relationship with risk of lung cancer
Lee et al. [28]	Cohort study	Pesticide applicators exposed to chlorpyrifos	Incidence of lung cancer was statistically significantly associated with both chlorpyrifos lifetime exposure-days (p(trend) = 0.002) and chlorpyrifos intensity-weighted exposure-days (p(trend) = 0.036). After adjustment for other pesticide exposures and demographic factors, individuals in the highest quartile of chlorpyrifos lifetime exposure-days (>56 days) had a relative risk of lung cancer 2.18 (95% CI = 1.31–3.64) times that of those with no chlorpyrifos exposure
Hours et al. [29]	Cohort study	Synthetic textile spinning plant	The "hot-line fitters" (RR = 2.13; n = 9; 95% CI: 1.06–4.29) and the "fiber-drawing workers" (RR = 1.83; n = 20; 95% CI: 1.09–3.07) experienced statistically significant excess in mortality from lung cancer. A slightly elevated but not significant risk of death related to lung cancer (RR = 1.5; n = 41; 95% CI: 0.8–2.7) was observed in the groups with the highest exposure to mineral fibers

(continued)

Table 13.4 (continued)

Author	Study design	Carcinogenic agent/process	Effect magnitude
Jayaprakash et al. [30]	hospital-based case–control study	Wood dust (WD)	Regular WD exposure was associated with a statistically significant increased risk of 69% for lung cancer alone (OR 1.69; 95% CI 1.20–2.36; p-trend = 0.007). WD was associated with an 82–93% increased risk of squamous cell, small cell, and adenocarcinoma of the lung
Canu et al. [31]	Cohort study	Slowly soluble reprocessed uranium dioxide	Model with cumulative duration of exposure coded as binary (>1 vs ≤1 year) time-dependent variable: HR = 2.58(95% CI: 0.76–8.83)
			Model with cumulative exposure duration (in years) coded as continuous, time-dependent variable: HR = 1.07(95% CI: 1.01–1.14)
McHugh et al. [32]	Case–control study	Conventional and antimicrobial (e.g., sterilizers, disinfectants, antiseptics) pesticides	Conventional pesticides and antimicrobial pesticides combined: OR = 1.80, 95% CI 1.13–2.86; conventional pesticides: OR = 2.05, 95% CI 1.23–2.39; antimicrobial pesticides: OR = 2.48, 95% CI 1.46–4.21
Lenters et al. [33][a]	A systematic review and meta-analysis	Endotoxin	The summary risk of lung cancer was 0.72 (95% CI, 0.57–0.90) for textile workers and 0.62 (0.52–0.75) for agricultural workers. Studies tended to support a dose-dependent protective effect of endotoxins on lung cancer risk
Mehta et al. [34][a]	A nested case–control analysis within a historical cohort study	Coexposure to water-based soluble and synthetic metalworking fluids (MWF) and biocide	Greatest reduction in mortality was observed among those with the highest exposure (at 99th percentile) (MRR 0.63, 95% CI: 0.39–0.98). The protective effect was observed only among workers with coexposure to biocide and synthetic MWF

[a]These two studies showed protective effects for the related occupational exposures

limited numbers of lung cancers among never-smokers. In epidemiological research, interaction is thought to be present if the joint effect of smoking and occupational carcinogen on lung cancer departs from a multiplicative or an additive risk model [37, 38].

The classic example of the synergism between asbestos exposure and smoking on lung cancer risk has frequently been mentioned in various textbooks in epidemiology and occupational health [39]. Compared to nonsmokers with no asbestos exposure, nonsmoking workers exposed to asbestos had about five times the mortality risk for lung cancer and smokers not exposed to asbestos had about ten times mortality risk, whereas smokers exposed to asbestos had about 50 times the risk of lung cancer mortality [35]. The presence of synergism was evaluated based on the additive model, but the mortality ratios in the different subgroups actually fitted well with the multiplication model.

Crystalline silica is one of the most common occupational hazards worldwide, leading to the highest lung cancer burden among eight lung carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel exhaust, nickel, silica) reviewed by a working group of the WHO [15]. Whether smoking could act as a confounder or effect modifier in occupational lung cancer studies with silica exposures has long been debated. In a multicenter case-referent study in seven European countries [40], Cassidy et al. found that similar effect of exposure to silica dust was observed for current (OR = 1.41, 95%CI: 1.07–1.87%), former (OR = 1.31, 95%CI: 0.99–1.73%), and never-smokers (OR = 1.41, 95%CI: 0.79–2.49%), with no evidence of any interaction beyond a multiplicative model ($p = 0.37$). Hence, smoking was addressed as a confounding factor to be adjusted in the multivariable models. Nevertheless, no formal tests for possible additive interaction or synergistic effect between smoking and silica on the risk of lung cancer were done.

Both additive and multiplicative interactions were examined in a recent pooled analysis of two population-based case-referent studies (1979–1986; 1996–2001) in Montreal men, Canada [41]. Vida et al. claimed that the observed joint effects between smoking and silica were between additive and multiplicative, perhaps closer to the latter. However, such a statement was limited by the imprecise OR estimates in most of the exposure categories [41]. More recently (2011), a large population-based case-referent study (1,208 cases and 1,069 referents) among Hong Kong Chinese men showed a relatively larger effect of occupational exposure to silica dust on lung cancer risk among never-smokers (OR = 2.58, 95%CI: 1.11, 6.01%) [42] compared with ever-smokers (OR = 1.54, 95%CI: 1.01–2.36%). Joint effect of smoking and silica was further explored and there was a synergy index of borderline significance (1.61, 95%CI: 0.95–2.73%). The joint effect did not deviate significantly from a multiplicative model, while an additive-scale interaction was also likely to be present. Due to inherent limitations, such as self-reported silica dust exposure and a low statistical power in the stratified analyses, findings from this Hong Kong study should be confirmed by large analytic studies with better exposure assessment. Joint effect between smoking and silicosis was also explored by the same group of Hong Kong researchers using meta-analysis [36]. They found a significant negative multiplicative interaction with risk ratio (a weighed "relative

silicosis effect") of 0.29 (95% CI: 0.20–0.42%) between smoking and silicosis on the lung cancer risk, whilst the observed combined weighed synergy index was 1.00 (95% CI: 0.79, 1.26%), suggesting that the joint effect did not depart from an additive model [36]. The role played by smoking on the association between silica dust exposure and lung cancer risk remains unclear.

Overall, smoking is the most important risk factor for lung cancer and inadequate consideration of the effects of smoking on the associations between occupational exposures and lung cancer could lead to inaccurate risk estimations. This would be of particular importance for assessing occupational exposures with weak-to-moderate carcinogenicity. Whether smoking plays its role more as a confounder or an effect modifier in many associations between occupational exposures and lung cancer risk has yet to be established.

Prevention and Control

Occupational cancers are irreversible and self-propagating, usually with poor prognosis, and hence should best be prevented. The principles of prevention include primary prevention (removing the causative agent), secondary prevention (improving the results from therapy, partly by early detection), and tertiary prevention (alleviating the problems associated with the disease).

For occupational cancer, primary prevention is most relevant and has been found to be very successful in the past. Removing the agent is most effective and may involve closure of specific plants and elimination or substitution of known carcinogens with less toxic materials. Exposure can also be reduced through engineering means to very low levels by modification of the plant, the working environment, or the work process (e.g., total enclosure with automation, local exhaust ventilation systems). Legislative regulations would provide the necessary persuasion to adopt effective source control or engineering control. Close monitoring of the working environment would be needed to ensure adequate protection of the workers. As a last resort, workers can also be protected directly by using appropriate personal protective equipment.

Secondary prevention is theoretically needed even if primary prevention has been implemented because of the usual long latency period for cancer. Workers exposed in the past can be screened to identify occult diseases. In actual practice, its use has been quite limited. The success of such a program depends on the availability of appropriate, affordable, and acceptable tests with adequate sensitivity and specificity, as well as treatments that can alter the natural history of the disease. Education programs can be useful in reducing the delay in diagnosis in patients developing symptoms of the disease, but again must be accompanied by the provision of appropriate facilities for confirmation of diagnosis and treatment.

Most patients with occupational lung cancer have relatively short survival despite medical advances in the recent decades. Many of them are very symptomatic in the later course of the disease. Every effort should be made to alleviate the sufferings and improve the quality of life once diagnosis is confirmed.

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Chapter 14
COPD in Non-smokers

K.B. Hubert Lam, Om P. Kurmi, and Jon G. Ayres

Abstract Chronic obstructive pulmonary disease (COPD) is an important global public health challenge because of its high prevalence, morbidity, and mortality. While cigarette smoking has long been seen as the principal risk factor for COPD, recent data suggest that the actual population attributable fraction for smoking is highly variable across different populations. The fact that at least a quarter of the COPD cases identified in epidemiological studies are found in individuals who have never smoked further demonstrates the need to understand COPD in non-smokers. A number of putative risk factors other than smoking have been implicated, with some having strong evidence for causality, such as exposures to occupational agents, environmental tobacco smoke, and biomass smoke, although there is yet to be consensus on other novel factors. Our current knowledge on the clinical presentation, prognosis, and management of COPD has been based on studies conducted in either former or current smokers. Almost nothing is known about where there might be specific management features for COPD in non-smokers although this seems unlikely apart from removing any underlying contribution to continuing disease activity.

Keywords Chronic obstructive pulmonary disease • Non-smokers • Epidemiology • Risk factors • Prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is a clinical entity that is defined by a progressive and largely irreversible limitation to airflow as a result of chronic inflammatory processes in the airways [1]. Tobacco smoking has long been regarded

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as the major causative factor for COPD, a view held by contemporary clinical guidelines, clinicians, and scientists. It is therefore not surprising that COPD is known colloquially as *smoker's lung*. However, a significant proportion of patients diagnosed with COPD report never having smoked cigarettes, raising questions not just about etiology but also prognosis and therapy. In the past, the immediate negativity which surrounded a diagnosis of COPD, where the blame was put on cigarettes and therefore on the patients themselves (self-infliction), had meant that non-cigarette related causes of COPD were just not considered.

The relatively recent diagnostic label of COPD includes chronic bronchitis and emphysema, diagnoses which were clinically and pathologically defined, respectively. Modern guidelines advocate and mandate that COPD can only be diagnosed based on the presence of airflow obstruction, and the use of pulmonary function in the diagnostic process has revealed more individuals with spirometric COPD than would have been suspected using clinical criteria. Consequently, as a result of a pulmonary function derived definition, a label of COPD can be applied to any manifestation of airflow limitation regardless of its underlying cause.

It is against this background that COPD in non-smokers has received more attention. Accumulating evidence has suggested that cigarette smoking might account for a smaller-than-previously-thought proportion of COPD cases, although some caution needs to be used as self-reported past smoking history can be unreliable and some putative cases of non-smoking COPD may in fact be simply a case of exposure misclassification. Nevertheless, a review published in 2010 commissioned by the American Thoracic Society (ATS) collated 24 recent (2000–2008) reports from various populations and settings, mostly from Europe and Asia, and noted a very heterogeneous population attributable fraction for active cigarette smoking, ranging from 9.7 to 97.9% [2]. However, the majority of these population attributable fraction estimates are under 80% [2], indicating the urgent need to identify causes of COPD other than cigarette smoking. This has important implications: until now much of our knowledge on COPD has come from smokers who manifest classical smoking-induced COPD and yet relatively less is known about COPD in non-smokers. In this chapter, current knowledge and recent advances in different aspects of COPD in non-smokers are presented. A number of other lung diseases are associated with chronic airflow limitation, the most common being bronchiectasis and sarcoidosis, but these other pulmonary conditions are not considered further here.

Burden of COPD in Non-smokers

Estimating the global prevalence of COPD has never been a simple task due to the differences in disease definition across countries and the high level of under-diagnosis, in turn depending on approaches to case finding. The latter is even more pertinent in non-smokers since COPD has always been associated with cigarette smoking, and those who do not smoke are likely to slip through the diagnostic net. However, more common use of spirometry in the community has identified individuals with mild

COPD who are often asymptomatic. Consequently, attempts at discerning whether non-smoking COPD has increased in prevalence need to be considered in this light.

A systematic review and meta-analysis aggregated data from 28 countries during 1990 to 2004 and reported a pooled prevalence of 7.6% (95% confidence interval [CI] 6.0, 9.5%) [3]. When broken down according to smoking status, the prevalence among smokers was 15.4% (95% CI 11.2, 20.7%) and that among never smokers was 4.3% (95% CI 3.2, 5.7%), suggesting that approximately a quarter of COPD cases were in never smokers. This is supported by results from an international multicenter population-based burden of obstructive lung disease (BOLD) study aiming to unify the methodology in obtaining COPD prevalence estimates [4]. In this study based on 10,000 subjects from 14 sites (Australia, Austria, Canada, China, Germany, Iceland, Norway, Philippines, Poland, South Africa, Sweden, Turkey, UK, and USA), never smokers accounted for 27.7% (523/1,889) of all COPD cases (defined as post-bronchodilator FEV_1:FVC ratio <0.7). The proportion is substantially similar albeit slightly reduced (23.6%; 302/1,282) when the lower limit of normal (LLN) approach to normality is used to define airways obstruction. The LLN is the lower fifth percentile for predicted FEV_1:FVC, and its use reduces the over-diagnosis of COPD in the elderly. The BOLD study shows considerable geographical variation in COPD prevalence. For instance, one of the BOLD sites, Salzburg, Austria, had a relatively high proportion of non-smoking COPD (36.9%) on par with Wellington, New Zealand (38.8%), China (38.6%), and Korea (33.0%) and somewhat higher than the overall figure in BOLD and those previously reported in the USA (24.9%) and the UK (29.5%) [5]. While this could be a real variation due to differences in exposures or population susceptibility to environmental factors which predispose to COPD, some of these differences could be methodological. As an example, in the latter two studies spirometry was conducted without the use of bronchodilator, whereas the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines espouse post-bronchodilator spirometry in the diagnosis of COPD.

Risk Factors

The prevalence data from these epidemiological studies clearly show that a substantial fraction of COPD cannot be attributed to cigarette smoking, and therefore both genetic and other environmental exposures (including other lifestyle factors such as diet) need to be considered as potential contributors (Table 14.1). In terms of inhaled hazards, tobacco smoking is only one of the many carriers for noxious particles and gases to be inhaled, but even within a single category of inhaled hazard risks may vary. For instance, there is evidence suggesting cigar smokers are at a lower risk of developing COPD (relative risk [RR] 1.45%; 95% CI 1.10, 1.91%, compared to non-smokers) than those who smoke cigarettes (typical RR 9–25) [6]. Occupational and environmental exposures are important sources of inhalational exposures and are now known to be significant contributors to the development of COPD. On the other hand, COPD is not entirely an acquired disease. Hereditary α_1-antitrypsin deficiency

Table 14.1 Risk factors associated with COPD in non-smokers

Occupational exposure
Dust exposure from industrial processes (e.g., mining, tunneling, cement manufacturing) and crop and animal farming activities (e.g., grain dust)
Chemical exposure (e.g., sulfur dioxide)
Indoor air pollution
Biomass smoke exposure from biomass fuel (e.g., wood, charcoal, crop residues, dung) and coal combustion
Environmental tobacco smoke exposure
Outdoor air pollution
Traffic sources (notably particulate matter)
Industrial and agricultural sources (e.g., sulfur dioxide, hydrogen sulfide, ammonia)
Genetic factors
Alpha-1 anti-trypsin deficiency
Multiple genes relating to poor lung development
Chronic asthma
History of respiratory infection in childhood
History of pulmonary tuberculosis
Poor nutrition
Poor socioeconomic status
Aging

is a well-established example of the genetic risk factor for COPD. The risk factors for COPD are briefly outlined here, but a more in-depth description can be found in the recent ATS statement [2].

Occupational Exposure

A number of occupations have been identified as contributors to the development of COPD. The exposures involve inhalation of inorganic or organic dusts, fumes, or chemical agents and are mostly to be found in agricultural, mining, and manufacturing industries. While contemporary clinical guidelines include inhalation of "noxious (particles or) gases" as a cause of COPD [1], there is still a remarkable lack of awareness of the importance of occupational factors in COPD, being masked by the predominant shadow of cigarette smoking. There is evidence from animal studies that coal, silica, cadmium, and endotoxin can cause emphysema, while vanadium, mineral dusts, sulfur dioxide, and endotoxin can induce pathologically defined chronic bronchitis [7]. Exposure to certain hard crystalline metal compounds (such as tungsten carbide and cobalt) is known to cause the uncommon hard metal lung disease, which is characterized by chronic inflammation in the centrilobular area of the acinus. See also Chap. 11 for further detail on hard metal disease and Chap. 9 for pneumoconiosis.

Epidemiological studies conducted in specific occupational groups have demonstrated an association between workplace exposure and excess decline in pulmonary function, with an effect at least comparable if not greater than smoking alone [8].

This has become clear in the case of coal miners. Evidence accumulated over 30 years from observational studies in coal miners and experimental studies in animals has consistently shown that coal mine dust is associated with inflammation in the lung (both in the interstitium and the airways), loss of pulmonary function, and the presence of emphysema [9]. This finally led to the establishment of a causal relationship between coal dust and the development of COPD and the consequent decision by British and German governments to classify COPD as a compensatable disease for coal miners [9].

There is substantial evidence from a number of studies that farmers and farm workers have increased risk of reporting respiratory symptoms and reduced pulmonary function. Organic dust, ammonia (from livestock), and endotoxins are likely to be the agents responsible for the association.

Population-based studies from a number of countries also confirmed increased risks for chronic airflow limitation and/or respiratory symptoms consistent with COPD among those who are exposed in the workplace. An earlier ATS statement in 2003 summarized studies until 2000 and estimated the population attributable fraction for occupational exposures to be 15–20% [8]. A subsequent review in 2007 identified papers published after the previous review and concluded the median estimate to be 15% [7].

Biomass Smoke Exposure

Around half the world's population, the majority living in rural areas in developing countries, use solid fuels for cooking and heating. A number of different fuels are used, depending largely on local availability and therefore cost. These include coal and biomass fuels such as wood, animal dung, and crop residues although in many cases a mix of fuels is used. Very often, biomass fuels are burnt in stoves that are inefficient and in a poorly ventilated enclosed environment, generating very high levels of coarse and fine particulate matter (PM), reaching levels indoors during cooking of 15–20,000 $\mu g/m^3$, compared to the US Environmental Protection Agency's mean 24 h air quality standard for outdoor air of 35 $\mu g/m^3$. In addition, carcinogenic pollutants including polycyclic aromatic hydrocarbons (PAH), that are similar in chemistry to those present in tobacco smoke, are also present in significant amounts.

Most biomass users have been exposed to biomass smoke throughout the life course, from in utero through infancy to childhood and adulthood. However, women are often exposed at higher levels than men in the same households as they spend more of their time at home cooking for their families and often over long periods. Children, especially infants, are also exposed for similar periods of time. There is good evidence that this early exposure increases the incidence of and mortality from acute lower respiratory infections. In those children that survive this early exposure, pulmonary function is diminished by early adulthood, which may be the precursor for COPD in later life although as yet there are no longitudinal studies to confirm this. However, case–control studies have consistently reported associations between biomass use (cooking and/or heating) and respiratory symptoms and COPD (whether

diagnosed on the basis of symptoms or pulmonary function). Many of these studies have not, however, measured the degree of exposure and relied on self-reported frequency and/or duration of cooking, but as the exposures are unarguably very high and there is ample evidence demonstrating an exposure–response relationship, biomass smoke exposure can be regarded as a major global contributor to COPD. Pooled analysis of risk estimates from 15 studies shows that the overall odds ratio for COPD in those exposed to biomass smoke was 2.23 (95% CI 1.72, 2.90%) [2].

Environmental Tobacco Smoke Exposure

Environmental tobacco smoke (ETS) is a common indoor pollutant in both the developed and the developing world. An increasing number of countries have enacted smoking bans in enclosed public places, and studies of populations less exposed after these bans, notably occupational populations such as bar-workers, have shown significant improvements in health outcomes [2]. There has even been a consistent reduction in acute coronary syndrome in most countries studied post-ban, which suggests that ETS is perhaps more toxic than previously recognized. Indeed, there is evidence suggesting that exposure to ETS is four- to six-times more toxic, on a mass for mass basis, than mainstream smoke [10]. As the risk to health is, broadly speaking, the product of the intrinsic toxicity of the inhaled particles or gases and duration of exposure, crude assessment of the level or duration of exposure can help determine just how toxic ETS may be when considering it as a risk factor for COPD. ETS exposure remains widespread in households worldwide although the proportion of those exposed is lower now than in previous decades. For instance, in the elderly population alive today, exposure to ETS in childhood was almost uniform in most Western countries although less so in those countries which today we regard as the developing world as tobacco advertising took longer to infiltrate those countries. Therefore, it is surprising that while the association between parental smoking and both the incidence of childhood asthma and prevalence of respiratory symptoms in children is clear, the evidence for the development of COPD as a result of chronic ETS exposures alone had been inconclusive until recently. However, population-based studies have now shown an increased risk of spirometrically defined or self-reported physician-diagnosed COPD related to either cumulative lifetime or adulthood (home and/or workplace) exposure to ETS [3]. A meta-analysis of 12 studies suggested around a 50% increased risk (summary odds ratio of 1.56, 95% CI 1.40, 1.74%) [2].

Outdoor Air Pollution

In contrast to indoor air pollution due to solid fuel burning or ETS, outdoor air pollution, particularly in the urban environment, originates from vehicle exhaust and industry. Levels of particles (as $PM_{2.5}$) in urban air are usually measured in terms of

tens up to hundreds of μg/m^3 (at the roadside in the most polluted cities), but levels vary both in space and time largely driven by changes in meteorology rather than marked changes in local sources. There is evidence that long-term exposure to urban air pollution can affect both pulmonary function and chronic respiratory disease in those so exposed. The Harvard Six Cities Study first showed that life expectancy was worse in the most polluted cities and that this was mediated through both lung and cardiac health [11]. See also Chap. 7 for a more detailed discussion on air pollution and lung diseases.

Cohort studies in children and adolescents have demonstrated that traffic-related pollution impairs lung growth and pulmonary function, although these changes seem to be reversible during childhood when children move to areas of lower air pollution. There is also evidence for an exposure–response relationship when exposure is taken either as the distance between residence and highways or the concentration of nitrogen dioxide (NO_2), a marker of traffic, in relation to the increases in lung growth among those who moved to cleaner places.

However, when it comes to the causal relationship between outdoor air pollution and COPD risk in adults, the evidence is limited, owing to the lack of longitudinal data with spirometrically defined COPD as the outcome. In one study in women, the German Study on the Influence of Air Pollution on Lung Function, Inflammation, and Aging (SALIA), higher levels of PM_{10} were found to be negatively associated with FEV_1, FVC, and FEV_1:FVC ratio and also positively associated with increased risk of COPD [12]. In the Study on Air Pollution and Lung Diseases in Adults (SAPALDIA) in Switzerland, reductions in levels of particulate pollution were associated with a slower rate of pulmonary function decline [13]. Overall, there is evidence to suggest outdoor air pollution is causally related to poorer lung growth and accelerated pulmonary function decline, but there is insufficient evidence to conclude with confidence that it is causally related to COPD development.

Genetic Factors and Early Life Lung Development

Accumulating evidence has suggested the influence of genetic and early life components on subsequent susceptibility and severity of COPD. The best known example of a genetic risk factor for COPD is $\alpha(\text{alpha})_1$-antitrypsin deficiency, a rare hereditary condition affecting mostly individuals of Northern European origin. The deficiency of this anti-protease, which protects the lungs against neutrophil elastase, leads to the development of pan-lobular emphysema and decline in pulmonary function, affecting both smokers and non-smokers, although the former are at considerably higher risk [1]. Apart from $\alpha(\text{alpha})_1$-antitrypsin deficiency, there is some evidence to suggest a significant familial aggregation of both FEV_1 and FVC [2], although only very few of these familial aggregation studies have investigated non-smokers specifically, and the results from twin studies have so far been inconclusive [2].

A number of genomic regions and candidate genes related to COPD pathogenesis have been revealed through genetic linkage analysis and genetic association studies [1].

Some of these candidates are member components of pathways that are instrumental in airway and lung development. Findings from epidemiological studies also echo the link between perturbed lung development and subsequent higher risk for COPD. However, pulmonary function in early adulthood is often used as a surrogate for COPD, as reduced maximal attained pulmonary function may predict subsequent development of COPD, although this is arguably an optimistic assumption.

Cross-sectional and longitudinal studies, including birth cohorts, have identified low birth weight and low forced expiratory flow in infants as predictors of poor FEV_1 in adulthood. Recent data suggest that maternal smoking, parental and/or childhood asthma, and severe respiratory infection are likely to be causes of the perturbations in early life lung development, and the impact of these "childhood disadvantages" could be as large as that of heavy smoking [14]. There is some evidence from long-term longitudinal data from survivors of severe bronchopulmonary dysplasia (an acquired lung disease in premature birth) suggesting significantly reduced pulmonary function indices and emphysema being more common compared with those in normal individuals [15].

Chronic Asthma

Both asthma and COPD are characterized by airflow limitation, very often distinguished by the degree of reversibility of the obstruction among other differences. It has been shown that patients with longstanding asthma appear to have irreversible obstruction and emphysema, similar to that seen in COPD [2]. While this is worse in those who smoke cigarettes, it is clear that the chronic inflammatory process results in airway remodeling and consequent irreversible airway narrowing. Persistent wheezing and severe bronchial hyper-responsiveness in childhood are also associated with lower FEV_1 in adulthood [2].

Infections and Tuberculosis

There is strong suggestive evidence showing the association between a history of respiratory infection in early life and reduced pulmonary function in adulthood [1]. However, the evidence demonstrating the association between childhood or adulthood infection and subsequent accelerated decline in pulmonary function and the development of COPD is inconsistent. It is possible that early life infection, or the susceptibility to infection, may be associated with other underlying factors related to COPD.

It is known that survivors of pulmonary tuberculosis are left with permanent changes in lung anatomy and are at higher risk of airflow obstruction, as demonstrated by early and recent reports. Three population-based studies in countries with a high burden of tuberculosis (two in Latin America and one in China) have shown

prior tuberculosis (by self-report or by radiographic evidence) or previous treatment for tuberculosis was associated with a greater risk of spirometrically defined COPD and that the severity of airflow limitation was related to the radiographic severity of tuberculosis at the time of diagnosis. Even those individuals with minimal initial radiographic change have an increased risk of airflow limitation, probably reflecting the widespread inflammatory change seen in pulmonary tuberculosis. In the Chinese study, the adjusted odds ratio for COPD in never smokers was 1.30 (95% CI 1.02, 1.66%) [16].

Nutrition

As COPD is an inflammatory disease, diet that is rich in antioxidants may reduce oxidative stress, which in turn would be protective against COPD pathogenesis. Intake and serum levels of antioxidants such as carotenoids, vitamin C, and vitamin E have been found to be associated with better pulmonary function and attenuated decline in both cross-sectional and longitudinal studies [2]. On the other hand, intake of cured meat can increase oxidative stress through the generation of reactive species from the preservatives. Studies have shown an association between higher cured meat consumption and lower FEV_1 and increased risk of self-reported COPD [2]. Vitamin D, which has a potential effect on tissue remodeling, was found to be positively associated with mean FEV_1 and FVC [2]. While the results from these studies appear to be promising, none have exclusively investigated non-smokers. It is not impossible that diet, while being capable of modifying or counteracting (some of) the deleterious effects (particularly inflammation) due to smoking, is on its own unable to influence incident COPD.

Socioeconomic Status

Low social class (as measured by low income and educational attainment) has been implicated as a risk factor of COPD. However, it is entirely possible that low socioeconomic status is actually a reflection of other adverse exposures, such as those discussed previously.

Senescence

Consistent evidence has suggested that COPD is more prevalent in older individuals. While this could be partly explained by the spirometric definition (FEV_1:FVC ratio <0.7, which potentially over-diagnose the elderly) and the fact that older people are more likely to have a higher cumulative exposure to the risk factors discussed

above, it is possible that the senile lung could predispose COPD through structural and functional changes. Results from animal models seem to suggest accelerated aging as a contributory factor to increase susceptibility to COPD [17].

Pathology and Pathophysiology

Because COPD has almost always been attributed to cigarette smoking, a majority of the previous studies investigating the pathology and pathophysiology of COPD recruited only COPD patients who are either current or former smokers. Generally speaking, COPD in smokers involves chronic inflammation and structural changes in the proximal and peripheral airways, lung parenchyma, and pulmonary vasculature. Whether the same changes occur (or if indeed occurring, whether they are to the same extent) in COPD in non-smokers is less clear. In smoking COPD, there is a predominant involvement of neutrophils, macrophages, and $CD8^+$ T lymphocytes, while leukotriene B_4, interleukin-8, tumor necrosis factor-α(alpha), and transforming growth factor-β(beta) are the key mediators of inflammation.

In one of the very few studies studying non-smoking COPD, clinical, radiographic, and inflammatory profiles of 25 patients were compared [18]. The radiographic findings (chest radiograph and high-resolution computed tomographic scanning) and spirometry in these non-smoking patients did not suggest any material difference from the smokers. On the other hand, there were two distinctive inflammatory profiles based on sputum cell count, with nine patients having sputum eosinophilia and ten having sputum neutrophil counts at or above the upper limit of normal.

Based on the very limited evidence, there are no differences in the histopathology of COPD in non-smokers compared to smoking related COPD and no differences in the distribution of other measures of lung function other than spirometry such as gas transfer or static lung volumes.

Prognosis

Determinants of prognosis of COPD include age, gender, smoking history, co-morbidity (particularly cardiovascular conditions), baseline severity, exposure to respiratory infections, and therapeutic interventions including inhaled corticosteroids, long acting β(beta)-agonists, and anticholinergics. With the exception of a few population based studies (and thus included participants with a range of disease severities), most data on prognostic determinants to date pertain predominantly to patients with advanced COPD, and particularly those who had ever smoked. For example, Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE), a recent large-scale study aiming to delineate prognostic factors, included only smoke exposed individuals in the Western world.

Existing knowledge on the prognosis of COPD in non-smokers is limited. In a relatively young population with COPD, the European Community Respiratory

Health Survey (ECRHS) found that FEV_1 decline is greater in smokers and ex-smokers than among never smokers [19]. However, the rate of decline was not different between never smokers with COPD and healthy individuals. This latter finding is of particular interest as it implies that COPD among never smokers may not progress as much as that among smokers, indeed perhaps no more than in healthy aging. A trial in China showed that combined inhaled corticosteroids and long acting β(beta)-agonists reduced FEV_1 decline only in patients who smoked but not in never smokers [20], suggesting potentially different pathologies involved.

However, there are no studies which compare the outcome of non-smoking COPD to that seen in smokers although anecdotally such individuals are less likely to show accelerated decline in lung function and, where airflow obstruction is in the mild to moderate range, less susceptible to exacerbations.

Management

Management should be just as for smoking related COPD although individuals who have absent inflammatory markers (exhaled nitric oxide, serum c-reactive protein) are unlikely to respond to inhaled corticosteroids. Exacerbations should be managed with antibiotics and oral corticosteroids based on clinical severity.

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Chapter 15
Emerging Issues in Environmental and Occupational Lung Diseases

Yuh-Chin T. Huang

Abstract Humans continue to introduce new or greatly modified agents and techniques into the workplace and environment. These new agents and altered practices lead to evolving patterns of established diseases as well as entirely novel conditions never experienced before in medical history. Although many of these emerging conditions appear in the literature as case reports or case series, these sentinel cases frequently raise the public awareness that drives social movements or, in some situations, represent a warning sign for subsequent outbreaks. The emerging environmental and occupational lung diseases (EOLD) may be grouped arbitrarily into two categories: (1) conditions caused by novel utilization or routes of exposure to agents known to cause EOLD and (2) conditions caused by novel agents not known to cause specific EOLD in the past. Conditions in the first category may include those caused by new exposure scenarios in nonindustrial settings and thus a large population may be at risk. The second category includes new risk factor(s) that were not known to be associated with a specific EOLD, and thus the association between the agent and the new condition could be easily missed. Clinicians should remain astute and vigilant when evaluating the potential role of environmental risk factors in any lung diseases and especially pay attention to the identification of clusters of cases of disease of unknown etiology.

Keywords Environmental • Occupational • Work-related • Residential • Public

As discussed in Chap. 1, the historical pageant of environmental and occupational lung disease (EOLD) has been driven by many key forces, ranging from astute recognition and characterization by clinicians and researchers interested in these

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conditions, social movements that help shape the practice of occupational and environmental health, and advances in technology that continually introduce new or greatly modified occupational and environmental hazards. The latter is especially important as it leads to evolving patterns of established diseases as well as entirely new and novel conditions never experienced before. Although many of these emerging conditions initially appear in the literature as case reports or case series, these sentinel cases frequently raise the public awareness that drives social movements or, in some situations, represent a warning sign for subsequent outbreaks.

The emerging EOLDs may be grouped arbitrarily into two main categories: (1) conditions caused by novel routes of exposure or utilization of agents known to cause EOLDs and (2) conditions caused by novel agents not known to cause specific EOLDs in the past (Table 15.1). This paradigm will shape the presentation of information in this chapter.

Conditions Caused by Novel Routes of Exposure to Agents Known to Cause Environmental and Occupational Lung Diseases

Conditions in this category include lung disorders caused by novel exposure scenarios or different patterns of utilization of an agent already known to cause EOLDs. These new exposure scenarios may occur in nonindustrial or environmental settings that potentially put a large population at risk. As such, the relationship between exposure and the lung conditions would not be easily identifiable unless the individual is aware of their exposure, which is often not the case, and a detailed history regarding the potential for other exposures in the workplace, environment, or home is obtained. The conditions that are in this category include asthma induced by isocyanates in health care technicians working on casting material [1], roof bolters involved in mining and tunneling [2], in home occupants exposed to spray polyurethane foam (SPF) used as the "environmental-friendly" or "green" insulation materials [3], by methacrylate in nail salon technicians [4], and by cyanoacrylate in recreational glue users [5]. In the case of SPF, the inciting agents may also include amines, metal catalysts, and flame retardants in addition to isocyanates. Asthma has also been reported to be induced by linseed oil that is increasingly used as an environmentally friendly alternative to petroleum-derived materials [6]. Recent reports of silicosis occurring in denim sandblasting workers in Turkey have also been noted [7–10]. Jeans that are blasted with sand have a "distressed," already worn look that has been quite popular since the 1990s. The silicosis noted in these workers showed a high incidence of progressive massive fibrosis and a high mortality with a 5-year survival rate of 69%, indicating high levels of exposure [10]. The Turkish government has since banned sandblasting, but it is likely that this practice and industry has moved to other countries—including Bangladesh, Pakistan, China, and Egypt, where the issue has received little attention. Similar to this altered work practice, accelerated cases of coal worker pneumoconiosis (CWP) have been noted in younger

Table 15.1 Emerging environmental and occupational lung diseases

Disease	Exposure setting	Responsible agents
Conditions caused by novel routes of exposure to agents known to cause lung diseases		
Asthma	health care technicians working on casting material	Isocyanates
	Roof bolters in mining and tunneling	Isocyanates
	Home occupants exposed to spray polyurethane foam	Isocyanates and "off-gassing" chemicals
	Nail salon technicians	Methacrylate
	Recreational glue users	Cyanoacrylate
	Research chemists	Linseed oil
Silicosis	Denim sandblasting workers	Silica
Accelerated coal workers pneumoconiosis	Coal workers	Coal dusts
Acute lung injury	Leather protectant users, floor sealant users	Fluoropolymers
Conditions caused by novel agents not known to cause specific lung diseases in the past		
Asthma	Metal cutting operators	Synthetic machine cooling fluids
	Point-of-sale terminal users	*N*-propyl-acrylamide and acrylate tints
	Research chemists, laboratory technicians	Chamomile flower
	Research chemists, laboratory technicians	Peptide coupling reagents
Hypersensitivity pneumonitis	Animal feed industry	Phytase enzymes
lymphocytic bronchiolitis (flock-worker's lung)	Nylon workers	Short-length synthetic fibers
Bronchiolitis obliterans	Flavoring industry workers, consumers exposed to butter-flavored microwave popcorn	Diacetyl
Constrictive bronchiolitis	Deployed soldiers returning from Iraq and Afghanistan	Smoke from sulfur fire and burn pits (?)
Acute eosinophilic pneumonia	US Military personnel deployed in or near Iraq	New onset cigarette smoke (?)
Pulmonary alveolar proteinosis	Indium processing workers	Indium-tin oxide
Interstitial lung disease	Workers making liquid-crystal panels	Indium-tin oxide
	Tinners	Tin
	Workers in print plant	Aerosolized polyacrylate nanoparticles
Dendriform pulmonary ossification	Polisher at a crystal factory	Cerium

(continued)

Table 15.1 (continued)

Disease	Exposure setting	Responsible agents
Idiopathic pulmonary fibrosis	Metal and wood workers	Metal and wood dusts
Sarcoidosis	WTC responders	WTC dust
Respiratory infections	Hospital and animal laboratory workers	New strains of influenza viruses, zoonotic microorganisms
COPD	Users of biomass burning	Particulate matter

coal miners working in smaller mines in eastern Kentucky and western Virginia and may be related to increasing production and longer work hours [11]. Several outbreaks of acute lung injury/pneumonitis related to water-repellant sprays have also been reported [12, 13]. This condition was associated with fluoropolymers that are the key waterproofing ingredient in leather protectants, such as boot sprays, or grout and floor sealants.

Conditions Caused by Novel Agents Not Known to Cause Specific Lung Disease in the Past

As new agents are constantly being introduced into the workplace and other environments, more EOLDs are to be expected (Table 15.1). Compared to those in the first category, there are many more emerging lung conditions that belong to this category. With the continued advance in technology, more risk factors for EOLD will likely be identified in the future. Some examples of agents that cause occupational asthma include synthetic machine cooling fluids [14, 15], *N*-propyl-acrylamide and acrylate tints on thermal paper printed from point-of-sale terminals, chamomile flower, a medicinal agent with sedative and anti-inflammatory properties [16], and a peptide coupling reagent [17]; occupational hypersensitivity pneumonitis induced by phytase enzymes in animal feed industry [18]; lymphocytic bronchiolitis in nylon workers (flock-worker's lung); and bronchiolitis obliterans caused by diacetyl in flavoring industry workers and in consumers exposed to butter-flavored microwave popcorn [19–21]. More recently, several studies have reported constrictive bronchiolitis in deployed soldiers returning from Iraq and Afghanistan [22] and acute eosinophilic pneumonia among US military personnel deployed in or near Iraq [23]. Many soldiers who developed constrictive bronchiolitis had exposure to smoke from a sulfur mine fire and burn pits, although a firm causal relationship has not yet been established. The etiology of acute eosinophilic pneumonia remains unclear, but there was an association with new-onset smoking in these military personnel.

In addition to new agents causing EOLD, novel occupational and environmental exposure scenarios have also been implicated in the development of lung diseases.

For example, significant interstitial changes were found on high-resolution computed tomography (HRCT) in about 20% of Japanese workers exposed to indium-tin oxide in the manufacture of liquid crystal panels used in large screen TVs [24]. In the USA, workers in this industry were noted to have pulmonary alveolar proteinosis [25]. Various interstitial lung diseases (respiratory bronchiolitis-associated interstitial lung disease (RBILD), usual interstitial pneumonitis (UIP), and nonspecific interstitial pneumonitis (NSIP)) were described in approximately 50% of Turkish tinners [26]. Dendriform pulmonary ossification as a new form of "rare earth (cerium) pneumoconiosis" was reported in a crystal factory polisher whose workplace was heavily contaminated with greenish polishing powder [27]. There is concern that recent introduction of a nanoparticulate cerium oxide-based additive to diesel fuel in United Kingdom may carry a larger environmental risk to general public [28, 29], although no human cases of interstitial lung disease have been reported to date. Pulmonary fibrosis and pleural granuloma were found in Chinese factory workers exposed to polyacrylate nanoparticles [30]. Carbon nanotubes were found in the lung of seven World Trade Center (WTC) responders who developed severe respiratory impairment or interstitial lung disease [31]. These man-made nanoparticles and nanotubes could represent a new threat to respiratory health since nanotechnology is being applied increasingly to the manufacture of many industrial products.

Also included in this category are idiopathic lung diseases with newly identified causes. A cluster of 28 sarcoidosis cases was reported in responders of the WTC attack, further underscoring sarcoidosis as a potential environmental lung disease [32]. Exposure to metal and wood dusts has been linked to idiopathic pulmonary fibrosis (for more detail, please refer to Chap. 9) [33, 34]. Biomass exposure is considered the most important environmental cause for COPD in nonsmokers globally (for more detail, please refer to Chap. 14) [35]. Occupational respiratory infections may also be caused by novel agents, such as severe acute respiratory syndrome (SARS) virus, new strains of influenza virus (avian, H1N1) and zoonotic microorganisms, and the risks are especially high for hospital and animal laboratory workers [36].

In summary, with new agents and exposure scenarios continually being introduced into the environment and workplace, novel lung diseases are likely to emerge. Clinicians should always obtain a detailed environmental and occupational history even when evaluating common lung disease and consider a shared etiology in clusters of disease with a shared environment, so that potential environmental risk factors may be identified and preventive measures can be implemented in time.

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Chapter 16
Disability Assessment in Occupational and Environmental Lung Diseases

Clayton T. Cowl

Abstract Assessment and management of administrative issues surrounding occupational and environmental lung disease are often one of the more challenging aspects of caring for individuals encountering illnesses or injuries associated with workplace exposures. Lack of formalized training in providing the forensic aspects of diagnosing and treating these types of conditions is often the reason why many health care providers experience significant frustration in prosecuting this type of work. This includes being able to define and understand the essential concepts of impairment and disability, recognizing the need for work restrictions and how to compose useful recommendations to the employer in order to avoid unnecessary time away from work when the individual patient could be accommodated in alternative work environments, and understanding the variety of programs available to compensate individuals affected by work-related exposures or injuries. The ability to perform these administrative tasks is vital to adequately serve the patient with these conditions.

Keywords Work restrictions • Disability • Workers' compensation • Impairment ratings

Introduction

Perhaps one of the more challenging aspects of assessing the patient with occupational or environmental lung disease is addressing administrative issues that inevitably arise when one hypothesizes or draws a causal relationship between an

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environmental or occupational exposure and a physical impairment. This occurs not only due to lack of familiarity with the nuances involved with restricting an individual from continued environmental exposure but also due to the complexity and variety of compensation systems that exist for the purpose of reimbursement of medical expenses, income, and retraining issues should that individual be unable to perform their regular work duties due to an illness or injury encountered at work, or an impairment that precludes them from continuing their prior job duties. The ability to separate the clinical from the forensic aspects of evaluating and managing conditions caused or exacerbated by workplace exposures is vital to the success of treatment.

Defining Impairment and Disability

Impairment has been defined by the World Health Organization as "any loss or abnormality of psychological, physiological or anatomic structure or function" [1]. Therefore, an abnormality in expiratory airflow measured upon spirometric testing would be considered an impairment, as would the presence of emphysema on a chest radiograph, or thoracic splinting due to pleuritic chest pain. *Disability*, meanwhile, refers to "an alteration of an individual's capacity to meet personal, social, or occupational demands because of an impairment" [2]. It is important to identify specific impairments while performing a diagnostic assessment of an individual with respiratory disease. However, not all impairments result in a disability. For example, if a welder who is a current smoker experiences an upper respiratory infection and complains of cough symptoms, spirometry may be performed as part of a diagnostic evaluation, which might reveal air flow limitation (that likely resulted from tobacco abuse). Mild airflow obstruction does represent impairment; however, if the individual is experiencing no functional limitation and is able to perform their usual job duties, no disability is present. Conversely, in an individual who has become sensitized to isocyanate-related compounds (resulting in dramatic bronchospasm with exposure to just minute amounts of the offending agent), that individual may have relatively minor impairment in terms of specific respiratory symptoms or even normal baseline spirometry but would be considered to have disability if the essential functions of their normal occupation involves frequent or predictable exposure to isocyanates.

Managing Work Restrictions

The ability to manage workplace restrictions is particularly challenging for patients who are experiencing impairment regarding the respiratory system. This is due to a variety of factors, including the frequent presence of multifactorial etiologies for the symptoms, confounding factors such as active tobacco abuse, frequent inability to identify a specific inciting factor that is causing the respiratory symptoms, inexperience

of the health care provider in writing workplace restrictions, and significant time commitment to modify work restrictions as the course of the respiratory condition changes. It is important for the medical provider to have as detailed an understanding of the patient's work environment as possible in order to provide precise and reasonable workplace restrictions.

Taking a detailed occupational and environmental history is the first step in obtaining these data. Information should be obtained regarding prior and current occupations, job duties involved in each position, prior and current workplace exposures, and required physical maneuvers for the specific job performed. In addition, the history should include whether or not the patient participated in prior military service or is/was involved in any secondary jobs or hobbies that involve(d) significant environmental exposure. Identifying if the individual is self-employed or whether they work for a smaller or larger business is also frequently helpful in determining how to best structure work restrictions. Not only should information be garnered from the patient, but with the patient's permission, data regarding the nature of the specific exposures involved for the occupation in question should also be obtained from a representative of the employer in order to more thoroughly ascertain all of the variables involved in the care of the individual. A patient's refusal to allow dialogue with the employer may introduce consideration of suspicion as to the possible underlying agenda of the patient, such as secondary gain. Other reasons for the reluctance of disclosure may also include a concern over job loss, the legal status of the employment, or a preexisting problematic relationship between the worker and the employer. The medical provider should always attempt to obtain as much information as possible in order to make a more precise and accurate determination as to the need for workplace restrictions and how best to safely return an individual to work.

Obtaining Material Safety Data Sheets (MSDS) for any potential substance encountered in the workplace is a key piece of information required for better understanding of the nature of products to which the patient has or will become exposed to in the future. An MSDS is a document that contains information on the potential health effects of exposure to chemicals or other potentially dangerous substances (see Table 16.1). It also provides recommendations for ensuring safe handling of hazardous chemical products and contains hazard evaluations on the use, storage, and emergency procedures related to that material. The MSDS contains much more information about the specific product in question than what is listed on the label, and it is intended to outline specific product hazards, how to use the product safely, what to expect if the recommendations are not followed, what to do if accidents occur, how to recognize symptoms of overexposure, and what to do if such incidents occur. Employers must make sure that all controlled products have an up-to-date (less than 3 years old) MSDS when they enter the workplace. Since the MSDS must be readily available to workers who are exposed to the controlled product, any treating medical provider or the patient should be able to obtain this information from the employer. While examining the MSDS is a good first step, one should realize that MSDS may not list the proprietary information or products with concentrations <2%. The health effects listed also may not be comprehensive.

Table 16.1 Information required on Material Safety Data Sheets (MSDS)

Product information
Specific compounds or ingredients used in product
Hazard identification
First aid measures
Firefighting strategies
Accidental release recommendations
Recommended storage and handling parameters
Exposure controls and suggestions for personal protective equipment
Physical and chemical properties of the substances included in the product
Stability and reactivity data
Toxicology data
Ecology information
Disposal considerations
Transportation information
Regulatory data

Based on data from ANSI Z400.1-1998 ("Standard for Hazardous Industrial Chemicals—Material Safety Data Sheets—Preparation"), European Directive 91/155/EEC, and International Standard ISO 11014–1

Once all available data regarding the patient's exposures and specific workplace requirements have been obtained and reviewed and the diagnostic assessment has been completed, the treating provider may then decide to restrict the individual from certain physical maneuvers or from certain types of exposures. It is important to recognize that simply taking the individual out of work altogether is often not necessary. In many cases, the employer is willing and able to accommodate workplace restrictions by modifying the specific requirements of the position, changing the location of where the individual performs their work duties, or allowing adjustment of productivity measures in order to keep the patient active in the workplace. Taking time to speak to a representative of the employer may often identify return-to-work options available that are not otherwise intuitively obvious. If the employer is able to keep the patient active in gainful employment during their recovery and treatment period, the individual will continue to receive full income and continued fringe benefits. While employers may ultimately not be able to accommodate some respiratory-related work restrictions, the health care provider should at least offer the option for the employer to make that determination prior to completely restricting the individual from working in any capacity. "Administrative restrictions" should be avoided. These include work restrictions that specifically preclude an individual from working in a specific building, with a certain person, or during a certain time frame. Work restrictions should center on limiting specific physical exertions, or in conjunction with specific dialogue with the employer, certain environments or exposures (e.g., excessive smoke, dust, or chemical fumes). However, if the respiratory condition in question involves severe impairment, or a situation in which exposure to specific inciting compounds is required as an essential function of the job, then the individual should be completely restricted from their prior work environment.

This should also be accompanied by discussion with the employer as to the general nature of the condition (details of which need to be handled with care due to privacy concerns) and input regarding prognosis and long-range planning of returning the patient to work if that appears to be feasible at some point in the future. Ultimately, if the patient is unable to have their work restrictions accommodated, or the condition involves severe impairment resulting in total disability, the patient may ultimately require retraining in a different occupation or require plans for long-term care if the individual is unable to serve in any form of gainful employment because of their underlying illness.

Types of Compensation Available to Injured or Ill Respiratory Patients

There are a number of different compensation systems available to workers who encounter impairment of the respiratory system. Compensation systems vary between states, between employers, and even among occupations within a specific business. There are a variety of jurisdictions for each type of compensation system, each with specific plan language and definitions. Although it is certainly not imperative that a treating provider possess expertise in navigating benefit options for their patients, it is important for the treating provider of individuals with respiratory impairment to have a general working knowledge of benefits available.

Workers' Compensation

Although the history of compensation for workers who became ill or injured from work dates back to antiquity [3], the development of English common law in the late Middle Ages and Renaissance provided the legal framework that generally governed what injuries were ultimately compensable through the time frame spanning the early Industrial Revolution across Europe and the Unites States. Several legal defenses were utilized frequently by defendants but were recognized as being very restrictive and favorable to the employer. These defenses included "contributory negligence," in which if the worker was in any way responsible for the illness or injury suffered then the employer was not to be considered culpable and should not have to pay benefits. For example, despite the hazardous nature of many forms of machinery or equipment utilized in that era, if the job description held that the employee was to inspect or maintain the equipment, and was later injured as a result of equipment failure, then the employee did not receive compensation because inspecting the equipment was considered an essential function of the job. Another defense was the "fellow servant" rule that dictated that employers were not held liable if a worker's injuries resulted in any part from the action or negligence of a

fellow employee. One of the most far-reaching and generalized forms of defense was that of "assumption of risk," which inferred that when an employee took on a new job they became aware of the hazards of that job at the time a contract to work was agreed upon. Consequently, by agreeing to serve in that workplace environment, the individual would assume all inherent risks involved in that occupation. Many employers at that time required potential employees to sign a contract with language holding the employer free of liability. Not only were legal defenses stacked in favor of the employer, plaintiff employees were also required to utilize the tort law process to advance claims for injury or illness. Eventually, early forms of disability insurance were offered to workers who were more affluent. Some of these claims were awarded in prolonged court battles despite the odds against them. Gradually, legislative changes were approved that changed the landscape of workers' compensation. Pursuit of claims for serious injury or death proved to be extremely time-consuming, expensive, and brought unwanted publicity to many employers who were subjected to public display of employees with severe injuries for which the company argued against protecting or providing compensation.

Following efforts to reform compensation for injured or ill workers in Europe and Asia in the late 1800s, the United States Congress passed the Employers' Liability Acts of 1906 and 1908, which effectively lightened the common-law doctrine of contributory negligence. In addition, failed or limited efforts to pass comprehensive workers' compensation acts were attempted in several states, including New York (1898), Maryland (1902), Massachusetts (1908), and Montana (1909). At the federal level, efforts at reforming workers' compensation were generally tempered with the notion that specific compensation programs should be left for individual state legislatures to decide. However, the federal government did regulate interstate commerce, resulting in what may be considered the first workers' compensation system in the nation eventually put into law in 1908 to cover those workers involved in interstate trade [4]. The first comprehensive workers' compensation law was eventually passed in Wisconsin in 1911. Nine other states passed regulations that year, followed by 36 others before the decade was finished. Currently, there are workers' compensation programs in all 50 states in the US as well as three different federal jurisdictions [5].

The central theme of most workers' compensation statutes in the United States involves a form of "no-fault" insurance in which work-related illnesses and injuries are accepted as inevitable, and the system exists to provide equitable compensation in an expeditious fashion. Employers, who are mandated to participate in state-regulated programs if the size of the business is large enough to meet specific criteria, are afforded the ability to avoid civil lawsuits for injuries or illnesses covered under workers' compensation. Employees are provided the right to sue third parties who may be responsible for their on-the-job injuries, but any proceeds from such lawsuits must first go toward the reimbursement of their employer's compensation self-funded program or to the insurance carrier. All workers' compensation programs available in the United States are fully employer-funded, either by the purchase of commercial insurance or by setting up a self-insurance account. Most states have exclusion criteria for small firms and for agricultural workers [6].

Specific details regarding how claims are administered vary between states and jurisdictions. Many used the American Medical Association guides to set up the compensation systems [2]. Some states have legislated "schedules" that outline a specific impairment and define a proportion of disability involving the whole person. Most schedules involve measurement of spirometry, interpretation of radiographic data, or physiologic exercise information in order to establish the degree of disability for individuals with respiratory impairments. Other states have complex systems involving compensation boards or appointed committees that assist in expediting and adjudicating claims. In general, compensation is paid both in the form of wage replacement (usually at about two-thirds salary) for the period of total disability and in the form of lump sum payments for any residual permanent partial disability. Employers also must pay for the workers' medical and rehabilitation costs. Many employers quite aggressively pursue rehabilitation and pay for services such as work-hardening programs or educational programs for re-training that are not required under statute. They have found these to be highly cost-effective, given that if the outcome fails to return the employee to work in any capacity then permanent total disability involving payments for life in certain jurisdictions could result. Of note, federal employees are not covered by state programs. They are covered by the Federal Employees' Compensation Act. There are also specific federal programs for specific pulmonary diseases, such as Black Lung Benefits Act, Uranium Miners Compensation, and the Energy Employees Occupational Illness Compensation Program Act (EEOICPA) for Division of Energy employees. Readers are referred to Chaps. 9 and 12 for the discussion of some of these programs.

Short-Term Disability

Short-term disability involves a type of insurance that compensates a percentage of an employee's income for a specified amount of time, should they become ill or injured and cannot perform the duties required in their job should those specific impairments not be found to be caused or exacerbated by a workplace injury or exposure (workplace illnesses and injuries are covered under workers' compensation). Coverage usually begins from 1 to 14 days after the employee suffers a valid impairment that results in the inability to work. Often employees are required to utilize "sick days" or paid time off (PTO) before short-term disability insurance can be collected. The cost of a short-term disability policy is often covered by the employer as a paid benefit, or purchased by an employee, resulting in certain implications regarding income tax reporting and deductibility. Most of the short-term disability plans available are included as a paid benefit. Although most short-term disability insurance is provided through contract agreements in which a third-party insurance company charges premiums to an organization and then administers the program, other businesses elect to establish a self-funded plan using a specified set aside account to pay claims. Most short-term disability policies require some form of documentation from the treating provider to validate the presence of a

medical impairment. In most instances, employees are required to work for an employer for a certain length of time before becoming eligible for short-term disability insurance benefits, and employees typically must work full-time (defined in many policies as more than 30 h per week). Depending on the specific policy, benefits may include a proportion of an average weekly salary, a maximum duration of disability benefits numbering anywhere from 10 to 26 weeks, and either a total maximum time benefit or monetary benefit paid out over time. Short-term disability benefits are not required, but in certain states short-term disability benefits are mandated to be provided for varying lengths of time depending upon the jurisdiction.

Long-Term Disability

If a worker has an illness or injury involving the respiratory system, many cases involve substantial time off work, especially during the diagnostic and early treatment phases of the evaluation. While some companies provide short-term disability programs, many more employers offer long-term disability compensation schemes to their employees funded through a third-party administrator such as a disability insurer should the impairments be found unrelated to a workplace exposure and deemed not to be specifically exacerbated while at work. The cost associated with funding long-term disability insurance previously was a burden accommodated by the employer. However, this has evolved into the employee sharing some if not all costs associated with this coverage. The specific details of long-term disability policies vary considerably and are determined primarily by the employer. Employers decide how much coverage to elect for their employees, and there are a variety of limitations to most policies offered. Common restrictions include that of covering a worker's usual occupation for a period of 12–36 months ("own occupation coverage"), followed by a change in disability definition after that time in which the worker must be unable to perform any form of gainful employment within certain parameters in order to continue to qualify for disability benefits ("any occupation"). Many policies require that individuals apply for Social Security Disability Insurance and mandate that any benefits awarded be used as an offset against prior and future funds awarded under the long-term disability plan. Most policies cover 50–70% of an individual's monthly income. Some plans have limitations on the length of time benefits that are paid out to claimants, while other plans provide benefits until age 65, based on a rate schedule.

Social Security Disability Insurance

In the United States, benefits to workers with respiratory conditions are available through the federal government. The Social Security Administration (SSA) administers two programs that provide benefits based upon determination of disability; namely, the Social Security disability insurance program (Title II of the Social Security Act)

and the supplemental security income (SSI) program (Title XVI). Title II provides for payment of disability benefits to individuals who are covered under the Act by virtue of their contributions to Social Security through the Social Security tax on their prior workplace earnings as well as to certain disabled dependents of insured individuals. Title XVI provides for payments to individuals (including children under age 18) who are disabled and have limited income and resources. These programs have specific definitions for disability, definitions that are not necessarily congruent with terms or definitions outlined in private insurance programs, or even other government compensation systems. Disability is defined as the inability to engage in any substantial gainful activity by reason of any medically determinable physical or mental impairment(s) that can be expected to result in death or that has lasted or can be expected to last for a continuous period of not less than 12 months. A "medically determinable physical or mental impairment" is defined as an impairment that results from anatomical, physiological, or psychological abnormalities that can be shown by medically acceptable clinical and laboratory diagnostic techniques. A physical or mental impairment must be established by medical evidence consisting of signs, symptoms, and laboratory findings above and beyond that identified subjectively by the individual's statement of symptoms. Most disability claims under Social Security Disability are initially processed through a network of local Social Security field offices and State agencies (usually called disability determination services). Subsequent appeals of unfavorable determinations may be decided by administrative law judges or other pointed agencies. Benefits are typically provided until age 65 or the age at which the individual would have normally retired under standard Social Security benefit availability [7].

In conclusion, in addition to diagnosis and treatment of a work-related disease, a medical provider also needs to understand the implications of workplace exposure and recognize the need for work restrictions so that useful recommendations to the employer can be composed in order to avoid unnecessary time away from work when the individual patient could be accommodated in alternative work environments. The ability to perform these administrative tasks is vital to adequately serve the patient with occupational and environmental lung diseases.

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Chapter 17
Global Impact of Occupational and Environmental Lung Diseases

Eric D. Amster and David C. Christiani

Abstract The burden of occupational and environmental lung disease varies widely throughout the world. Prevalence and incidence of disease, predominant exposures, clinical prognosis, and mortality rates vary widely. Global disparities are in part a result of disparate occupational health and safety norms; environmental standards and enforcement; and a severe lack of screening and access to care in much of the developing world. This chapter will review the differential prevalence of occupational and environmental lung disease worldwide and will explore some of the factors influencing variation in estimated rates. Common occupational and environmental diseases and their specific regional burdens will be reviewed. Global differences in occupational and environmental exposures will be explored. Finally we will discuss international interventions to mitigate the global burden of occupational and environmental lung disease.

Keywords Global health • Disease burden • DALYs • Morbidity

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Global Burden of Disease

Occupational and environmental lung disease is a global problem. While occupational and environmental exposures influence respiratory morbidity and mortality in every region of the world, the distribution of disease prevalence, and along with it the associated economic and social consequences, varies widely. Global disparities in disease prevalence are in part a result of disparate occupational health and safety norms; environmental standards and enforcement; and a severe lack of screening and access to care in much of the developing world. Most importantly, the prevalence of occupational and environmental lung disease is dependent on the extent workers and communities are exposed to the causal agents. The level at which communities are exposed to environmental pollution and workers are exposed to occupational hazards varies widely throughout the world. Certain causative agents, such as asbestos, are banned from use in some parts of the world. Consequently, the incidence, prevalence, and burden of malignant mesothelioma in those regions are low. This situation is in stark contrast to other regions of the world where the burden of disease has increased with the increased production and use of asbestos-containing products.

Estimating the global prevalence of occupational and environmental lung disease is technically challenging. Isolating occupation and the environment as the etiology of disease is an imperfect science. Certain lung diseases by definition are entirely attributable to occupational exposures. For example, 100% of the attributable fraction of the estimated 7,000 annual deaths globally due to asbestosis, 9,000 due to silicosis, and 14,000 due to coal workers pneumoconiosis (CWP) are work related [1] . Other diseases, such as COPD or asthma, are multifactorial, with estimates of the occupational or environmental attributable fraction varying widely. Estimates of disease burden, therefore, rely on accurate assessment of occupational and environmental exposures, knowledge of competing causes of disease such as tobacco use, and regular screening for disease in potentially exposed populations. The availability and accuracy of this information vary widely as many countries lack government ministries responsible for preventing and tracking occupationally and environmentally related diseases.

Occupational Lung Diseases

The World Health Organization's (WHO) Global Burden of Disease project provides the most comprehensive and consistent estimates of disease specific estimates of mortality and morbidity [2]. Occupational burdens of disease are calculated from national and regional data on the participation of the population in the workforce, work location, and typical trades. The WHO presents its data on burden of disease both in terms of total mortality and disability adjusted life years (DALYs) lost. DALYs are a measure of overall disease burden as expressed in the equivalent number of years of life lost due to disability, ill health, or premature death.

The WHO estimates that there are 850,000 deaths globally resulting from occupational exposures. Of these, COPD is the most common cause of occupational

Table 17.1 WHO estimates of global morbidity and mortality from selected occupational exposures in Year 2000

	Global deaths (×1,000)			Global DALYs (×1,000)		
Outcome	Males	Females	Total	Males	Females	Total
COPD	240	78	318	3020	713	3733
Lung and trachea cancer	88	14	102	1110	511	1621
Mesothelioma	28	15	43	825	144	969
Asthma	23	15	38	356	207	563
CWP	14	–	14	366	–	366
Silicosis	9	–	9	486	–	486
Asbestosis	7	–	7	376	–	376

Based on data from Nelson et al. [1]

death, accounting for 318,000 deaths annually from workplace exposures. Approximately 102,000 lung cancer deaths globally are attributed to occupational exposures to beryllium, cadmium, chromium, diesel exhaust, nickel, arsenic, asbestos, or silica. Currently, pneumoconiosis accounts for only 4% of all occupation related deaths, including 14,000 deaths annually from CWP, 9,000 from silicosis, and 7,000 from asbestosis (Table 17.1).

The number of DALYs attributed to occupational lung disease worldwide is relatively small when compared to other occupational causes of disease. Morbidity of COPD due to occupational exposures is estimated at 4,150,000 DALYs annually. This is roughly a third of the estimated morbidity attributable to occupational injuries that are more likely to cause significant and permanent disability at a younger age than occupational lung disease. Global annual DALYs from occupational asthma are estimated at 1,621,000, while global annual DALYs from pneumoconiosis are estimated at 1,228,000 (Table 17.1).

In general, the burden of lung disease due to occupational exposures is greater in developing countries, reflecting differences in types of occupation, exposures, availability of screening, and medical care. Despite this, one of the primary limitations of the WHO's estimates is that there is incomplete data for exposures and hazard-disease relationships in developing countries, resulting in an underestimation of reported morbidity and mortality. Consequently, some have suggested that the true global burden of occupational lung disease resulting from occupational risk factors is likely at least a factor of two greater than reported estimates [3].

Environmental Lung Disease

The global burden of environmental lung disease is primarily due to ambient urban air pollution and indoor combustion exposures from solid fuels and tobacco smoke. The WHO assess the global and regional burdens of environmental lung disease by using estimates of urban air pollution from 3,211 cities with populations over 100,000 [4]. Exposure to indoor pollution is assessed using national censuses and World Bank Living Standard Measurement surveys. Approximately 1.1 million

Table 17.2 Attributable deaths (×1,000) by risk factor in WHO regions, estimates for 2004

Exposure	World	Africa	America	Eastern Mediterranean	Europe	South-East Asia	West Pacific
Urban air pollution	1,152	61	143	95	225	207	421
Indoor air pollution	1,965	551	30	142	20	630	591
Occupational exposures	987	77	73	65	115	270	387

Based on data from World Health Organization [76]

deaths annually are attributed to global exposure to ambient urban air pollution (Table 17.2). This is roughly half the morbidity attributed to indoor smoke from solid fuels, which account for approximately 1,965,000 deaths annually. Indoor air pollution is responsible for an estimated 41 million DALYs, while urban air pollution is responsible for less than nine million DALYs.

Roughly half of the burden of disease attributed to indoor and ambient air pollution is due to elevated risk of ischemic heart disease and cerebrovascular disease rather than lung disease. Of the estimated 1.1 million deaths annually from ambient air pollution, approximately 120,000 of these deaths are due to lower and upper respiratory infections, 168,000 is due to COPD, 11,000 are asthma related deaths, and 108,000 are from lung cancers. Indoor combustion exposures are believed to cause one million deaths globally from COPD each year, 870,000 deaths from respiratory infections, and 36,000 from lung cancers [5].

Similar to occupational lung disease, the burden of environmental lung disease varies regionally with excess burden of disease in developing countries. The bulk of lung disease morbidity and mortality due to ambient air pollution is concentrated in the Western Pacific region, undoubtedly due to the contribution from China's large population and significant exposures. The 166,000 deaths from lung disease attributed to air pollution in the Western Pacific is equivalent to the cumulative burden from all other regions combined. The mortality associated with indoor pollution is more evenly distributed throughout the world since the use of biomass for fuel is a ubiquitous problem internationally. Approximately 600,000 die annually in Africa, South-East Asia, and the Western Pacific from indoor pollution exposure. When considering Africa has a population of 740 million people and the South-East Asian population is more than double, the proportion of people dying in Africa due to indoor pollution exposure far exceeds that seen elsewhere.

Global Differences in Occupational and Environmental Lung Diseases

Pneumoconiosis

The incidence of asbestosis and other asbestos related diseases has been directly correlated with national levels of consumption [6]. Global estimates of pneumoconiosis morbidity is based on the distribution of the economically active population

by economic sub-sector and the percentage of workers exposed to silica, asbestos and coal mine dust in each economic sub-sector [1]. Asbestosis causes an estimated 7,000 deaths annually, roughly 1% of all occupation related deaths worldwide. A similar estimate, roughly 9,000 deaths, is attributed to silicosis and 14,000 from CWP [7] . The primary limitation of these estimates is that the proportion of workers exposed to silica and asbestos in a specific economic sub-sector was assumed to be constant throughout the world.

The Western Pacific Region is responsible for approximately half of the global deaths and DALYs from asbestosis and silicosis. China alone is responsible for nearly half of the global deaths and DALYs from CWP. A registry of asbestosis deaths from the US National Institute of Occupational Safety and Health (NIOSH) reports an average of 710 annually over the past 40 years in the United States [8]. Unlike asbestosis where prevalence in the developed world has been declining, there has been a documented recent increase in the prevalence of CWP in the US [9]. The relative proportion of different diagnosis of pneumoconiosis varies widely. In China, where research has been undertaken comparing the pulmonary function and clinical presentation of workers with different pneumoconiosis [10], silicosis and CWP accounted for 48.3 and 39.1%, respectively, of the total number of pneumoconiosis cases, and asbestosis accounted for 1.1% of all pneumoconiosis patients [11].

Asthma

The WHO estimates that 38,000 people die annually from occupational asthma with 1,621,000 DALYs attributed to occupational asthma. Approximately one third of the asthma deaths related to occupation occurred in impoverished countries from the South-East Asia Region (WHO region SEAR-D). Occupational exposures are estimated to cause 11% of all cases of asthma in developed European and North American countries [12]. Estimates from population based studies in developed European countries are comparable with 5–10% of asthma determined to be from occupational exposures [13, 14]; however, it has been argued that this is a low estimate [15]. The American Thoracic Society statement on occupational exposure and lung disease estimates that occupational exposures account for approximately 15% of all cases of asthma in the US [16].

Africa has twice the attributable fraction than Europe and the US with nearly 25% of all causes of asthma being work related [7]. Approximately 11% of morbidity (as expressed in DALYs) worldwide is attributed to occupational exposures. In general, in all regions of the world, the attributable fraction of asthma morbidity and mortality caused by workplace exposures is twice that for men than it is for women. A noted exception to this is in the Eastern Mediterranean region where men have five times the morbidity from occupational asthma than women, most likely reflecting occupational demographics amongst women in those countries.

There have been scores of studies conducted throughout the world linking both long- and short-term exposure to air pollution with increased asthma morbidity and mortality. Large cohort studies and time-series analysis have been conducted in

Europe [17], Asia [18], Africa [19], and North America [20]. The WHO attributes 11,000 annual deaths globally to asthma exacerbations caused by ambient air pollution. Roughly one fourth of these deaths are attributed to exposures in low to middle income South-East Asian countries. Indoor exposure to smoke from burning of biomass fuels is another important environmental cause of asthma. Exposures from indoor smoke have been associated with increased burden from asthma in China [21] and Africa [22].

Lung Cancer

An estimated 1.4 million people annually die from lung cancer around the globe [23]. It is the most prevalent type of cancer in men and the most frequent cause of cancer death for both sexes. The overwhelmingly predominate causal factor is personal smoking history [24]. Consequently, much of the international variation in lung cancer incidence and mortality rates is explained by variable use of tobacco products. In the US, 90% of lung cancer deaths among men and 80% in women is attributable to smoking [25], while the percentage is much less (51% in men; 15% in women) in China [26].

An estimated 10–15% of all deaths from lung cancer, up to 210,000 deaths annually, are caused by risk factors other than smoking. Thun and colleagues from the American Cancer Society [27] analyzed lung cancer incidence and mortality rates from 21 cancer registries and 13 large cohort studies, representing 2.5 million self-reported non-smokers. The lowest recorded incidence rates of lung cancer in non-smokers were among women in Africa and India (5/100,000) while the highest (40/100,000) was found in China. Non-smoking related lung cancer incidence in Asian women was found to be two to three times higher than in the same age European population.

When assessing the risk of exposure to nine lung carcinogens (arsenic, asbestos, beryllium, cadmium, chromium, diesel fumes, nickel, silica, and radon) amongst US workers, it is estimated that roughly 12,000 people develop lung cancer annually in the US due to occupational exposures. This accounts for approximately 9% of all lung cancer deaths in US men. Estimates from Europe where a job exposure matrix was used to assess exposure among cases in a cancer registry attribute 24% of lung and bronchus cancer to occupational exposures [28].

While some of the variation in lung cancer rates in non-smokers may be attributable to genetic differences, most of the discrepancy is due to differences in environmental and occupational exposures. The elevated risk of lung cancer among non-smokers in China is in part due to environmental exposures to indoor burning of coal [29], secondhand smoke [30], and volatilization of cooking oils [31]. Elevated risk to occupational lung cancer has been shown in Chinese workers exposed to diesel exhaust, silica dust, and both spray and non-spray painting work [32]. Environmental exposure to arsenic, an IARC group 1 carcinogen, in drinking water has been associated with elevated risk of lung cancer in China, Taiwan, Japan, Bangladesh, and Chile [33].

Chronic Obstructive Pulmonary Disease

COPD is the fourth leading cause of death worldwide and is the leading cause of occupationally related deaths accounting for 40% of all deaths due to occupational exposures [12, 34]. Unlike lung cancer, never smokers comprise a substantial proportion of patients with COPD. Estimates of patients with COPD who are never smokers vary from 25 in the US [35] to nearly 40% in China [36]. Lamprecht and colleagues analyzed data from 14 countries that participated in the international, population-based Burden of Obstructive Lung Disease (BOLD) study. They estimate that 33% of mild airway obstruction (GOLD stage I) and 23% of moderate to very severe obstruction (GOLD stage II+) globally are not related to smoking. Highest rates of COPD in never smokers were observed in Krakow, Poland, while the lowest rate was in Uppsala, Sweden. The American Thoracic Society statement on occupational exposure and lung disease estimates that occupational exposures account for 11–24% of COPD [16]. Estimates of population attributable risk from occupational exposures in the US have been put at 20% [37]. A Swedish cohort of 317,000 male construction workers found that COPD attributable to any airborne exposure was estimated at 10% overall and 52% for never smokers [38].

Much of the research demonstrating increased prevalence of COPD in specific occupational groups has been carried out in countries where there is little enforcement or knowledge of occupational safety and health standards. In a population-based cohort in China, chronic respiratory symptoms from COPD were positively correlated with occupational exposure to dust and fumes [39]. Increased risk of COPD among miners has been reported in Mongolia [40]. A WHO report on occupational risk factors estimates that roughly half of the African male population and nearly 40% of the female population has ever been exposed to agents causing COPD. This is compared to 8% of the male population and 3% of the female population in parts of North America, and 5.6% of the Western European male population and 2.5% of the female population [12].

A significant association between exposure to ambient air pollution and worsening of obstruction on PFT has been shown in studies worldwide; particulate matter exposure in the North American [41, 42], European [43], and Asian populations is correlated with reduction of FEV_1 in cross-sectional studies. It is difficult to compare studies and relative magnitudes of effect across the globe as assessment of ambient exposure and exposure indices vary widely in the literature. Time-series analysis has been utilized internationally to assess the relationship between exposure to ambient air pollution and excess emergency room admission rates for COPD. The APHEA project in six European cities (Amsterdam, Barcelona, London, Milano, Paris, and Rotterdam) reported 3.5 and 4.3% increase in COPD admissions for each increase in 50 μg/m of particulates and ozone, respectively [44]. An increase of 5.1 and 1.5% in admission rate with a comparable increase in particulates and ozone concentration, respectively, was reported in Australia [45], while a 12 and 3.0% was observed with increases of particulates and ozone in the United States [46].

Global Differences in Environmental and Occupational Exposures

Asbestos

Asbestos has been banned in 52 countries throughout the world [47]. Despite this, an estimated 125 million people around the globe continue to work with asbestos [48] with its use growing in Asia and Latin America [49]. The proportion of people exposed to asbestos is highest for the Western Pacific region, with up to 3% of the male population being exposed. The second highest exposure region is Western Europe and North America where roughly 2.5% of the male population is exposed. South America, Southeast Asia, Africa, and the Eastern Mediterranean regions have similar exposure levels of roughly 2% of the male population. In nearly every region throughout the world, the proportion of the female population exposed is roughly 20% that of the male population.

Metals

Both occupational and environmental exposure to metals such as arsenic, beryllium, nickel, cadmium, and chromium is a pervasive lung cancer risk in much of the world. Occupational exposures to arsenic and cadmium were found to be as high as 200 times OSHA Permissible Exposure Level (PEL) in some developing countries [50]. Exposure to arsenic in Bangladesh has reached endemic levels; millions of people are at risk of arsenic exposure from contaminated drinking water, and 34% of people surveyed have dietary intake above the WHO's tolerable daily intake levels [51]. Environmental exposure to arsenic, and consequently prevalence of arsenic associated respiratory disease, is significantly lower in the US when compared to Asia [52].

Silica

Data on exposure to crystalline silica among US miners indicate that 16% of samples were above the OSHA PEL [53]. This level of exposure is drastically different from those found among workers in China, where roughly 75% of samples are exposed above the PEL [54]. A study of South African brick workers indicates that 45% of presented sample values were above the PEL [55].

Ambient Air Pollution

The primary ambient air pollutants relevant in the development of environmental lung disease include particulate matter, ozone, NO_X, and SO_2. The UN and the World Bank have assessed PM10 concentration as a surrogate for overall ambient air pollution in 1,100 cities from 91 countries. The highest concentrations of particulate matter are found in Africa and the Eastern Mediterranean Region where PM10 concentrations averaged over 90 and 140 μg/m^3, respectively. Lowest concentrations were recorded in New Zealand (16 μg/m^3) and Western Europe (29 μg/m^3) and North America (21 μg/m^3) [56, 57].

Indoor Biomass Fuel

According to the WHO millennium development goals, approximately half of the world's population utilizes biomass (wood, crop residues, and dung) and coal as their primary source of domestic energy. Indoor air pollution caused by these fuels is estimated to cause more than 1.6 million deaths annually. Sub-Saharan Africa and Asia both have biomass fuel use at 80% of all households. This percentage has remained relatively unchanged since 1990. Virtually no households in developed countries use solid fuel as the primary source of domestic energy [58].

Second-Hand Smoke

The world health organization estimates that 600,000 people per year worldwide die from exposure to second-hand smoke (SHS). Worldwide, roughly 35% of adults and 40% of children are exposed to SHS. The proportion of women exposed is generally higher than the proportion of men. The highest exposures to SHS are found in Eastern Europe, the Western Pacific, and South-East Asia where greater than 50% of the population is exposed. In parts of Eastern Europe, up to 66% of non-smokers are exposed to second-hand smoke. The lowest rates of exposure to SHS are found in Africa where 10% of the non-smoking population is exposed [59].

Radon

Highest exposures of radon are found occupationally in mines. Eleven cohort studies have assessed radon exposure and risk of lung cancer in a total of 60,000 miners in Europe, North America, Asia, and Australia [60]. The average worldwide indoor radon concentration is estimated at 39 Bq/m^3. Highest exposures have been measured in Mexico, Czech Republic, Finland, Sweden, and Luxembourg, all with over

100 Bq/m^3 of average indoor exposures. Countries with the lowest measured concentrations are Iceland (10 Bq/m^3), Australia (11 Bq/m^3), and Japan (16 Bq/m^3). Indoor exposure to radon is primarily dependent on composition of local soil and design of residential structures [61].

Global Prevention of Occupational and Environmental Lung Disease

Occupational Health Standards

The WHO's Workers' Health Global Plan of Action begins by expressing concern, "that there are major gaps between and within countries in the exposure of workers and local communities to occupational hazards and in their access to occupational health services" [62]. Simply put, occupational health standards and their enforcement vary widely throughout the world. Respiratory occupational hazards, such as asbestos, are extensively regulated in many countries, while others have yet to institute even the most preliminary safety measures.

For example, the Canadian Occupational Health and Safety Act specifically regulates who may work with asbestos, required training, specific occupational procedures, as well as both air and medical monitoring. The Provincial Physician maintains a registry of asbestos workers and coordinates regular screening for asbestos related diseases [63]. However, stricter regulations and declining use of asbestos in Canada have both decreased incidence of asbestos related lung disease and created a large export market. Canada has become one of the world's leading exporters of asbestos, shipping 150,000 metric tons annually to India and Indonesia, where little or no protection exists for workers exposed to asbestos [64].

Banning products is only one aspect of occupational health rule making that has helped protect workers worldwide. Monitoring of work environments, use of personal protective equipment, and medical monitoring programs are important components in the global prevention of occupational lung disease. In the United States, the Occupational Safety and Health Administration is the regulatory body responsible for enforcing such programs. The extent to which different countries have occupational health legislation and regulatory bodies varies greatly. Beyond this, the efficacy of legislation and the extent regulatory bodies are empowered to protect occupational health also vary widely.

Environmental Emission Standards

Regulating environmental emissions is a key factor in preventing lung disease and mitigating its burden worldwide [65]. A poignant example of this was the impact of regulating of environmental emissions during the 2008 Beijing Olympics. Beijing

had a roughly 50% reduction in air pollution during the Beijing Olympics [66]. This was associated with reduction in exhaled nitric oxide (a biomarker of acute lung inflammation) [67] and a significant reduction in mortality from lung disease [68]. Data from the German SALIA (Study on the influence of Air pollution on Lung function, Inflammation and Aging) demonstrated that improvement in air pollution standards has attenuated progression of disease in women with COPD [69]. Attempts at mitigating Arsenic exposure due to mining in Chile have been associated with reduction in cancer rates [70].

The setting of environmental standards is often a lengthy, expensive, and political process. Even once an environmental emission standard is set, the public's health will not be protected if sufficient resources are not allocated to enforce the standards. Often engineering controls are a more effective and efficient means to preventing environmentally related lung disease. Levels of indoor concentration of particulate matter in homes that use solid fuels can reach peak levels of 30 mg/m^3 [71]; this is associated with increased respiratory symptoms, chronic bronchitis, and chronic airflow obstruction [72, 73]. Installation of venting stoves in 90% of homes in a rural area of Guatemala has resulted in a 26% decline in clinic visits for lung disease [74]. Interventions such as this can have a significant global effect in lowering the burden of environmental lung disease, as its efficacy is not tied to government standards and enforcement.

Vulnerable Populations

A key aspect to preventing occupational and environmental causes of lung disease is identifying communities with elevated risk of hazardous exposures and high prevalence of disease. Such vulnerable populations include migrant workers and child laborers. Migrant workers often work without the sanction and protection of governmental occupational health programs. Additionally, the transient and temporary nature of their work puts them at greater risk for hazardous exposures. Migrant workers are frequently un-empowered and lack the basic information needed to protect themselves from potential exposures [75]. Consequently, migrant workers are more likely to work with substances that will cause lung disease and are less likely to use personal protective equipment. The result is an elevated prevalence of occupational lung diseases in migrant workers at near epidemic proportions. While the rates of pneumoconiosis in miners is known to be high, a study of Botswana men formerly employed in the South African mining industry found 31% had pneumoconiosis; nearly 7% suffered from progressive massive fibrosis [76]. Increased risk of silicosis among migrant workers in mainland China has led to spread of silico-tuberculosis after their return to their rural villages [77]. Proper education and protection of migrant workers is crucial to curtail the global burden of occupational lung disease.

Many communities in the developing world are particularly vulnerable to the respiratory health effects of environmental hazards. Financial and social insecurities often result in people living in communities located in close proximity to road traffic,

industrial pollution, and other sources of inhalational hazards. These insecurities also influence the indoor environment. Roughly three billion people living in low and middle income countries rely on solid fuels such as wood, dung, or coal for home heating and cooking. The elevated exposure to indoor particulates in these communities leads to increased risk of environmentally related lung disease. Nearly all of the 2.3 million deaths annually attributed to indoor smoke from solid fuels occur in low and middle income countries [78]. Mitigating the global burden of environmental lung disease relies on addressing the underlying social and financial inequalities which influence the extent vulnerable populations are exposed to environmental hazards.

Conclusions

Lung disease resulting from occupational hazards and environmental pollution is a global problem. The differential burden of disease worldwide is largely due to variation in exposures resulting from dramatically disparate occupational health and safety norms; environmental standards and enforcement; and a severe lack of screening and access to care in much of the developing world. In our review of the global burden from occupational and environmentally caused COPD, asthma, and lung cancer, we see that the attributable fraction from occupational and environmental exposures varies widely, with up to 25% of asthma in Africa being work related while the estimate is 10% for North America and Western Europe. Likewise, the contribution of indoor air pollution in the development of asthma is significantly higher in Africa when compared to the rest of the world, while the contribution of ambient air pollution is significantly lower in Africa when compared to parts of South-east Asia and Eastern Europe.

The burden of disease from pneumoconiosis in different regions of the world reflects the variable use of silica and asbestosis in the workforce as well as the varying extent workers are protected from exposure. Monitoring of crystalline silica in China reflects concentrations above recommended exposure levels in 75% of samples compared to 16% of measurements in the US. While strengthening of occupational health standards in one part of the world may lead to improved working conditions and a decrease in the burden of disease locally, it can also inadvertently lead to increased exports of the hazardous agent to other regions and a consequent increase in the burden of disease globally.

While we have presented the global burden of occupational and environmental lung disease in terms of total mortality and estimated DALYs, this does not fully capture the total morbidity of disease. Estimated QALY (quality-adjusted life year) would better assess the burden of disease by assessing the impact of occupational and environmental lung disease on the quality of life lived. Unfortunately, published regional estimates on QALYs for occupational and environmental lung disease are lacking and further research geared at estimating the complete global burden of disease is needed. What is clear, however, is that a significant gap exists in the extent workers and

communities are protected from the occupational and environmental exposures that cause lung disease. Better environmental legislation, occupational health standards, and screening and tracking of disease in highly exposed populations can help to alleviate the global burden of occupational and environmental lung disease.

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