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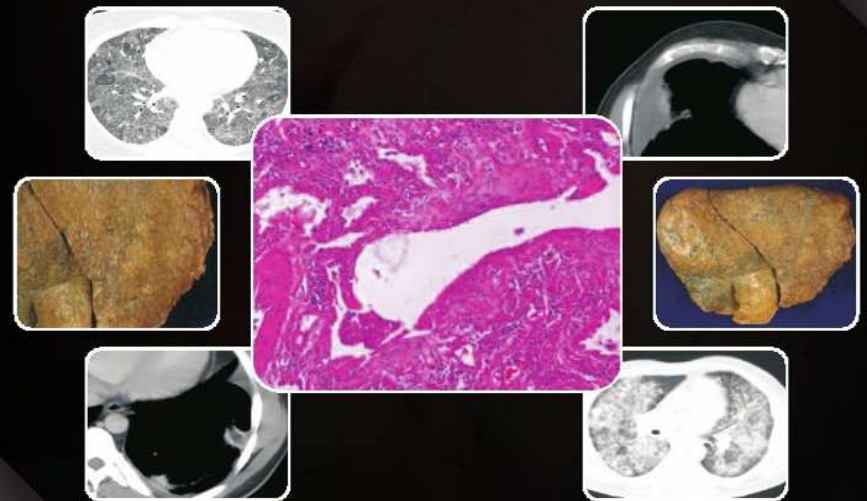


*Environmental and Occupational Lung Health*

**VP**

# *Environmental and Occupational Lung Health*

A Pathological Analysis



**V. K. Vijayan  
Henry D. Tazelaar  
Ritu Kulshrestha**

# **Environmental and Occupational Lung Health**

**A PATHOLOGICAL ANALYSIS**

# Environmental and Occupational Lung Health

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## Foreword

Medical and scientific knowledge in the field of environmental lung diseases has grown exponentially in the last decades. This has been boosted by and also resulted in an increased awareness in the etiopathogenesis of diseases associated with indoor and outdoor air pollution, environmental and occupational. Simultaneously enormous progress has been made in the last decade in understanding the pathological basis of diseases such as silicosis, asbestosis and pulmonary toxicity arising out of their exposure. These diseases have a long latent period and are often misdiagnosed in the absence of tissue diagnosis.

In this edition we examine the environmental and occupational lung diseases from the point of view of improving the diagnostic accuracy by being a ready handbook for the students, pathologists and pulmonologists and focus on the common indoor and outdoor air pollutants in India. The pathologist who is faced with having to diagnose these diseases on small/open lung biopsy samples and the pulmonologist who has to frustratingly bear the result of an inconclusive histopathology report on preciously taken samples will benefit from this systematic evaluation with clinical-pathological-radiological approach to environmental lung diseases and their correlation will help in increasing the accuracy of diagnosis.

Lung involvement by indoor air pollutants is now a leading field of interest and investigation. Burning of biomass fuel is an important source of particulate matter and indoor air pollution in developing countries and women and children are affected by this. Secondhand smoke is another important source of indoor air pollution. The effects of these pollutants as precursors of lung cancer and carcinogenesis along with the molecular diagnostic techniques in identification and categorization of lung cancer are covered by leading experts, in this edition.

Recently there has been a lot of focus on the role of identification of biomarkers in blood samples and bronchoalveolar lavage fluid, which are less invasive techniques when compared to biopsy and have therefore become the object of much research and interest in the recent times. Nanoparticles being generated by nanotechnology industry are a new cause of environmental lung disease. The nanotechnology industry creates extremely small particles of different substances such as carbon, which are called nanoparticles. The effects of the nanoparticles on human health are not exactly known. The role of biomarkers for early diagnosis



of tumors associated with pneumoconiosis, for example asbestos exposure and other environmental exposures to agents such as benzene from vehicular exhaust in environmental lung diseases are covered.

It is our hope that the pathologists and pulmonologists and chest radiologists will find this edition useful and practical and that this book helps others find the field of environmental lung diseases as gratifying and challenging an area in which to work in as we do.

The science of pulmonary pathology is the extraction of the maximal amount of information from a minimal amount of tissue by careful and systematic observation and it is our hope that this edition will serve as a useful guide to these complex and challenging illnesses.

V. K. Vijayan  
H. D. Tazelaar  
R. Kulshrestha

# Chapter 1

## Environmental lung diseases: An overview

V. K. Vijayan, Ritu Kulshrestha

Introduction  
Classification  
Indoor air pollution  
Outdoor air pollution  
Occupational lung diseases  
Diagnosis

## **Introduction**

Environmental lung diseases occur as a result of Indoor or Outdoor air pollution and are an increasing cause of concern worldwide. India being a developing nation is faced with traditional public health problems like communicable diseases, malnutrition, etc. On the other hand rapid industrial growth and globalization in the last few decades has resulted in emergence of environmental and occupational health related issues. Both indoor and outdoor air pollution are of rising concern to the pulmonary physicians and public health officials since they can cause or exacerbate most respiratory diseases, including asthma, Chronic obstructive pulmonary disease (COPD), interstitial lung disease and lung cancer. The major occupational diseases of concern in India are silicosis, coal workers pneumoconiosis, chronic obstructive lung diseases, asbestosis and byssinosis<sup>1</sup>. The silicosis include pneumoconioses caused by exposure to talc (magnesium silicate), kaolin (aluminium silicate), mica (aluminium silicate), and fuller's earth (calcium montmorillonite). Less common include berylliosis, siderosis, stannosis, aluminosis, thesaurosis and baritosis.

## **Classification of environmental lung disease**

The environmental lung diseases are classified by their causative agent, clinical presentation/disease, and histopathological features. There is a lot of overlap in these categories due to two important factors which need to be considered in all cases: 1) A given exposure can cause more than a single disorder, for example, asbestosis. 2) The accurate estimates of the contribution of occupational and environmental exposures to specific lung diseases are difficult to measure<sup>2</sup>. Assessing the pathologic changes from the different environmental/occupational exposures, needs to be done keeping in mind, the nature of the exposure, host response/primary disease, and major site of respiratory system pathological injury (upper airways vs. lower airways vs. alveoli vs. interstitial tissue vs. pleura) (Table 1).

## Chapter 2

# Tobacco Smoke-Related Airway Disease Pathology of Environmental Lung Disease

Henry D. Tazelaar

Background  
Chronic obstructive pulmonary disease  
Chronic Bronchitis  
Disease of Bronchioles  
Small Airways in COPD  
Respiratory Bronchiolitis  
Pulmonary Langerhans' Cell Histiocytosis

## **Background**

Smoking is associated with inflammation in the large airways, the small airways and the lung parenchyma: histologic studies and bronchoalveolar lavage data confirm increases in lymphocytes, eosinophils, neutrophils, and macrophages. A relative increase in CD8 positive lymphocytes has been identified in smokers with chronic obstructive airway disease (COPD). Langerhans cells are increased in airway epithelium. Neutrophils are activated and pool in the pulmonary circulation in smokers. Pro-inflammatory cytokines are increased in BAL fluid of smokers. Smokers have increased immunoglobulin levels in BAL and serum. Alterations in glutathione metabolism are present and recognized as a central feature of inflammation in smoking. All of these factors contribute to the pathology of the large and small airways in the lung [1-3].

## **Chronic Obstructive Pulmonary Disease (COPD)**

COPD refers to persistent abnormalities of expiratory flow. COPD has been associated with a wide range of morphologic abnormalities. Chronic bronchitis and emphysema are the two most classically described correlates of COPD, but a complex array of small airway pathology may also result in functionally significant airflow limitation. We will briefly consider the pathology of chronic bronchitis, and lesions included under the generic heading of small airways disease. Emphysema, while closely related, is not strictly speaking an airway disease and so will not be considered.

## **Chronic Bronchitis [3, 4]**

The term chronic bronchitis is somewhat ambiguous and generic, but at least in the United States refers to chronic or recurrent hyper secretion of mucus into the bronchial tree resulting in a productive cough. Intrabronchial mucus is derived from two sources, submucosal mucus glands and mucosal goblet cells, and the former are thought to be responsible for the bulk of mucus production. Thus, most morphologic studies of chronic bronchitis have focused on abnormalities of tracheobronchial mucus glands.

There is general agreement that mucus glands are increased in size in patients with clinically significant chronic bronchitis. This is due to both cellular hyperplasia and hypertrophy, although mucus gland hyperplasia is thought to account for the majority of the increase in gland size. The Reid Index is the best known method for quantifying the change in gland size in chronic bronchitis. The Index is defined as the ratio of the

## Chapter 3

# Idiopathic Interstitial Pneumonias

Henry D. Tazelaar

Introduction  
Usual Interstitial Pneumonia (UIP)  
Acute Exacerbation of Idiopathic Pulmonary Fibrosis (IPF)  
Desquamative Interstitial Pneumonia (DIP)  
Non-Specific Interstitial Pneumonia  
Respiratory Bronchiolitis  
Diffuse Alveolar Damage (DAD)  
Organizing Pneumonia  
Lymphoid Interstitial Pneumonia  
Differential features

## Introduction

The idiopathic interstitial pneumonias represent a heterogeneous group of diseases. There are those which develop over a very short period of time e.g. *acute interstitial pneumonia* and those in which patients may have a several year history of symptoms prior to diagnosis e.g. *usual interstitial pneumonia*. Some really do not appear associated with any predisposing factor e.g. many cases of *nonspecific interstitial pneumonia*, and others, despite the The American Thoracic Society/European Respiratory Society<sup>1</sup> endorsed classification scheme shown in Table 1 of the *idiopathic interstitial pneumonias*, are not actually idiopathic e.g. *respiratory bronchiolitis associated interstitial lung disease* is strongly associated with cigarette smoking. That all the diseases discussed below are referred to as “idiopathic” is a bit of a mystery, especially when other idiopathic interstitial diseases e.g. *sarcoidosis* are not included in the classification.

What the diseases have in common, however, is that they are all characterized histologically by varying combinations of interstitial fibrosis, organization, and chronic inflammation in both or either the pulmonary interstitium and alveolar spaces, without the presence of granulomas or specific cell types e.g. Langerhans’ cells, eosinophils. For this reason, they are often grouped together.

**Figure 1**

Usual interstitial pneumonia. Early case without honeycomb change, but the slide illustrates the patchy nature of the disease, and the subpleural and paraseptal accentuation of the process. Normal lung is present centrally.

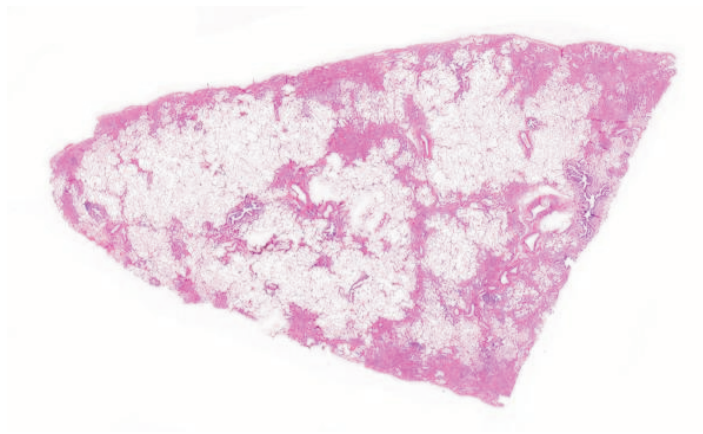
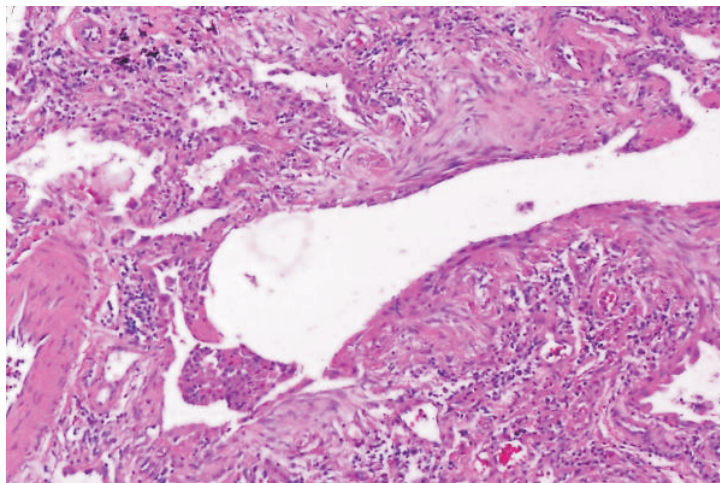


Figure 2: Usual Interstitial Pneumonia with several fibroblast foci.





# Chapter 4

## Epidemiology of Lung Cancer

Manoj Singh

Environmental and Occupational Agents

Smoking

Smoking Cessation:

The Changing Cigarette:

Lung Cancer Histopathology and Smoking:

Diet

Occupational Exposures

Asbestos

Radiation

Host Factors

Epidemiology of Lung Cancer in India

Lung cancer is the leading cause of cancer-related deaths for both men and women. The incidence and mortality attributed to lung cancer has been rising steadily since the 1930's, mainly due to the increasing popularity of cigarette smoking. By the end of the 20th century, lung cancer had become one of the world's leading causes of preventable death. It was a rare disease at the start of that century, but exposures to new etiologic agents and an increasing lifespan made lung cancer a scourge of the 20th century. While tobacco had been widely used throughout the world for centuries, the present pandemic of lung cancer followed the introduction of manufactured cigarettes with addictive properties, which resulted in a new pattern of sustained exposure to inhaled carcinogens.

While its predominant cause is now well-known (*i.e.*, tobacco smoking), there are other causes as well, some acting in concert with smoking to synergistically increase risk. The suspicion that radon was a cause of lung cancer in underground miners led to what was probably the first occupational respiratory carcinogen to be identified. Radon in indoor environments is now considered to be a significant cause of lung cancer. The list of human occupational causes of lung cancer also includes arsenic, asbestos, chromates, chloromethyl ethers, nickel, polycyclic aromatic hydrocarbons, radon progeny, and other agents. Outdoor air pollution, which includes combustion-generated carcinogens, is also considered to contribute to the lung cancer burden in urban dwellers. Indoor air contains several respiratory carcinogens, including radon, asbestos, and cigarette smoke. In some developing countries, exposure to fumes from cooking stoves and fires is associated with lung cancer risk.

Lung cancer is the most commonly diagnosed cancer worldwide, but its geographic distribution shows marked regional variation. The global variation in age-standardized incidence rates is greater than fourfold among men, and a fivefold among women. Lung cancer tends to be most common in developed countries, particularly in North America and Europe, and less common in developing countries, particularly in Africa and South America. Within countries, lung cancer incidence among men invariably outpaces that in women, by well over 100% in most nations.

Although the causes of lung cancer are almost exclusively environmental, it is likely that there is substantial individual variation in the susceptibility to respiratory carcinogens. The risk of the disease can be conceptualized as reflecting the joint consequences of the interrelationship between (1)

# Chapter 5

## Precursor Lesions of Lung Cancer

Kusum Joshi

Introduction  
Preinvasive Bronchial Squamous Lesions  
Normal Bronchial mucosa  
Epithelial Hyperplasia  
Squamous Metaplasia  
Squamous Dysplasia  
Other histological types of bronchial epithelial dysplasia  
Carcinoma in situ (CIS)  
Micro-invasive squamous cell carcinoma  
Roentgenographically occult lung cancer  
Molecular and genetic changes in precursor lesions  
Changes in extra cellular matrix  
Atypical Adenomatous Hyperplasia (AAH)  
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH)  
Atypical Mesothelial Hyperplasia  
Other Precancerous Lesions Of Lung  
Future Aspects of Precursors of Lung Cancer

## **Introduction**

Lung Cancer is common the world over. Its incidence in males is declining, but continues to increase in females. The prognosis is poor and five year survival has remained unchanged. Hence early detection is important by adequate and effective screening of at least the high risk population. The goal of early detection naturally brings the precursor or pre-neoplastic lesions of lung cancer into focus. The concept of pulmonary incipient neoplasia is similar (albeit less developed ) to that for other epithelial malignancies such as cervix, gastro-intestinal tract, breast, urinary bladder etc.

The precursor lesion of squamous cell carcinoma in the form of bronchial squamous dysplasia and carcinoma in situ have been recognized for long and found a mention in the 1981 WHO classification of lung tumors. Atypical adenomatous hyperplasia (AAH) was proposed by Mori et al (1990) as a potential precursor of adenocarcinoma. Diffuse idiopathic pulmonary neuron-endocrine cell hyperplasia (DIPNECH) was proposed as a potential precursor of carcinoid tumors by Aguayo et al (1992). Both lesions, although not yet fully understood, found a place in the 1999 WHO classification. The precursor lesion of malignant mesothelioma has been proposed by Whitaker et al, 1992 and by Henderson et al in 1998, but is still not widely accepted. Explosion of molecular data in the recent years has also contributed greatly to the understanding of genetic events involved in the pathogenesis of lung cancer.

## **Preinvasive Bronchial Squamous Lesions**

Bronchial carcinogenesis is a multi-step process, Normal bronchial mucosa undergoes a spectrum of lesions basal cell hyperplasia squamous metaplasia dysplasia carcinoma in situ. Destruction of the epithelial basement membrane and changes in extra cellular matrix leads to invasion. Squamous dysplasia and carcinoma in situ are termed as “pre invasive lesions” or “precursor lesions”, but it does not imply that invasion would have to occur.

## **Normal Bronchial mucosa**

It is a pseudo stratified epithelium sitting on the basement membrane and composed of ciliated cell, goblet cells, basal cells, parabasal cells (in proximal airways) Clara cell (in distal airways) and scattered neuron-endocrine cells. The epithelium is 3-4 layers thick proximally and single cell layer in terminal bronchioles.

## Chapter 6

# Indoor Air Pollution From Cooking Fuel And Lung Health

Raj Kumar

Indoor Air Pollutants: Sources and Health effects  
Combustion by-products  
Radon and decay products  
Bio-pollutants  
Volatile Organic Compounds  
Asbestos fibers  
Control Measures for Indoor Air Pollution

Air pollution and its health hazards are well known since the beginning of human civilization. Air pollution is a major environment related health threat to human being and a risk factor for both acute and chronic diseases with major impact on respiratory system. While second-hand tobacco smoke and certain outdoor pollutants are known risk factors for acute respiratory infections, indoor air pollution from biomass fuel is one of the major contributors to the global burden of disease.

More than three billion people worldwide continue to depend on solid fuels, including biomass fuels (wood, dung, agricultural residues) and coal, for their energy needs. Cooking and heating with solid fuels on open fires or traditional stoves results in high levels of indoor air pollution. On a global scale, the household use of solid fuels is the most important source of indoor air pollution<sup>1</sup>.

Indoor air pollution is a major global public health threat requiring greatly increased efforts in the areas of research and policy-making. Research on its health effects should be strengthened, particularly in relation to tuberculosis and acute lower respiratory infections. A more systematic approach to the development and evaluation of interventions is desirable, with clearer recognition of the interrelationships between poverty and dependence on polluting fuels. Air pollution control strategies must be established and should effectively be implemented. However, indoor – outdoor relationship is a complex interaction of various factors such as meteorological, indoor sources, ventilation and construction material used. Smoking and cooking has been identified as major sources of air pollution in indoor than outdoor. There is growing evidence that evaluation of indoor as well as outdoor exposures to air pollution is essential for realistic health effects assessment. A study conducted in Delhi, India on 394 children showed there is association of indoor and outdoor air pollutant level with respiratory problems<sup>2</sup>.

If indoor exposures are not taken into account in epidemiologic investigations of air pollution, systematic and random biases may give rise to spurious conclusions. Total personal exposures are often better correlated with indoor than with outdoor concentrations<sup>3</sup>.

### **Indoor Air Pollutants: Sources and Health effects**

Several pollutants from indoor sources affect human health. Indoor air pollutants include Environmental tobacco smoke (ETS), radon and radon decay products, asbestos fibers, fiber glass, formaldehyde, combustion by-products (such as polycyclic aromatic hydrocarbons, particulate matter,

## Chapter 7

# Pathological approach to Environmental lung disease

Ritu Kulshrestha

Introduction  
Magnitude of the problem in India  
Pneumoconiosis  
Pathogenesis  
Classification of pneumoconiosis  
Environmental exposure and Lung neoplasm  
Radiological Correlation

## **Introduction**

Environmental factors play a major role in the etiopathogenesis of a majority of lung diseases. Disease such as asthma, chronic obstructive lung disease, lung cancer and many interstitial lung diseases are caused or are influenced by environmental factors. These factors need to be accurately identified and for this a systematic pathological evaluation is required in each and every case. The science of pulmonary pathology is the art of extracting maximal information from the small amount of tissue available and correlating the histopathological pattern identified with the clinical and radiological features along with an accurate estimate of history and duration of environmental and/or exposure to air pollutants. Exposure to more than one etiological agent and aggravation of preexisting diseases by the inhaled dusts and fumes further aggravates the diagnostic dilemma. The relationship between silica exposure and the tubercle bacillus giving rise to the distinct disease silicotuberculosis and exacerbation of asthma by wood smoke are two such examples<sup>1,2</sup>.

## **Magnitude of the problem in India**

India is one of the most rapidly industrializing countries and occupational exposure to air pollutants is high, especially in the small scale unorganized sectors. Silicosis is the most prevalent and under diagnosed disease of this group. Nearly three million people in India are exposed to silica in mines and industries like stone cutting, silica milling, agate, slate pencil<sup>3,4</sup>. A substantial proportion of workers in construction activities like road building, also have potential exposure to silica. Studies carried out by National Institute of Occupational Health (NIOH) have shown high prevalence of silicosis in small factories<sup>5,6</sup> and even in nonoccupational exposed subjects<sup>7</sup>. In the agate industry of Khambhat (Gujarat) not only workers but also people staying in the vicinity of the agate-grinding facilities have been found to be exposed to crystalline silica. Another cause of great concern is the making of asbestos yarn and ropes, mostly in the unorganized sector of industries with very poor safety measures. Here the average levels of air borne asbestos fibres have been found to be much above the permissible level of 2 fibres/ml.

In rural areas, agricultural workers are exposed to many air pollutants including pesticides, herbicides and organic natural materials, which can cause airway disease including, bronchitis, asthma, and/or bronchiolitis or lung tissue reactions such as alveolitis, pulmonary edema and pulmonary fibrosis. The diseases caused by organic dusts include: 1) hypersensitivity pneumonitis, 2) organic dust toxic syndrome, 3) occupational asthma and bronchitis. Organophosphorous compounds,



## Chapter 8

# Broncholaveolar lavage (BAL) in environmental lung diseases

Helmut H. Popper

Introduction  
Processing of BAL  
Where and when doing BAL?  
BAL fluid cellularity and its diagnostic utility

## **Introduction**

By bronchoalveolar lavage (BAL) a proportion of inflammatory cells are washed out from the lung. The mechanism is still poorly understood. The normal composition of BAL cells is 80-85 % macrophages, up to 15 % lymphocytes, mainly of T lineage, 1-3 % neutrophils, < 0.5 % eosinophils, and < 0,1% mast cells. Since there is also macrophage alveolitis, it is necessary to study the phenotype of macrophages. Normally there will be a mixture of a small portion of small, monocyte-like cells, a large portion of mature large macrophages, but rarely giant cells. If necessary maturation of macrophages can be studied by immunocytochemistry for different enzymes or surface molecules. In case of macrophage alveolitis, the cells will be more uniform – adapted to the disease (RB, DIP).

## **Processing of BAL**

Ovoid the first 30-40 ml portions, since they usually contain mucus and bronchial cells. These portions are suitable for culture of microbes. The 3rd and 4th portion is rich in cells from the terminal bronchioles and alveoli.

The first step is assessment of cell types, exclusion of carcinoma cells, and exclusion of infections. Then a BAL cell count has to be performed. At least 300 cells should be counted. This will result in macrophagocytic, granulocytic, eosinophilic, or lymphocytic alveolitis, respectively. In case of a lymphocyte count over 18% (adults) or 15% (children), these lymphocytes are immunotyped. The minimal investigation should differentiate between B- and T-lymphocytes and natural killer cells, and CD4+ and CD8+ lymphocytes. Additional investigations might focus on subsets of CD4+ and CD8+ cells as well as regulatory T cells.

## Chapter 9

# Radiology of Environmental Lung Diseases

Balakrishnan Menon

Introduction  
Pneumoconiosis  
Silicosis and Coal Worker Pneumoconiosis  
Acute Silicosis  
Siderosis  
Hard Metal Pneumoconiosis  
Asbestos-related Pleural and Parenchymal Disease  
Asbestos-related Benign Pleural Disease  
Asbestosis  
Rounded Atelectasis  
Bronchogenic Carcinoma with Asbestos Exposure  
Malignant Mesothelioma  
Chemical Pneumonitis  
Carbamates  
Paraquat  
Hydrogen Sulfide  
Ammonia  
Hydrocarbon  
Mercury  
Occupational Infection  
Hypersensitivity Pneumonitis  
Organic Dust Toxic Syndrome  
Conclusions

## **Introduction**

Environmental lung disease comprises a wide variety of disorders caused by the inhalation or ingestion of dust particles or noxious chemicals. These disorders include pneumoconiosis, asbestos-related pleural and parenchymal disease, chemical pneumonitis, occupational infection, hypersensitivity pneumonitis, and organic dust toxic syndrome. Most of these disorders produce diffuse lung disease. Although many of the disorders can be detected at chest radiography, high-resolution computed tomography (CT) has been shown to be superior to chest radiography in depicting parenchymal, airway, and pleural abnormalities<sup>1</sup>. Some environmental lung diseases have characteristic radiologic features suggesting the correct diagnosis, whereas in others, a combination of clinical features, related occupational history, radiologic findings, and literature supporting an association between the exposure and the disease process is required for diagnosis. With advances in chest radiology, including high-resolution CT, radiologists play a key role in the clinical evaluation of environmental lung diseases and should continue their involvement in the diagnosis and treatment of these diseases<sup>2</sup>.

Thousands of environmental toxins and commercial chemicals are in use today. These agents may become aerosolized or airborne in the form of fibers, fumes, mists, or dust. The greatest increase in pulmonary hazards over this period has been in occupational allergic disorders, asthma, and hypersensitivity pneumonitis, with new sensitizing agents being described frequently<sup>3</sup>. Individuals living in major metropolitan areas may inhale more than 2 mg of dust each day, and workers in dusty occupations may inhale up to 100 times that amount. The development of environmental lung disease in an individual worker is dependent on the toxic effects of the inhaled substance, the intensity and duration of the exposure, and the physiologic and biologic susceptibility of the host. The physical state of the inhaled substance (eg, solid, fume, or mixture), its solubility, and its aerodynamic dimensions determine the initial location of disease activity. Depending on the solubility and reactivity of the inhaled substance, acute or chronic reactions occur as particles are deposited in the lower respiratory tract. Acute reactions with associated inflammation and edema, or more chronic reactions characterized by fibrosis or granuloma formation, have been demonstrated following inhalation of many environmental agents<sup>3</sup>.

## **Pneumoconiosis**

Pneumoconiosis is a tissue reaction to the presence of an accumulation of dust in the lungs. One clinicopathologic form of this reaction is fibrosis,

## Chapter 10

# Occupational asthma and its pathogenesis

Amit K. Dinda

Introduction  
Pathogenesis  
Mediators of airway remodelling.

## Introduction

Asthma is a serious public health problem worldwide. The Global Initiative for Asthma has reported the disease involving more than 300 million people all over the world<sup>1</sup>. Asthma is conventionally defined as a chronic airway disease characterized by reversible airflow obstruction, airway inflammation, hyperresponsiveness and remodelling. The chronic inflammatory process of the airways followed by healing may result in an altered structure referred to as airway remodelling. The airway remodeling include structural airway changes like epithelial metaplasia, increased size and amount of airway smooth muscle, thickened basement membrane, mucus hypersecretion and oedema in the airway wall with neoangiogenesis. The pathogenesis and progression of airway remodeling is yet to be understood fully in spite of our great understanding of allergy associated immunology. Thus, understanding of airway remodeling is the most important area of recent advances in pathogenesis of asthma<sup>2,3</sup>.

## Pathogenesis

Asthma occurs in two phases, acute or early phase and late phase response. Early phase response is mediated by initial sensitization to inhaled antigen in the airways which stimulate induction of Th2 type T cells which release cytokines IL-4, IL-5 and IL-13 while late response involved various inflammatory cells and their mediators. Th2 cells are required for antigen-induced allergic airway inflammation and airway hyperresponsiveness<sup>4</sup>. IgE antibodies have been linked to the severity of asthma and the initial and sustained responses of the airway to allergens. To initiate the synthesis of IgE, inhaled allergens must encounter dendritic cells that line the airway. These dendritic cells then migrate to draining lymph nodes, where they present processed antigen to T and B cells through CD3 on MHC class II and TCR<sup>5</sup>.

Interactions among these cells elicit responses that are influenced by cytokines (IL-4, IL-5 and IL-13) and the presence or absence of costimulatory molecules. When these cytokines (IL-4/IL-13) bind to receptors on B cells for a switch to the synthesis of IgE, the first signal is delivered as the receptors for interleukin-4 and interleukin-13 share a common chain and use the same signal-transduction pathway (STAT-6)<sup>4</sup>. CD40 is expressed on B cells which binds to its ligand on T cells also regulates IgE production<sup>6</sup>.

IgE antibodies bind to high-affinity IgE receptors (FcεRI) on the surface of mast cells in tissue Molecular bridging of FcεRI receptors, which occurs when allergen interacts with receptor-bound IgE molecules, causes

activation of the cell and the release of preformed and newly generated mediators<sup>7</sup>. Mast cell as CD34+ mononuclear cells that are positive for stem-cell factor and FcεRI, travel to mucosal and submucosal sites in the airway, and undergo tissue-specific maturation<sup>8</sup>. There are at least two subpopulations of mast cells: mast cells with tryptase and mast cells with both tryptase and chymase. Mast cells produce several cytokines, including IL-1, IL-2, IL-3, IL-4, IL-5, granulocyte macrophage colony-stimulating factor (GM-CSF), interferon-γ, and tumor necrosis factor<sup>9</sup>. The potential for the extracellular release of these cytokines raises the possibility that mast cells contribute to both acute and chronic allergic inflammation.

IL-5 stimulates the release of eosinophils into the circulation and prolongs their survival. Challenge of the airway with allergen increases the local concentration of IL-5, which correlates directly with the degree of airway eosinophilia<sup>10</sup>. IL-5 causes terminal differentiation of eosinophils. Circulating eosinophils enter the area of allergic inflammation and begin migrating to the lung by rolling, through interactions with P-selectins, and eventually adhering to endothelium through the binding of integrins to members of the immunoglobulin superfamily of adhesion proteins: vascular-cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1)<sup>11</sup>. As the eosinophils enter the matrix of the airway through the influence of various chemokines and cytokines, their survival is prolonged by IL-5 and GM-CSF. The chemokines RANTES, macrophage inflammatory protein 1, and the eotaxins are central to the delivery of eosinophils to the airway. These chemoattractants are produced by epithelium, macrophages, lymphocytes, and eosinophils<sup>12</sup>. On activation, the eosinophil releases inflammatory mediators such as leukotrienes and granule cationic proteins to injure airway tissues. In addition, eosinophils can generate GM-CSF to prolong and potentiate their survival and contribution to persistent airway.

### **Mediators of Airway remodelling.**

Airway remodelling is a complex process that involves all of the component tissues of the airway from the epithelium to the adventitia. Each of the changes has the potential to alter airway physiology so as to promote airway narrowing, hyperresponsiveness and inflammation<sup>13</sup>. Chronic inflammation and airway smooth muscle dysfunction are consistent features of asthma responsible for disease progression and airway remodeling<sup>14</sup>. Airway smooth muscle cells (ASMC) may also play a secretory or immunomodulatory role by producing pro-inflammatory cytokines, chemokines, polypeptide growth factors, extracellular matrix

# Chapter 11

## Occupational Lung Diseases

Allen R. Gibbs

Introduction  
Asbestos related diseases  
Coal Workers pneumoconiosis  
Silicosis



## Introduction

A wide spectrum of pulmonary pathologic reactions may follow exposures to environmental agents (table)<sup>1,2</sup>. The majority seen nowadays are chronic reactions due to exposure to the mineral(s) over a period of many years and have latencies often exceeding several decades. In some of these cases, occupational histories need to be very detailed and complete since the offending exposure may be quite early on in an individual's career or an indirect exposure, for example, malignant mesotheliomas may result in individuals from indirect exposures to asbestos via the contaminated clothes of a household relative who worked directly with asbestos. In contrast, pneumoconioses related to coal or silica are usually associated with greater than twenty years of direct exposure to the injurious dust and therefore the occupational history should be clear cut.

**Table 1. Examples of pleuropulmonary reactions to various environmental agents**

<b>Reaction</b>	<b>Agents</b>
Asthma	Isocyanates, metals
Macular/nodular pneumoconiosis	Coal, silica, silicates
Diffuse interstitial fibrosis	asbestos, hard metal
Granulomatous inflammation	Beryllium
Diffuse alveolar damage	toxic fumes eg beryllium, cadmium
Emphysema	coal, cadmium
Lung cancer	asbestos, nickel, arsenic, chromium compounds
Pleural plaques	asbestos, talc
Diffuse pleural fibrosis	asbestos
Mesothelioma	asbestos

In order to attribute a particular disease to occupational factors, certain questions need to be answered by the pathologist. These include :

- Is the pathological response appropriate to implicate a particular agent?
- Has there been sufficient exposure to the relevant injurious agent?
- Is there an appropriate latency?
- Can confounding factors be excluded?

Assessment of exposure to a particular agent can be done by anecdotal, clinico-radiological and histopathological means. Frequently the

pathologist is given poor or sketchy information concerning exposure(s) to agents which may potentially have caused the particular disease. It is not adequate to say the individual has been exposed to asbestos or coal or silica etc.; one needs to have knowledge of both severity, duration and frequency. A lifelong work history should be listed and sometimes information about the jobs of household contacts needs to be obtained. Ideally one should be provided with accurate details concerning exposure which would include the type of industrial process, the length of service in the industry and the frequency of exposure (continual or intermittent). Verification of exposure to a particular agent may rely on macroscopic and light microscopic appearances; for example coal workers' pneumoconiosis or silicosis or sometimes may require mineral analysis.

### **Asbestos related diseases**

Asbestos is a generic term for two groups (amphibole and serpentine) of naturally occurring fibrous silicate minerals. The commercial amphiboles include crocidolite (blue asbestos) and amosite (brown asbestos) and the non-commercial amphiboles, anthophyllite, tremolite and actinolite. The serpentine group comprises chrysotile (white asbestos). The amphibole and serpentine groups have different physico-chemical properties but share a fibrous form. They show very different potencies with regard to the development of asbestos associated diseases<sup>3-5</sup>. Asbestos-related diseases may be divided into non-neoplastic and neoplastic groups.

#### **The non-neoplastic group comprises:**

- Asbestos-related pleural effusion
- Pleural plaque
- Diffuse pleural thickening/fibrosis
- Diffuse interstitial pulmonary fibrosis (asbestosis)

#### **The neoplastic disease group comprises:**

- Malignant mesothelioma
- Lung cancer
- Pleural plaques are merely markers of asbestos exposure, can occur with relatively trivial exposures and not clinically significant.

The clinically significant forms of asbestos-related disease which result in death are asbestosis, malignant mesothelioma and lung cancer.

## Chapter 12

# Pathogenesis of Asbestos Induced Pulmonary Toxicity

Anjana V. Yeldandi

Asbestos Mineralogy  
Pathogenesis  
Ferruginous bodies/Asbestos bodies:  
Asbestos bodies  
Asbestos Associated Lung Diseases:  
Pleural Effusion  
Pleural Plaque  
Pleural plaque on the parietal pleural surface  
Asbestosis

### **Asbestos Mineralogy:**

Defined as a mineral that readily separates into long flexible fiber that is suitable for use as a non-combustible, non-conducting, chemically resistant material. The asbestos fibers are a group of hydrated silicate minerals with a high aspect ratio (length:diameter). Occurs as two major groups:

- 1) Serpentine
  - a. Chrysotile, white –curvilinear fibers. It is the only type of asbestos fiber that is used commercially.
  
- 2) Amphibole
  - a. Crocidolite- blue- straight fibers
  - b. Amosite- brown
  - c. Tremolite
  - d. Anthophyllite

### **Pathogenesis:**

Asbestos causes pulmonary fibrosis, mesothelioma and lung cancer by mechanisms that are not fully clear. The fiber toxicity is related to particle size, shape, dissolution, precipitation, ion exchange, acid-base catalysis and oxidation-reduction. Smaller the particle, further it can be transported to the respiratory tract. Particles with aerodynamic diameter of less than 5 $\mu$ m are likely to reach the lower respiratory tract and fibers >5 $\mu$ m elicit a constant local inflammatory response. After asbestos inhalation, alveolar epithelial cells and macrophages internalize the fibers, which results in oxidative stress to the lungs. The mechanisms underlying free radical generation by asbestos are in part related to the reactions occurring on the surface of the mineral dust, by activation of alveolar macrophages and neutrophils.

DNA damage and apoptosis are important down stream deleterious effects of reactive oxygen species (ROS). By mechanisms that are still uncertain mitochondrial ROS signaling from asbestos exposure stabilize p53 and promotes p53 dependent transcription of a variety of proteins involved in tumor suppression, cell cycle arrest, apoptosis and cell survival. Asbestos induced AEC intrinsic apoptosis is augmented by mitochondrial translocation of pro-apoptotic bcl-2 family members. Exuberant apoptosis results in pulmonary inflammation and fibrosis. Some of the putative mediators involved in inflammatory and fibrogenic responses to asbestos includes ROS, reactive nitrogen species, Transforming growth factor  $\alpha$  (TGF-  $\alpha$ ), Transforming growth factor  $\beta$

## Chapter 13

# Molecular and Genetic Aspects of Lung Cancer.

Sunita Saxena

Molecular alterations in lung cancer  
Oncogenic pathways  
Role of Microarray Technology in Lung Cancer

Lung cancer is one of the most common causes of cancer death in both men and women worldwide with 1.3 million new cases diagnosed every year. Nearly 70% of all new cases of lung cancer occur in developed countries, USA, Canada, New Zealand and Europe having the highest incidence. It accounts for the highest number, about 1,201 (17.1%), of cancer deaths in both men and women. In men it accounts for the highest (22.5%) cancer related deaths whereas in women it is second (10.4%) to the breast cancer (14.9%). Incidence of lung cancer is showing rising trend in India. It accounts for around 9.42% of total cancer cases among males and 2.55% cases among females. Around 80% of the patients come from rural areas. A history of active tobacco smoking is present in 87% of males and 85% of female lung cancer patients, showing smoking as the prime cause of the disease.

Although tobacco smoking is accepted as the number one cause of this devastating disease, our understanding of the acquired genetic changes leading to lung cancer is still rudimentary. Lung cancer is classified into two major clinico-pathological groups – Small cell lung carcinoma (SCLC) and Non Small cell lung carcinoma (NSCLC). Squamous cell carcinoma (SCC), adenocarcinoma (AD) and large cell carcinoma are the major histologic types of NSCLC. India does show its own variation in the sense that squamous cell carcinoma is the commonest histological type in contrast to Western countries where adenocarcinoma is more common, however cases of adenocarcinoma are being reported in Indian patients also. As with other epithelial malignancies, lung cancers are believed to arise from a series of progressive pathological changes (preneoplastic lesions). Many of these preneoplastic lesions are frequently detected in cells accompanying lung cancer and in the respiratory mucosa of smokers. Although many molecular abnormalities have been described in clinically evident cancers, relatively little is known about the molecular events preceding the development of lung cancer and the underlying genetic basis of tobacco related lung carcinogenesis.

Over the last decade, advances in molecular biology have provided important information about significant determinant of lung carcinogenesis. The molecular abnormalities include chromosomal aberrations, telomerase expression, expression of oncogenes and loss of tumor suppressor genes. Based on understanding of abnormalities at the cellular and molecular levels, new biomarkers can be identified, new therapies can be pursued.

# Chapter 14

## Pathology Of Silicosis

Jaishree Jagirdar

Introduction  
Mineralogy  
Acute Silicosis  
Chronic Silicosis  
Silicosis and Tuberculosis  
Silicosis and Lung Carcinoma  
Autoimmunity and Silicosis  
Amorphous Silicosis (Talcosis, Silicatosis)

## **Introduction**

Silicosis is the commonest occupational disease plaguing man and has been present for a long time. Hippocrates made one of the most astute observations in miners who had developed breathing difficulty and connected the breathing difficulty with the mining. At the turn of the 20<sup>th</sup> century an insurance company remarked that certain mine workers at the quarry had more sick days than other workers. The concern came to a head when the Hawk's Nest disaster came to light in 1930. The Hawk's Nest Tunnel project was a hydroelectric power project constructed by blasting into massive natural rock formations in the area of Gauley Bridge, West Virginia. Approximately 400 workers died as a result of heavy silica exposure. Stronger preventive measures were instituted. Despite this effort occupational exposure to silica continues. Recently, the Occupational Safety and Health Administration (OSHA) have reported that as many as two million American workers may be chronically exposed to crystalline silica. The good news according to Goldyn et al is that it is declining in the US. In India it is the top occupational hazard like in the US in terms of number of people exposed. However, the rate of exposure is increasing in India unlike the US.

Silicosis is a potentially fatal, irreversible, fibrotic pulmonary disease that could develop subsequent to the inhalation of large amounts of silica dust over time. Commonly, silicosis only develops subsequent to substantial occupational exposures. The disease has a long latency period and may clinically present as an acute, accelerated, or chronic disease.

The pathophysiology of chronic silicosis involves chronic inflammation arising as a result of the accumulation of various inflammatory mediators and fibrogenic factors. In acute pulmonary silicoproteinosis or pulmonary alveolar proteinosis (PAP) eosinophilic proteinaceous material accumulates in the pulmonary alveolar spaces after a massive but short exposure to silica. In Accelerated silicosis morphologic features of chronic silicosis may present within a few years of exposure. In chronic silicosis the exposure latency period is usually greater than 20 years. The rate of disease progression appears to depend upon the rate of silica deposition in the lungs, as well as the total amount of crystalline silica that is retained in the lung.

## **Mineralogy**

Free Silica comes in 2 forms: Amorphous and Crystalline. Freshly cut crystalline silica is the most fibrogenic. The earth's crust is full of silica.