Chapter 2

The Respiratory System and Its Response to Harmful Substances

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INTRODUCTION

People can live for days without food or water, but if they stop breathing, they die within minutes. The apparatus of breathing—the respiratory system—supplies a critical component of life, oxygen, and disposes of a major waste product, carbon dioxide. To supply the amount of oxygen required for survival, the respiratory system must be capable of handling between 10,000 and 20,000 liters of air per day.

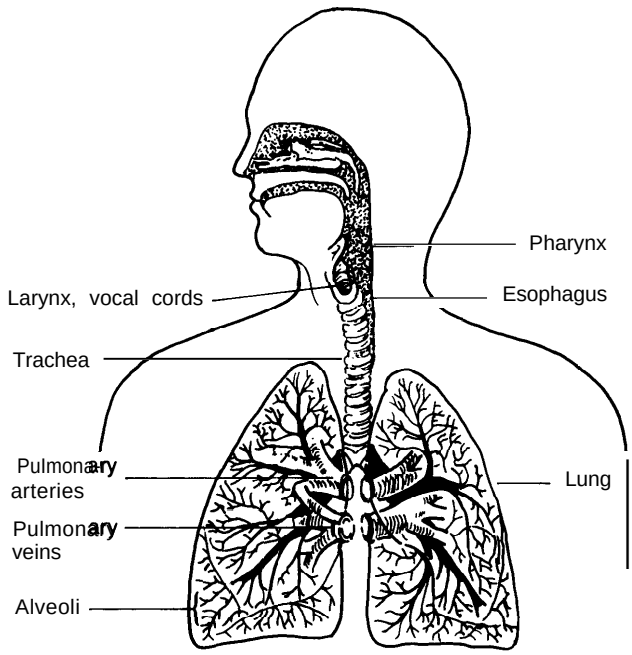
The air that enters the respiratory system contains many substances other than oxygen, including natural constituents (e.g., nitrogen) and human contributions (e.g., fossil fuel combustion byproducts). Various defense mechanisms of the respiratory system eliminate the unnatural components of air from the body and repair any damage they do. But exposure to large amounts of toxic substances or chronic exposure to lower levels can overwhelm the ability of the respiratory system to protect and repair itself, sometimes resulting in impaired lung function.

This chapter describes the structure and function of the respiratory system and some of the ways the respiratory system protects itself against harmful substances. It then briefly describes major diseases associated with exposure to toxic substances. This chapter does not cover the effects of exposure to radiation or infectious agents, nor does it describe lung cancer. More detailed descriptions of the respiratory system and respiratory diseases are presented elsewhere (7,13,26,28,29).

STRUCTURE AND FUNCTION OF THE RESPIRATORY SYSTEM

Air enters the body through the nose and mouth and moves through the major airways to deeper portions of the lungs (figure 2-l). There oxygen can pass across thin membranes to the bloodstream. Each region of the respiratory system is made of specialized cells that work together to transport air, keep the lung clean, defend it against harmful or infectious agents,

Figure 2-l—The Human Respiratory Tract



SOURCE: Office of Technology Assessment, 1992.

and provide a thin, large surface for the exchange of oxygen and carbon dioxide.

Upper Respiratory Tract

The upper airways begin at the nose and mouth and extend through the pharynx to the larynx. This nasophoryngeal region is lined with ciliated cells and mucous membranes that warm and humidify the air and remove some particles. Gases that are very water soluble are also absorbed readily by the mucus in this part of the respiratory tract, protecting the more delicate tissues deeper in the respiratory tract from the effects of exposure to such gases.

The Tracheobronchial Tree

After passing through the larynx, air flows through the trachea, or windpipe. The trachea divides into two

bronchi which carry air into the two lungs. The bronchi subdivide repeatedly into smaller and smaller bronchi and then into bronchioles, which also successively divide and narrow (figure 2-2). The smallest bronchioles, found at the end of the tracheobronchial region, are less than a millimeter in diameter.

The Pulmonary Region

In the pulmonary region, the bronchioles divide into alveolar ducts and alveolar sacs. Budding from the walls of these last portions of the airways are tiny, cup-like chambers called alveoli (figure 2-3). The alveoli are only one-quarter of a millimeter in diameter (just *barely* visible to the unaided eye) and have extremely thin walls. Their outer surface is covered by a dense network of fine blood vessels, or capillaries. Gas exchange occurs when oxygen diffuses from the space inside an alveolus through its lining fluid, past the alveolar membrane and its supporting membrane, through the space between the alveolus and the capillary ("the interstitial space"), and finally across the membranes of the capillary. Carbon dioxide diffuses in the opposite direction, from the red blood cells in the capillaries to the space inside the alveolus (figure 2-4).

Figure 2-2—Branching of the Tracheobronchial Region (Human Lung Cast)

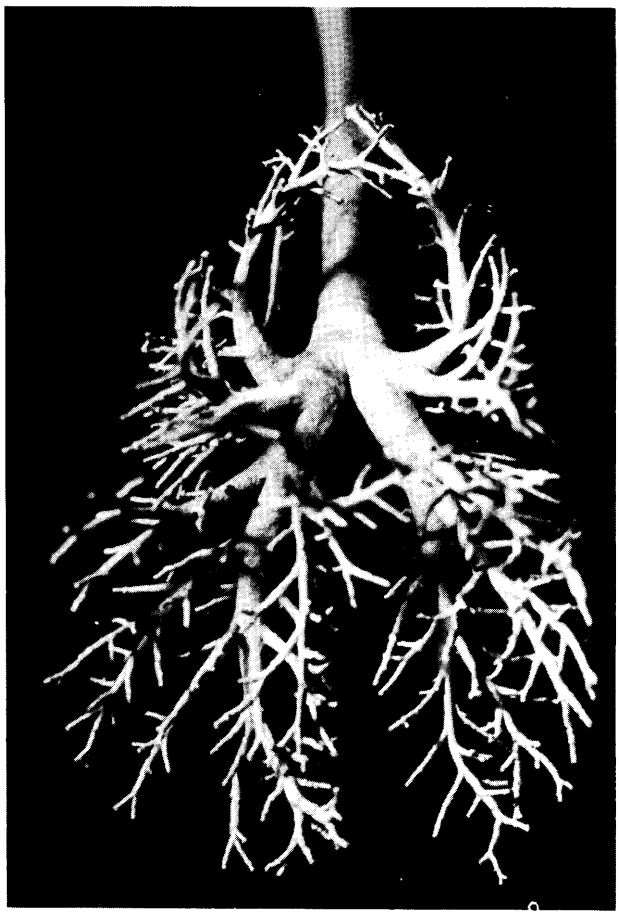
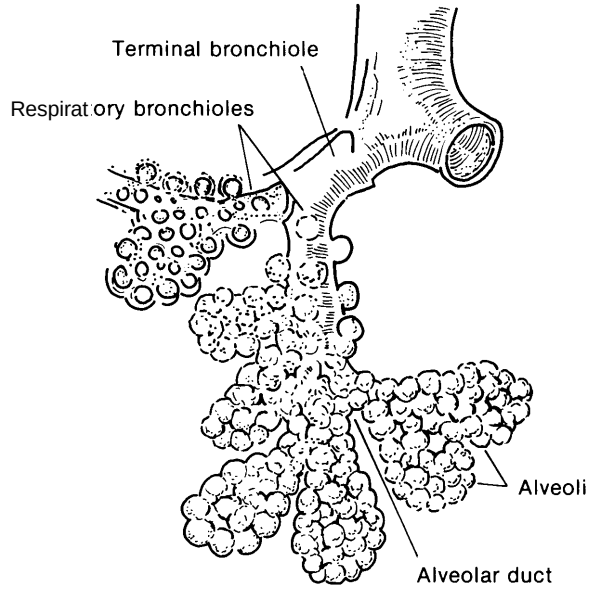


Photo credit: D. Costa, Environmental Protection Agency

Figure 2-3—Alveoli



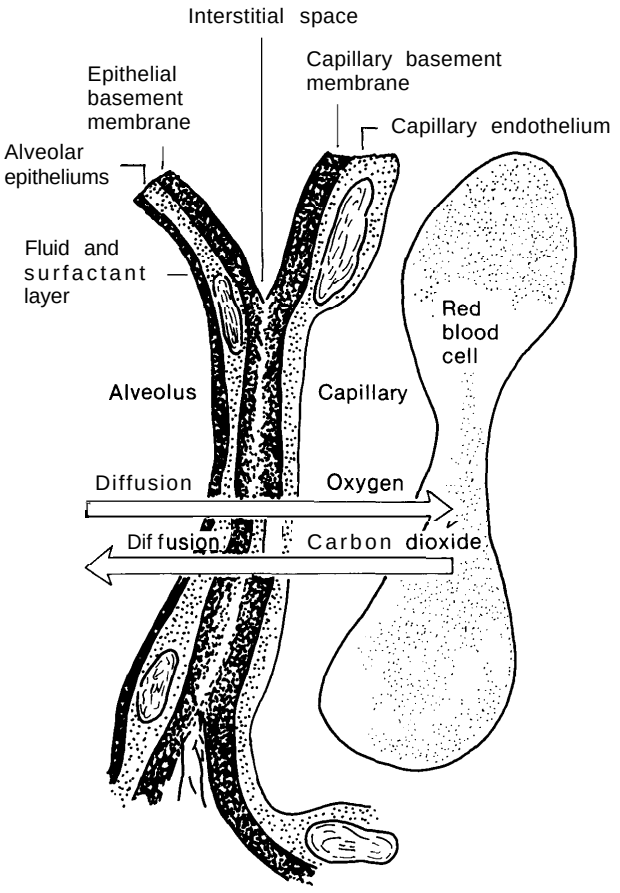
SOURCE: Office of Technology Assessment, 1992.

The adult human lung contains approximately 300 million alveoli. Taken together, the alveoli give the human lung a huge internal surface, about 70 square meters. This large area allows for enough oxygen to diffuse into the blood to supply the body's needs, but it also exposes a very large, thin-walled area, about the size of a single tennis court, to toxic substances inhaled in the air.

The Pulmonary Circulation

Oxygen diffuses from the alveoli into the blood in the capillaries. Red blood cells contain a specialized protein, hemoglobin, which can reversibly bind molecules of oxygen. The heart pumps the blood to the rest of the body. Deep within the tissues, the oxygen is released to be used by cells in generating energy. As the body's cells use oxygen, they produce carbon dioxide. Veins carry blood from body tissues back to the right side of the heart, which pumps blood to the pulmonary capillaries to be oxygenated again. Carbon dioxide diffuses from the capillaries into the alveoli and is exhaled.

Figure 2-4--Gas Exchange in the Pulmonary Region



SOURCE: Office of Technology Assessment, 1992.

The Pleural Cavity

The lungs are contained within the chest cavity, but are not attached to the wall of the chest. The pleural space that separates the lungs from the chest wall contains a small amount of fluid and is bounded by membranes called the pleura. This arrangement allows the lungs to move freely in the chest, permitting full expansion.

During inhalation, the muscles in the rib cage and the diaphragm, a dome-shaped muscle beneath the lungs, contract. As the diaphragm contracts, it flattens, increasing the space in the chest. The ribs lift, further increasing the space for the lungs to expand. As the chest expands, the pressure within the lungs falls below atmospheric pressure, and air is drawn into the lungs, inflating them. As the muscles relax, air is exhaled, and the lungs deflate. The rate of respiration changes in response to physical and mental conditions, such as sleep, exercise, or changes in altitude.

Cells of the Respiratory System

The respiratory system contains over 40 different types of cells. Each cell type performs function important for efficient gas exchange.

A continuous sheet of cells forms a membrane, called the epitheliums, lining the airways. Healthy epithelium contains few or no gaps, so water, ions, or other substances that cross the epitheliums must pass through cells. The specific permeability properties of the cells control the rate at which substances, such as inhaled pollutants, cross the epitheliums.

Interspersed among the cells that make up the surface of the lining of the airways area variety of secretory cells. These secrete mucus which traps dust and other particles. Most of the cells of the epitheliums have microscopic hair-like structures on their surface called cilia (figure 2-5). The cilia beat rhythmically, brushing the mucus and particles trapped in it up to the pharynx where they are usually swallowed unnoticed and pass out of the body through the digestive system.

Different types of cells make up the lining of the alveoli. The area of the lining consists primarily of Type I cells, which are very thin and spread over a relatively large area. The lining also includes the Type II cells. Type II cells are more numerous, but because of their more rounded shape, they make up only about 7 percent of the area of the lining of the aveoli. The Type II cells release proteins and lipids that provide a thin, fluid lining for the inside of the alveoli. The fluid protects the delicate Type I cells and reduces the surface tension in the alveoli, preventing collapse of the alveoli under pressure.

The alveoli also contain macrophages, specialized defense cells that move freely over the surface of an alveolus (figure 2-5). Macrophages ingest foreign particles by a process called phagocytosis. During phagocytosis, a microphage extends flaps to form a membrane-bound pocket around a foreign body. The microphage releases enzymes into the pocket that can break down many foreign particles, especially organic materials. The breakdown products may be released or absorbed by the cell. Foreign matter that is not organic often cannot be broken down and may remain stored

Figure 2-5—Ciliated Cells and Alveolar Macrophages

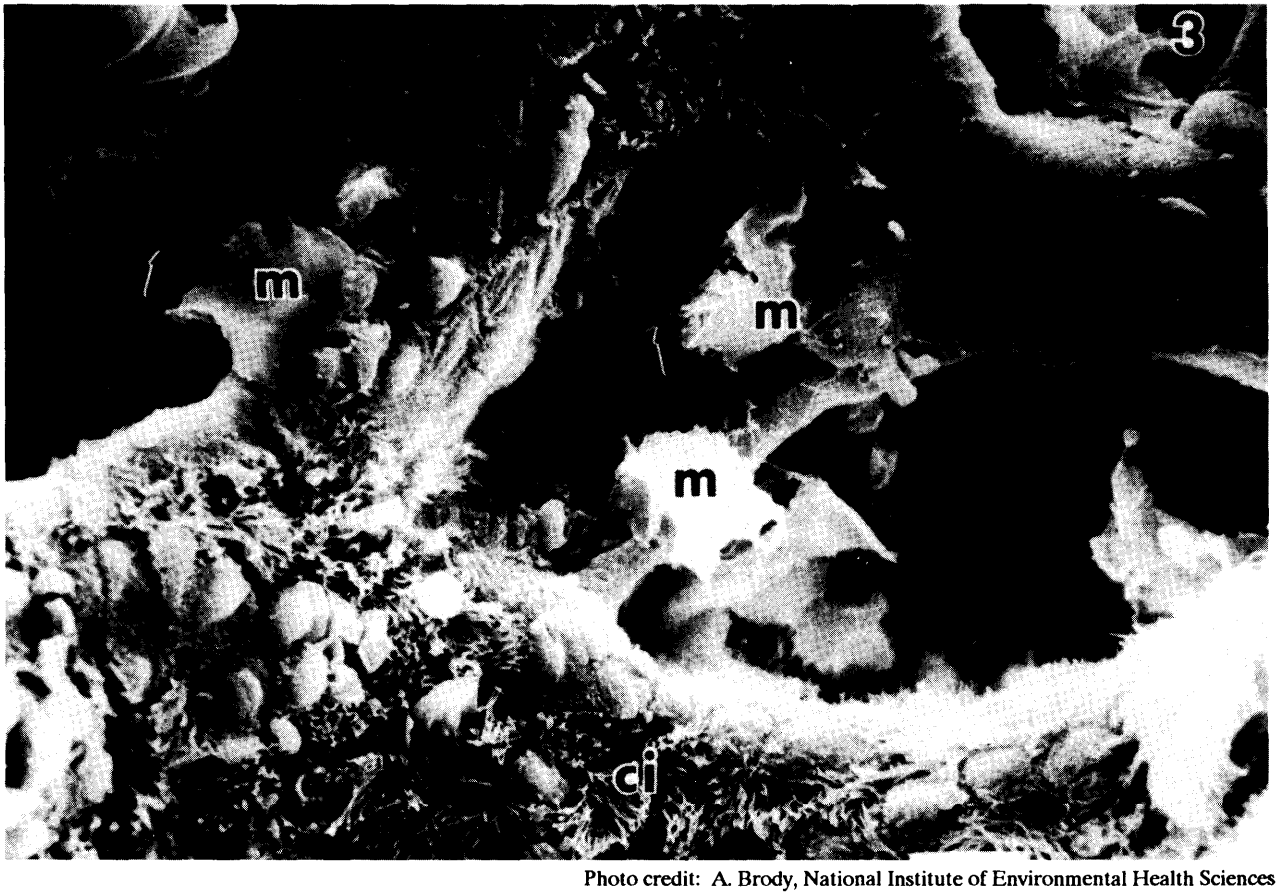


Photo credit: A. Brody, National Institute of Environmental Health Sciences

This photograph shows ciliated cells (ci) and alveolar macrophages (m) at the bronchiolar- alveolar duct junction. The arrows mark the presence of asbestos fibers.

in intracellular compartments. In addition to phagocytosis of foreign substances, macrophages also play important roles in immune responses in the lung.

The capillaries that surround the alveoli are also lined by a continuous sheet of cells, the endothelium. Unlike the lining of the airways, the endothelial lining of the capillaries is slightly leaky, allowing some exchange of water and solutes between the blood and the interstitial fluid.

The interstitial space, the small area separating alveoli from surrounding capillaries, contains cells of the immune system. It also contains fibroblasts, cells that produce fibers of collagen and elastin that form an elaborate network to provide a mechanical support system for the lung. Collagen fibers are very strong but cannot stretch much; elastin fibers are not as strong but can be stretched considerably before breaking. These collagen and elastin fibers are slowly but continually broken down and renewed.

Smooth muscle cells occur as circular sleeves surrounding the bronchi and bronchioles. They dilate when the body needs large volumes of air, for example, during exercise. When these muscles contract, as on exposure to irritant gases, they make the conducting airways narrower, increasing resistance to air flow. Smooth muscle cells also surround blood vessels that enter the lung. They control the distribution of blood flow to specific alveoli and determine how hard the right side of the heart must work to pump blood through the pulmonary blood vessels.

Defense Mechanisms

The respiratory system has elaborate defense mechanisms against damage from exposure to potentially hazardous particles and gases (table 2-l). Particles of 1-2 micrometers are the optimal size for reaching the alveoli. Relatively large particles get trapped in nasal hairs and never enter the lower respiratory tract, or they are removed by coughing or sneezing. Somewhat smaller particles (down to about 2 micrometers) enter the trachea but land on the airway surfaces and stick to the surface mucus. The finest particles settle less efficiently and are usually exhaled (19).

In the alveoli, some material may dissolve and be absorbed into the bloodstream or interstitial fluid. Particles that do not dissolve may be phagocytized by macrophages and the phagocytic cells are either swept up the tracheobronchial tree on the mucous blanket or they migrate to the interstitial fluid. Some insoluble particles may remain sequestered in the lung.

The immune system also plays an important role in protecting the lungs. A detailed description is beyond the scope of this background paper, but OTA has previously addressed immune system responses to toxic substances (23). Briefly, exposure to many substances, particularly those containing protein of animal or vegetable origin, sensitizes cells of the immune system. The cells respond with a complex variety of reactions to destroy or immobilize the inhaled substance. These processes, however, are often accompanied by inflammation of the surrounding tissues, which is part of the repair process necessary to restore normal function. Repeated exposure and inflammation is thought to result in serious and permanent tissue damage.

RESPIRATORY RESPONSE TO HARMFUL SUBSTANCES

When defenses are overcome or an agent is particularly toxic, the respiratory system can be injured. Damage occurs when defense and repair mechanisms cannot keep pace with damage wrought by acute exposures to relatively large amounts of harmful substances or by chronic exposures to small amounts of harmful substances. Some damage may result from the repair process itself. Some of the most common and best understood conditions are described here, excluding cancer, which is not being considered in this background paper.

Chronic Bronchitis

People with chronic bronchitis have increased numbers of secretory cells in the bronchial tree. They produce an excess of mucus and have a recurrent or chronic cough, familiar to many as “smoker’s cough.” This excess secretion of mucus may lead to impairment of normal clearance mechanisms. The normal ciliary movement cannot cope with this large volume of mucus, and consequently, it takes longer for particles to

Table 2-l—Respiratory Tract Clearance Mechanisms

Upper respiratory tract	Tracheobronchial tree	Pulmonary region
Mucociliary transport	Mucociliary transport	Microphage transport
Sneezing	Coughing	Interstitial pathways
Nose wiping and blowing	Dissolution (for soluble particles)	Dissolution (for soluble and “insoluble” particles)
Dissolution (for soluble particles)		

SOURCE: R.B. Schlesinger, “Biological Disposition of Airborne Particles: Basic Principles and Application to Vehicular Emissions,” *Air Pollution, the Automobile, and Public Health,* A.Y. Watson (cd.) (Washington, DC: National Academy Press, 1988).

be removed from the lungs of patients with chronic bronchitis than it does in healthy people. This reduced clearance makes people with chronic bronchitis more susceptible to respirator infections because bacteria entering the respiratory tract are not removed efficiently.

Almost 12 million people in the United States suffer from chronic bronchitis (l). The epidemiologic evidence linking smoking and chronic bronchitis is overwhelming (10,24). Epidemiologic studies have also shown a correlation between chronic bronchitis and exposure to industrial dust (5,15). In addition, recurrent infections may play a role in the development of chronic bronchitis (4,6). In industrialized urban areas, periods of heavy pollution with sulfur dioxide and particulate have shown a correlation with increased symptoms of chronic bronchitis or mortality due to chronic bronchitis (13,21,22,27).

Emphysema

The lung is supported by a network of protein fibers made of collagen and elastin. In people with emphysema, some of these fibers are lost and the structural network is disrupted. The fiber network in the damaged area becomes rearranged, resulting in destruction of the walls of the alveoli. The air spaces become enlarged, and part of the surface area available for gas exchange is lost (figure 2-6). Less force is needed to

Figure 2-6—Effects of Emphysema on Alveolar Walls

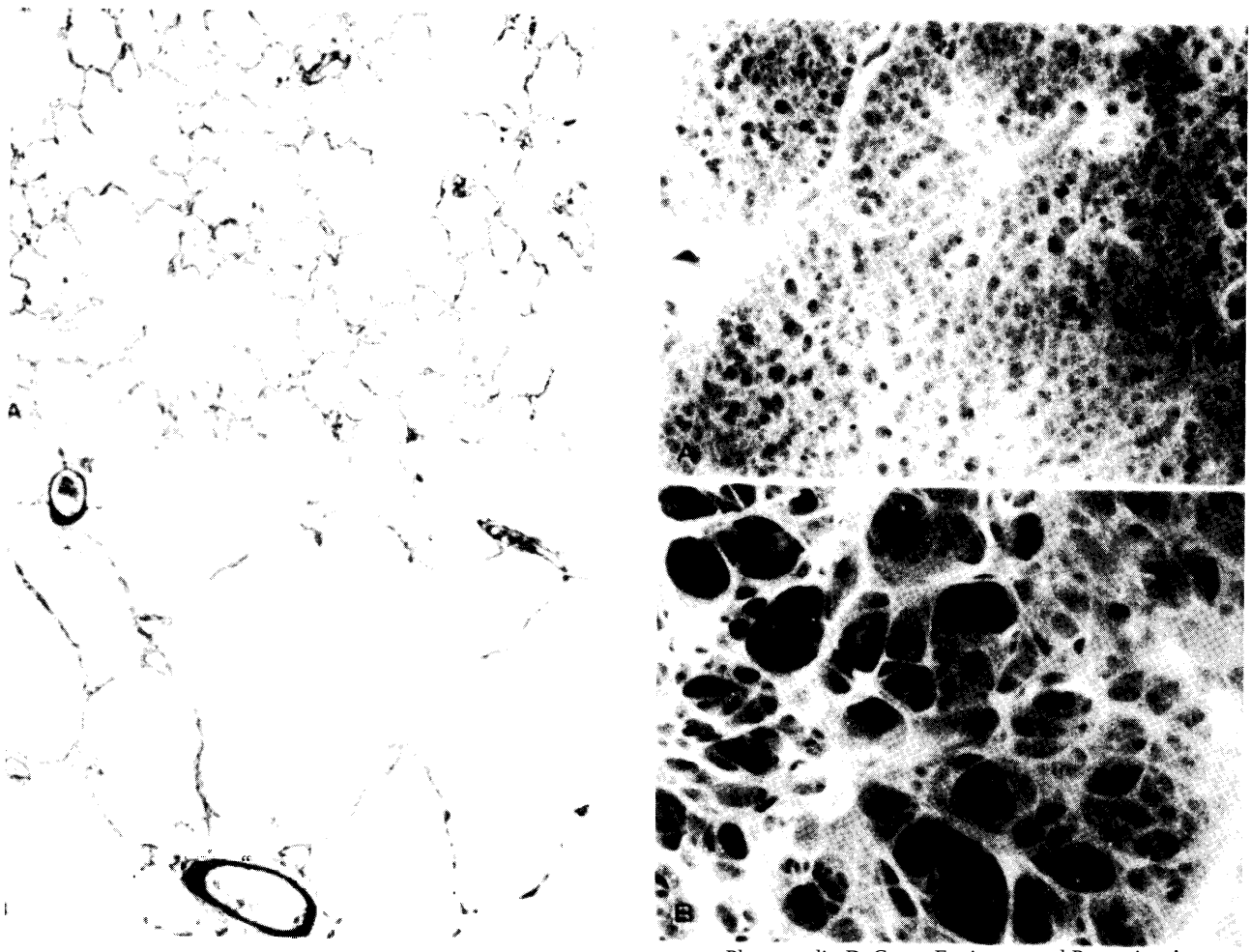


Photo credit: D. Costa, Environmental Protection Agency

The top photo in each column shows normal lung tissue while the bottom photos show destruction of the walls of the alveoli due to emphysema.

expand the lung, but air may remain trapped in the lung during exhalation because its ability to recoil is impaired.

Nearly 2 million Americans, mostly adults overage 45, have emphysema (l). Emphysema usually develops gradually. Impairment progresses steadily and includes labored breathing and wheezing. It frequently occurs along with chronic bronchitis.

There is a strong correlation between emphysema and heavy cigarette smoking (2). Industrial exposure to cadmium is also associated with emphysema (8). Some people have a genetic predisposition to the development of emphysema. In particular, people who have an inherited deficiency in the amount of a serum protein called alpha$_1$-antitrypsin are more likely to develop emphysema (14,31), especially if they smoke.

Byssinosis

Textile workers exposed to cotton, hemp, flax, and sisal dusts for several years may develop acute symptoms, such as chest tightness, wheezing, and cough. After long-term exposure, they may develop chronic symptoms of respiratory disease indistinguishable from chronic bronchitis but called byssinosis. Bronchoconstriction in this disease is not the result of an allergic response. It is apparently caused by a substance ("a histamine releasing agent") found, for example, in cotton seeds that are present as contaminants in raw cotton fiber.

Asthma

Asthma is a chronic disease of the airways in which symptoms appear intermittently. In healthy people, the smooth muscle surrounding the airways responds to strong environmental stimuli by contracting, increasing the resistance to airflow. Patients with asthma develop more intense constriction of the smooth muscle in response to milder stimuli than do healthy people. The reasons for this response are unclear. Inflammation is usually present, and is thought to play a key role in the disease. In addition to bronchial hyper-responsiveness, people with asthma have intermittent symptoms of wheezing, chest tightening, or cough.

The disease varies from individual to individual not only in its severity, but in the types of agents that provoke an attack. Some people develop symptoms

Table 2-2-Causes of Occupational Asthma

Complex salts of platinum
Ammonium hexachloroplatinate
Isocyanates
Toluene di-isocyanate; hexamethylene di-isocyanate; naphthalene di-isocyanate
Epoxy resin curing agents
Phthalic acid anhydride; trimellitic acid anyhydride; triethylene tetramine
Colophony fumes
Proteolytic enzymes
Bacillus subtilis (alkalase)
Laboratory animal urine
Rats, mice, guinea pigs, rabbits, locusts
Flour and grain dusts
Barley, oats, rye, wheat
Formaldehyde
Antibiotics
Penicillin
Wood dusts
South African boxwood *(Gonioma kamassi):* Canadian red cedar *(Thuja plicata);* Mansonia *(Sterculiacea altissima)*
Natural gums
Gum acacia, **gum** arabic, tragacanth

SOURCE: D.J. Weatherall, J.G.G. Ledingham, and D.A. Warren (eds.), Oxford Textbook of Medicine (New York, NY: Oxford University Press, 1987).

1 Emphysema and chronic bronchitis are two distinct processes. Emphysema, however, can only be diagnosed definitively after death, by direct examination of lung tissue. Incidence data are derived from postmortem surveys. These surveys show that almost all adult lungs have some signs of emphysema, although only a minority of adults have symptoms or disability. Clinicians and epidemiologists dealing with the living use the synonymous terms chronic obstructive pulmonary disease (COPD), chronic obstructive airway disease (COAD), and chronic obstructive lung disease (COLD) to describe patients whose airflow is limited as a result of bronchitis, emphysema, or a combination of the two.

only in response to one stimulus. In the United States, for example, many people with asthma develop symptoms only during the ragweed pollen season in late summer. Others have clear responses to particular occupational agents (table 2-2). But other patients respond to many substances. Even the mechanisms of the disease vary among individuals. In some people with asthma, the response seems to occur through an immunologic reaction, but in other people, the immune system does not seem to be involved in the response. Other mechanisms are the subject of active research. It may be that asthma is a family of diseases with similar symptoms but different underlying causes and mechanisms.

In the United States, about 11.5 million people have asthma (l). Children, African-Americans, and inner city residents are affected disproportionately (11). Both the prevalence and the severity of asthma in the United States have been increasing in recent years (12,30).

Although its causes are not precisely known, over 200 substances have been identified that can induce symptoms (16). In addition, attacks can be provoked by exercise, cold air, airway drying, infections, and emotional upsets. Sulfur dioxide, a component of air pollution, causes severe narrowing of asthmatic airways at concentrations as low as 0.5 parts per million (3,20). Exposure to respirable particles has been associated with reduced lung function and increased symptoms in asthmatic children (18), increased hospital visits (17) and increased rates of acute bronchitis, particularly in asthmatic children (9).

Pulmonary Fibrosis

Pulmonary fibrosis is a family of related disorders characterized by scar tissue in the lungs. Chronic injury and inflammation can result in the formation of scar tissue in the lung, similar to the process of normal wound-healing. In pulmonary fibrosis, however, the wounding and formation of scar tissue is not a specific event in a specific location. Rather it can be a chronic, continuing process that involves the entire lung or there may be scattered, nonuniform scarring. People with pulmonary fibrosis must work harder to breathe, have poor gas exchange, and often have a dry cough.

The inflammatory response of the lung varies depending on the substance causing the injury. In many cases, causative agents are clearly established. Pulmonary fibrosis is known to be caused by exposure to high concentrations of silica, asbestos, and other dusts (table 2-3).

Extrinsic Allergic Alveolitis

Workers sometimes develop severe immune responses to substances in the workplace, particularly to inhaled plant and animal dusts. The disease is easy to recognize in its acute form because workers themselves quickly learn to associate the flu-like symptoms with dust exposure. The chronic form, which seems to occur in response to low-level chronic exposures to dusts rather than high-level exposures, is more insidious. The chronic form of the disease usually progresses very slowly, but can result in pulmonary fibrosis.

Many causative agents have been identified. Most are molds or fungi contaminating organic material, or they are proteins found in animal or bird droppings. The best known form is probably farmers' lung, which is caused by allergies to ***Micropolyspora faeni,*** found in moldy hay, straw, and grain. There are many other examples, however, including bird fanciers' lung, associated with proteins found in parakeet and pigeon droppings; dog house disease, associated with a mold found in straw dog bedding; paprika splitters' lung, associated with a mold found in paprika; and maple bark strippers' lung, also associated with a mold.

LUNG DISEASE AND EXPOSURE TO **TOXIC SUBSTANCES**

The Federal Government, as described further in chapter 4, funds research in pulmonary diseases. Some research is aimed at understanding the mechanisms by which a particular substance damages the respiratory system. Often, this knowledge can provide insight into the mechanisms by which other toxic substances cause damage. Many toxic substances cause similar reactions in the respiratory system simply because the respiratory system has a limited range of responses to insults. Asthmatic attacks, for example, are induced by a wide variety of substances, and, similarly, many substances cause pulmonary fibrosis. Careful study of the effect of

Table 2-3—Industrial Toxicants Producing Lung Disease

Toxicant	Common name of disease	Occupational source	Chronic effect	Acute effect
Asbestos	Asbestosis	Mining, construction, shipbuilding, manufacture of asbestos-containing material		Fibrosis, pleural calcification, lung cancer, pleural mesothelioma
Aluminum dust	Aluminosis	Manufacture of aluminum products, fireworks, ceramics, paints, electrical goods, abrasives	Cough, shortness of breath	Interstitial fibrosis
Aluminum abrasives	Shaver's disease, corundum smelter's lung, bauxite lung	Manufacture of abrasives, sives, smelting	Alveolar edema	Interstitial fibrosis, emphysema
Ammonia		Ammonia production, manufacture of fertilizers, chemical production, explosives	Upper and lower respiratory tract irritation, edema	Chronic bronchitis
Arsenic		Manufacture of pesticides, pigments, glass alloys	Bronchitis	Lung cancer, bronchitis, laryngitis
Beryllium	Berylliosis	Ore extraction, manufacture of alloys, ceramics	Severe pulmonary edema, pneumonia	Fibrosis, progressive dyspnea, interstitial granulomatosis, cor pulmonale
Cadmium oxide		Welding, manufacture of electrical equipment, alloys, pigments, smelting	Cough, pneumonia	Emphysema, cor pulmonale
Carbides of tungsten, titanium, tantalum	Hard metal disease	Manufacture of cutting edges on tools	Hyperplasia and metaplasia of bronchial epitheliums	Peribronchical and perivascular fibrosis
Chlorine		Manufacture of pulp and paper, plastics, chlorinated chemicals	Cough, hemoptysis, dyspnea, tracheobronchitis, bronchopneumonia	
Chromium (VI)		Production of Cr compounds, paint pigments, reduction of chromite ore	Nasal irritation, bronchitis	Lung cancer fibrosis
Coal dust	Pneumoconiosis	Coal mining		Fibrosis
Cotton dust	Byssinosis	Manufacture of textiles	Chest tightness, wheezing, dyspnea	Reduced pulmonary function, chronic bronchitis
Hydrogen fluoride		Manufacture of chemicals, photographic film, solvents, plastics	Respiratory irritation, hemorrhagic pulmonary edema	

Table 2-3—Industrial Toxicants Producing Lung Disease (Cent'd)

Toxicant	Common name of disease	Occupational source	Chronic effect	Acute effect
Iron oxides	Siderotic lung disease; silver finisher's lung, hematite miner's lung, arc welder's lung	Welding, foundry work, steel manufacture, hematite mining, jewelry making	Cough	Silver finisher's: subpleural and perivascular aggregations of macrophages; hematite miner's: diffuse fibrosis-like pneumonconiosis; arc welder's; bronchitis
Isocyanates		Manufacture of plastics, chemical industry	Airway irritation, cough, dyspnea	Asthma, reduced pulmonary function
Kaolin	Kaolinosis	Pottery making		Fibrosis
Manganese	Manganese pneumonia	Chemical and metal industries	Acute pneumonia, often fatal	Recurrent pneumonia
Nickel		Nickel ore extraction, smelting, electronic electroplating, fossil fuels,	Pulmonary edema, delayed by 2 days (NiCO)	Squamous cell carcinoma of nasal cavity and lung
Oxides of nitrogen		Welding, silo filling, explosive manufacture	Pulmonary congestion and edema	
Ozone		Welding, bleaching flour, deodorizing	Pulmonary edema	Emphysema
Phosgene		Production of plastics, pesticides, chemicals	Edema	Bronchitis
Perchloroethylene		Dry cleaning, metal decreasing, grain fumigating	Edema	
Silica	Silicosis, pneumoconioi-sis	Mining, stone cutting, construction, farming, quarrying		Fibrosis
Sulfur dioxide		Manufacture of chemicals, refrigerant ion, bleaching, fumigation	Bronchoconstriction, cough, chest tightness	
Talc	Talcosis	Rubber industry, cosmetics		Fibrosis
Tin	Stanosis	Mining, processing of tin		Widespread mottling of x-ray without clinical signs
Vanadium		Steel manufacture	Airway irritation and mucus production	Chronic bronchitis

SOURCE: T. Gordon, and M.O. Amdur " Responses of the Respiratory System to Toxic Agents, "*Casarett and Doull's Toxicology." The Basic Science of Poisons,* M.O. Amdur, I. Doull and C.D. Klassen, (cd.) (New York, NY: Pergamon Press, 1991).

one substance helps researchers to understand the effects of other substances.

Other research is aimed at identifying which substances cause the development of disease, what levels of exposure are harmful, and why responses to toxicants differ among subgroups of the population (25). Identifying specific causes of respiratory diseases is no simple matter because different substances can cause similar kinds of damage, and, conversely, one substance can cause several kinds of damage. It is easier to establish causal relationships when a defined population exposed to high levels of a particular substance exhibits characteristic symptoms or changes in respiratory function. Dozens of examples among occupational groups illustrate how high-level exposures have allowed identification of many causes of occupational asthma, pulmonary fibrosis, and extrinsic allergic alveolitis (table 2-3).

It is more difficult to determine the effects of substances to which many people are exposed at much lower levels than the heavy occupational exposures. Five major components of air pollution, carbon monoxide, sulfur oxides, hydrocarbons, particulate, and oxidants, are widely distributed in varying concentrations throughout the United States. No single, well-defined group is exposed to any one of these at exceptionally high levels; instead virtually everyone is exposed at some level. Large proportions of the population are also exposed to varying concentrations of common indoor air pollutants such as environmental tobacco smoke; nitrogen oxides (from gas stoves); woodsmoke; allergens of the house dust mite, cats, rodents, and cockroaches; and formaldehyde and other volatile organic compounds. Sorting out particular effects of each of these substances is quite different from identifying the cause of bird fanciers' lung or maple bark strippers' lung. The high background level of respiratory disease in the population at large also makes pinpointing particular causal agents more difficult. The kinds of tests and studies aimed at elucidating the relationships between respiratory diseases and exposure to indoor and outdoor air pollutants are explored in the next chapter.

CHAPTER 2 REFERENCES

1. Adams, P. F., and Benson, V., ***Current Estimates From the National Health Interview Survey, 1989,*** National Center for Health Statistics, Vital Health Stat. 10(176), 1990.
2. Auerbach, O., Hammond, E. C., Garfinkel, L., et al., "Relation of Smoking and Age to Emphysema: Whole-Lung Section Study," ***New England Journal of Medicine*** 286:853-857, ***1972.***
3. Balmes, J. R., Fine, J. M., and Sheppard, D., "Symptomatic Bronchoconstriction After Short-term Inhalation of Sulfur Dioxide, "American ***Review of Respiratory Disease*** 136:1117-1121,1987.
4. Barker, D.J.P., and Osmond, C., "Childhood Respiratory Infection and Adult Chronic Bronchitis in England and Wales," ***British Medical Journal*** 293:1271-1275, ***1986.***
5. Becklake, M. R., "Chronic Airflow Limitation: Its Relationship to Work in Dusty Occupations," ***Chest*** 88:608-17, 1985.
6. Coney, J.R.T., Douglas, J. W. B., and Reid, D.D., "Respiratory Disease in Young Adults: Influence of Early Childhood Respiratory Tract Illness, Social Class, Air Pollution and Smoking," ***British Medical Journal*** 3:195-198, ***1973.***
7. Crystal, R. G., West, J. B., Barnes, P.J., et al., (eds.), ***The Lung: Scientific Foundations*** (New York NY: Raven Press, 1991).
8. Davison, A. G., Newman Taylor, A.J., Derbyshire, J., et al., "Cadmium Fume Inhalation and Emphysema," ***The Lancet*** Mar. 26, 1988, pp. 663-667.
9. Dockery, D. W., Speizer, F. E., Strain, D. O., et al., "Effects of Inhalable Particles on Respiratory Health of Children, ''American ***Review of Respiratory Disease*** 139(3):587-594, March 1989.
10. Doll, R., and Pete, R., "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," ***British Medical Journal*** 2:1525-1536, ***1976.***
11. Evans, R., Mullally, D. I., Wilson, R. W., et al., 'National Trends in the Morbidity and Mortality of Asthma in the U.S.," ***Chest*** 91(suppl. 6):65S-74S, 1987.
12. Gergen, P. J., and Weiss, KB., "Changing Patterns of Asthma Hospitalization Among Children: 1979- 1987," ***Journal of the American Medical Association*** 264:1688-1692,1990.
13. Gordon, T., and Amdur, M.O. "Responses of the Respiratory System to Toxic Agents," ***Casarett and Doull's Toxicology: The Basic Science of Poisons*** M.O. Amdur et al. (eds.) (New York, NY: Pergamon Press, 1991).
14. Mittman, C., "Summary of Symposium of Pulmonary Emphysema and Proteolysis," American ***Review of Respiratory Disease*** 105:430-448, ***1972.***
15. Morgan, W.KC., 'Industrial Bronchitis," ***British Journal of Industrial Medicine*** 35:285-91, ***1978.***
16. Newman Taylor, A.J., 'Occupational Asthma," ***Thorax*** 35:241-245, ***1980.***

17. Pope, C.& III, "Respiratory Hospital Admissions Associated With PM_{10} Pollution in Utah, Salt Lake, and Cache Valleys," Archives *of Environmental Health* 46(2):90-97, March/April 1991.
18. Pope, C.A. III, Dockery, D.W., Spengler, J.D., et al., "Respiratory Health and PM_{10} Pollution: A Daily Time Series Analysis," *American Review of Respiratory Disease* 144(3 Pt. 1)668-674, 1991.
19. Schlesinger, R.B., "Biological Disposition of Airborne Particles: Basic Principles and Application to Vehicular Emissions," Air *Pollution, the Automobile, and Public Health,* A.Y. Watson, et al. (eds.) (Washington, DC: National Academy Press, 1988).
20. Sheppard, D., Saisho, A., Nadel, J.A., et al., "Exercise Increases Sulfur Dioxide-Induced Bronchoconstriction in Asthmatic Subjects," *American Review of Respiratory Disease 123Y186-491, 1981.*
21. Sherrill, D. L., Lebowitz, and Burrows, B., "Epidemiology of Chronic Obstructive Pulmonary Disease," *Clinics in Chest Medicine* 11:375-387,1990.
22. Speizer, F., 'Studies of Acid Aerosols in Six Cities and in a New Multi-city Investigation: Design Issues," *Environmental Health Perspectives 79:61-68, 1989.*
23. U.S. Congress, Office of Technology Assessment, *Identifying and Controlling Immunotoxic Substances-Background Paper, OTA- BP-* BA-75 (Washington, DC: U.S. Government Printing Office, April 1991).
24. U.S. Department of Health and Human Services, *The Health Consequences of Smoking. Chronic Obstructive Airways Disease: A Report of the Surgeon General,* U.S. Department of Health and Human Services, Public Health Service, Office on Smoking and Health, 1984.
25. Utell, M.J., and Frank, R. (eds.), *Susceptibility to Inhaled Pollutants, ASTM STP 1024,* (Philadelphia, PA: American Society for Testing and Materials, 1989).
26. Utell, M.J., and Samet, J. M., "Environmentally Mediated Disorders of the Respiratory Tract," *Medical Clinics of North America* 74(2):291-306, 1990.
27. Wailer, R. E., "Atmospheric Pollution," *Chest* 96(3):363S-368S, 1989.
28. Weatherall, D.J., Ledingham, J. G. G., and Warrell, D.A. (eds.), *Oxford Textbook of Medicine (New* York, NY: Oxford University Press, 1987).
29. Weibel, E. R., *The Pathway for Oxygen: Structure and Function in the Mammalian Respiratory System* (Cambridge, MA: Harvard University Press, 1984).
30. Weiss, KB., and Wagener, D.K., "Changing Patterns of Asthma Mortality," *Journal of the American Medical Association* 264:1683-1687,1990.
31. Welch, M. H., Guenter, C.A., Hammerstein, J.F., "Precocious Emphysema and $alpha_1$-Antitrypsin Deficiency," *Advances in Internal Medicine 17:379-92,* 1971.