SECTION X

HEART DISEASE—COR PULMONALE

HEART DISEASE, COR PULMONALE

Richard L. Naeye

INTRODUCTION INCLUDING DEFINITIONS

Cor pulmonale is defined as heart failure caused by lung disease. The right ventricle of the heart malfunctions due to pulmonary arterial hypertension. Increased pulmonary vascular resistance resulting in pulmonary arterial hypertension may be caused by anatomic or vasomotor narrowing of small arteries and arterioles or both. A variety of occupational agents can produce pulmonary vascular abnormalities and cor pulmonale. Each will be considered. Despite their variety, there are only a limited number of ways in which pulmonary blood vessels can react to noxious stimuli. Knowledge of these response patterns will explicate cor pulmonale in individual occupational disorders—particularly its diagnosis, clinical features, reversibility, and prevention.

There may be important interactions between occupational and nonoccupational agents that affect pulmonary vessels. These interactions will be discussed together with genetic factors that likely affect pulmonary vascular resistance in occupational lung disease. Pulmonary vascular abnormalities in occupational lung disease usually affect the heart by increasing the pressure load on the right ventricle. Factors that may affect the reaction of the heart to this pressure load are also to be considered.

In adults, about half of normal pulmonary vascular resistance is located in the pulmonary arteries, one third in the capillaries, and the remainder in the pulmonary veins (5). This differs from systemic circulation distribution where most of the resistance lies in the arterioles. Before birth, both circulations have arterioles. Muscle normally disappears from the arterioles in the pulmonary circulation within two weeks of birth, markedly decreasing its resistance. Lacking arterioles, blood flow cannot be as finely controlled in the lung as in the systemic circulation. Autonomic nervous system regulation of blood flow, so important in the systemic circulation, is almost absent in the pulmonary circuit. Many drugs that affect systemic vascular resistance have almost no influence on pulmonary vascular resistance.

Arteriolar disease is the principal cause of increased resistance and hypertension in the systemic circulation. Since the pulmonary circuit lacks arterioles, it might be assumed that increased resistance and hypertension would be rare in the lesser circuit. Such is not the case. The pulmonary blood vessels are in much closer proximity to the external environment than are their systemic vascular counterparts. As a result, environmental agents more frequently damage pulmonary than systemic blood vessels. Many of these agents are in the daily work environment and are thus the cause of occupationally induced pulmonary arterial hypertension and cor pulmonale.

In some respects, the cardiac right ventricle is less suited to respond to pressure load increases than is the left ventricle. By 6-8 years of age, the two ventricles no longer respond to increased workloads with myocardial fiber hyperplasia. From that age, hypertrophy is the main response. Hypertrophy is more limited as a response mechanism to pressure loads than is hyperplasia because fiber surfaces available for nutrient and gas exchange are relatively decreased with fiber hypertrophy; they are not much challenged by hyperplasia. Hypertrophy effectively limits the size which individual myocardial fibers can reach without metabolic impairment. Occupationally induced pulmonary arterial hypertension develops at an age when the heart can only respond to increased loads with hypertrophy. Resultant pressure workload increases on the right ventricle are often greater than comparable pressure workload increases in the left ventricle, associated with hypertension in the systemic circuit.

For this reason, the right cardiac ventricle is vulnerable to failure when it is subjected to high pressure loads in a variety of occupational pulmonary disorders.

LIST OF AGENTS THAT CAUSE OCCUPATIONALLY RELATED COR PULMONALE

Acute cor pulmonale may be associated with any disorder causing severe alveolar hypoxia including pulmonary edema associated with toxic exposures.

Documented Causes of Chronic Cor Pulmonale

1. Free silica (silicon dioxide) including quartz, flint, granite, sandstone, slate, and diatomaceous earth
2. Silicates: talc, kaolin
3. Asbestos
4. Beryllium
5. Coal mine dust
6. Tungsten carbide
7. Antigenic agents that cause allergic alveolitis

Probable Causes of Chronic Cor Pulmonale

1. Cadmium
2. Graphite
3. Hemp
4. Uranium mine dust

LIST OF OCCUPATIONS AND INDUSTRIES INVOLVED

(See chapters on these entities)

1. Free silica
2. Silicates
3. Asbestos
4. Beryllium
5. Coal mine dust
6. Tungsten carbide
7. Allergic alveolitis
8. Cadmium
9. Graphite
10. Hemp, cotton, and flax workers
11. Uranium mine dust
12. Nitrogen oxides

EPIDEMIOLOGY

The epidemiology of cor pulmonale in occupational pulmonary disorders is largely the consequence of the epidemiology of individual disorders.

ESTIMATE OF POPULATION AT RISK AND PREVALENCE OF COR PULMONALE

No credible data for cor pulmonale are available for any occupational pulmonary disorder because the diagnosis is often made only at autopsy and postmortem examinations are not performed on most workers. Cor pulmonale is difficult to detect in its early stages by commonly available, noninvasive clinical and laboratory techniques. Clinical surveys of at-risk populations have almost never used diagnostic techniques that would detect any but the most advanced cases of cor pulmonale. The little information that is available is summarized in Table X-1.

PATHOLOGY

The pathology and genesis of occupationally induced pulmonary vascular disease can only be understood against the background of normal changes in vascular structure with age. No significant resistance resides in the large, elastic pulmonary arteries, but atherosclerosis (in them) sometimes reflects an increased resistance in the more peripheral, smaller pulmonary arteries. The structure of muscular pulmonary arteries has great influence on pulmonary vascular resistance. In normal adults, the thickness of the muscular artery walls is similar in the upper and lower lobes of the lungs and uniform from beginning to end in individual muscular arteries (55). By contrast, such thickness varies greatly from one muscular arterial segment to another in aged nonsmokers and in middle-aged cigarette smokers (55). These segmental changes are mainly due to the uneven deposition of collagen and longitudinally oriented smooth muscle in the walls of the arteries. Between the ages of 30 and 70, the collagen content of pulmonary muscular artery walls increases in nonsmokers from 8% of total wall constituents to 25%. The comparable change in cigarette smokers is from 15% to 40% (38).

Longitudinally oriented smooth muscle increases with age in the walls of muscular pulmonary arteries. It appears sooner and is more extensive in cigarette smokers than in nonsmokers (38). In themselves, the collagen and longitudinally oriented muscles appear to have little functional significance. For example, there is no significant increase in the frequency of cor pulmonale if these vascular lesions are the only vascular ab-

Table X-1

POPULATIONS AT RISK OF DEVELOPING COR PULMONALE

Agent or Disorder	Population at Risk	Prevalence of Cor Pulmonale
1. Free silica	Those exposed to free silica and diatomaceous earth (11)(56).	No prevalence studies published, but cor pulmonale usually present when pulmonary fibrosis is both severe and widespread.
2. Silicates	The chemical composition of talc and exposures to it vary so greatly it is not possible to precisely define the populations at risk.	Kleinfeld et al. reported that 27% of one group of talc workers followed for 29 years died of pneumoconiosis and its complications, mainly cor pulmonale (23). The frequency of pulmonary parenchymal disease and cor pulmonale was apparently even higher in earlier years (24). In most industrial settings where talc is used, cor pulmonale is probably rare (21). Workers with kaolin pulmonary fibrosis can have cor pulmonale (61).
3. Asbestos	All population groups that have sustained contact with asbestos.	No prevalence data have been published for cor pulmonale, but some workers with advanced pulmonary parenchymal disease have cor pulmonale (1).
4. Beryllium	The U.S. Beryllium case registry should provide such data but it does not. Most current cor pulmonale is the result of sustained contact with beryllium as an antigen.	No prevalence data have been published, but some individuals with advanced pulmonary parenchymal disease develop cor pulmonale (15). Hansan et al. have reported that 16% of individuals with chronic beryllium pulmonary disease develop heart failure, but they gave no indication what proportion of these cardiac failures were related to cor pulmonale (19).
5. Coal mine dust	At least 6 different pulmonary disorders in coal workers can contribute to cor pulmonale. In general, coal workers exposed to substantial free silica and those who develop chronic bronchitis and/or emphysema are at risk of cor pulmonale.	In a study of 178 Appalachian bituminous miners who died between 1960-1968, 58% had moderate or severe cor pulmonale (40). In a much larger unpublished study of cases collected prospectively since 1970, less than 5% of miners of low rank Appalachian bituminous coal had cor pulmonale (37). Cor pulmonale has a higher prevalence among higher rank bituminous and anthracite coal miners, but exact figures are not available (26).
6. Tungsten carbide	Several studies have reported diffuse, interstitial, pulmonary fibrosis in some workers (8)(14).	No prevalence data are available.

Table X-1 (Continued)
POPULATIONS AT RISK OF DEVELOPING COR PULMONALE

Agent or Disorder	Population at Risk	Prevalence of Cor Pulmonale
7. Allergic alveolitis	All farm and mushroom workers exposed to the fungal antigens. All cork workers exposed to these antigens.	No prevalence data for cor pulmonale are available because most of the cases are sporadic in their appearance.
8. Cadmium	Acute cor pulmonale follows acute pulmonary edema resulting from large exposure to cadmium fumes.	Interstitial pulmonary fibrosis develops in a few individuals who are exposed to such fumes but no data have been published on the prevalence of chronic cor pulmonale.
9. Graphite	There is one published case of cor pulmonale in an individual who had severe granulomatous lung disease due to graphite exposure (28).	There are non-U.S. reports of up to 23% of graphite workers having dyspnea and cough, but no data on the prevalence of cor pulmonale (28).
10. Byssinosis	Individual cases of cor pulmonale have been reported in hemp workers (4).	It is not known if there is any increase in cor pulmonale in cotton workers. There may be an increase in hemp workers, but no prevalence data have been published (4).
11. Uranium mine dust	Most underground uranium miners.	Trapp et al. reported in 1970 that 4 out of 27 uranium miners had pulmonary arterial hypertension during exercise (57). No other prevalence data are available.
12. Nitrogen oxides	All workers who have large exposures.	A large exposure to nitrogen dioxide can produce acute pulmonary edema which in turn produces acute cor pulmonale (50).

normalities in the lungs (38). It is important that these pulmonary arterial changes, due to age and smoking, not be attributed to occupational exposures.

Pathophysiologic Causes of Pulmonary Hypertension Which May Be Associated With Occupational Exposures

Emboli—There are a large number of substances that can embolize to the pulmonary arteries and capillaries. Only a few are related to occupational exposures. The most frequent are bone marrow and fat that result from bone and adipose tissue trauma at the workplace (6). Gas emboli occur in divers. When repeated, such gas emboli produce occlusive sclerotic lesions in the pulmonary arteries of experimental animals. It is not known if similar lesions develop in humans.

Hypoxia—Alveolar hypoxia is probably the commonest cause of chronic pulmonary arterial hypertension in the United States. A list of occupationally related disorders to which alveolar hypoxia contributes would include fumes and gases that induce acute pulmonary edema; occupations that require residence at high altitude; brain stem trauma that affects central mechanisms of respiratory control; and by far the most common, disorders that obstruct the airways and lead to uneven distribution of inspired air. All of these disorders decrease alveolar levels of oxygen. Adjacent pulmonary arteries have a characteristic response. They constrict and in time develop a coat of hyperplastic and hypertrophied smooth muscle fibers (20)(39)(40). Pulmonary vascular resistance increases. Muscular hypertrophy and hyperplasia are reversible if normal alveolar oxygen levels are restored (9)(45). Most occupational diseases responsible for severe alveolar hypoxia cannot be completely reversed (39), and any improvement in the pulmonary arterial lesions may require the use of supplemental oxygen.

Both genetic and acquired factors appear to influence the pulmonary vascular response to alveolar hypoxia. Some individuals living at high altitude have pulmonary arterial pressures as low as those found at sea level while others have very high pressures (35)(36)(60). Such genetically based differences in the pressor response to alveolar hypoxia also appear to influence the outcome of patients with airways obstruction and pulmonary emphysema. In individuals with severe emphysema, cardiac failure due to cor pulmonale develops later and survival is longer in those who have only a small pulmonary arterial pressor response to alveolar hypoxia than in those who have a larger pressor response (27).* The intimate mechanism involved in the pulmonary arterial pressor response to alveolar hypoxia is not fully known, but it appears to be locally mediated through the adventitia of the arteries. Prostaglandin release may be involved (58). It is important to note that thrombotic or occlusive sclerotic lesions are rare in the pulmonary arteries of individuals with hypertension due to alveolar hypoxia. The vasoconstrictor effects of alveolar hypoxia are potentiated by acidosis.

Finally, the wall of the pulmonary artery can be made hypoxic with resultant chronic constriction and muscular hypertrophy in a number of occupational disorders in which environmental materials (e.g., dust macules) collect around the artery (40). The functional significance of this mechanism has not been assessed in most occupational pulmonary disorders because quantitative studies have not been undertaken.

Obliterative Lesions—Many different lung diseases include inflammatory or fibrotic processes that engulf and then destroy blood vessels. Such lesions probably make a major contribution to cor pulmonale in some diseases, but this has not been proven by quantitative, morphologic studies.

It is not enough to describe types of pulmonary vascular lesions associated with occupational disorders. Such listings give no clues to the relative functional importance of various lesions. There are additional problems. The arterial medial hypertrophy induced by hypoxia is a major factor in the development of cor pulmonale in many occupational lung disorders. Because increased pulmonary blood volumes commonly dilate hypertrophied arteries, the arterial wall does not appear unusually thick and the hypertrophy is usually not recognized.

There are further difficulties in interpreting the significance of pulmonary vascular abnormalities in occupational lung diseases. Both surgeons and pathologists are apt to select lung tissues that have obvious gross abnormalities for

*Individuals with advanced cirrhosis of the liver have little or no pressor response to alveolar hypoxia (10). The mechanism of this loss is unknown. Cirrhosis of the liver can be occupationally induced, e.g., those who use carbon tetrachloride.

microscopic analysis. Obliterative vascular lesions are apt to be both more extensive and severe in such samples than in the lungs as a whole. Finally, emboli are often unevenly distributed to the pulmonary vascular bed so that many microscopic sections must be taken from different areas of the lungs to assess their number and role in changing pulmonary vascular resistance. With the partial exception of coal workers' pneumoconiosis, published analyses of occupational lung diseases are inadequate for quantitative distinctions. For many occupational lung diseases there is no published information at all.

With so little information published on occupationally induced cor pulmonale, another approach must be used to assess its possible impact on the work force. This can be done by identifying major disease processes in various occupational lung disorders, and then predicting probable extant pulmonary vascular lesions.

Before describing (published) pulmonary vascular abnormalities in individual occupational disorders, it is useful to describe vascular abnormalities associated with major diseases that are constituents of most occupational lung diseases. The most frequent occupationally induced pulmonary disorder in the United States is bronchitis/bronchiolitis. It is found with exposures to a wide range of environmental agents. Its anatomic correlates are mucous gland hyperplasia, goblet cell metaplasia, increased mucous production, inflammation and sometimes a mild fibrosis in the airways. In autopsy studies, these findings correlate poorly with functionally significant chronic airways obstruction present during life (32)(51). Cor pulmonale almost never develops with chronic bronchitis/bronchiolitis in the absence of airways obstruction (52)(53). The presence of emphysema correlates more closely with airways obstruction. Emphysema without airways obstruction reportedly does not cause cor pulmonale (54). Functionally significant airways obstruction must usually be present if cor pulmonale is to develop in patients with bronchitis/ bronchiolitis and/or emphysema (25)(31) (32)(52) (54).

Alveolar hypoventilation and ventilation/ perfusion imbalances which cause hypoxemia are not easily correlated with the morphologic abnormalities. Thus, although the level of pulmonary artery pressure is correlated with the severity of arterial hypoxemia in patients with chronic airways obstruction (7), the relationship between right ventricular weight and anatomic emphysema is weak (31). The pulmonary vascular abnormality mainly responsible for cor pulmonale in cases of airway obstruction is medial hypertrophy in small muscular arteries (39). Such hypertrophy is potentially reversible because several weeks of oxygen administration sometimes lowers pulmonary arterial pressures in patients with severe airways obstruction (7).

Alveolar hypoventilation, hypoxia, and consequent pulmonary arterial hypertension are probably responsible for the acute cor pulmonale occasionally reported in cases of occupationally induced acute pulmonary edema. Acute cor pulmonale is probably far more common in cases of acute pulmonary edema than has been reported (50).

Destruction of blood vessels is another major mechanism involved in the genesis of pulmonary arterial hypertension in occupational lung disease. Such disorders are usually inconsistently distributed throughout the lobes of the lungs which makes quantitation of the vascular destruction difficult. The functional significance of such vascular destruction is also difficult to assess, because as much as two-thirds of the total pulmonary vascular bed must be destroyed to produce pulmonary arterial hypertension (62). Thus, the striking obliterative vascular lesions present in many occupational pulmonary disorders may (sometimes) have less functional significance than authors have claimed.

Pathology of Specific Disorders

Silicosis

In silicosis, macrophages characteristically phagocytize toxic particles, move to new sites, die, release the toxic particles and the cycle is repeated. Each cycle produces fibrosis which spreads, often concentrically. The macrophages characteristically invade the adventitia of pulmonary vessels which contributes to the vascular obliteration characteristic of the disorder (44)(56) (Figure X-1). Both the direct toxicity of the silicic acid released by the silica particles and immunologic mechanisms may be involved in the genesis of the fibrosis. Pulmonary vessels often display an intimal fibrosis and published reports have frequently mentioned thrombi in pulmonary arteries (48) (Figure X-2). It would be unwise to accept these obliterative and thrombotic

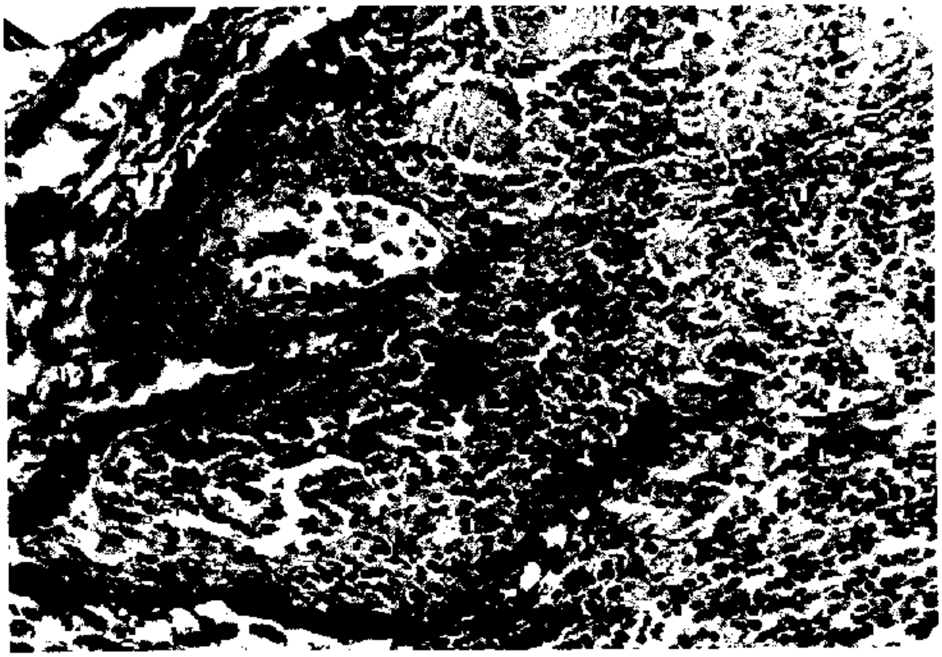

Figure X-1. Macrophages with silica particles and chronic inflammatory cells have infiltrated the wall and obliterated a segment of a muscular pulmonary artery in a case of acute silicosis (aldehyde fuchsin elastic stain, X560).

Figure X-2. Marked intimal fibrosis in a muscular pulmonary artery. The artery is entering a large fibrotic area in a case of chronic pulmonary silicosis (aldehyde fuchsin stain, X225).

Figure X-3. A small pulmonary artery enters a granulomatous area and is obliterated in a case of asbestosis (aldehyde fuchsin, X225).

Figure X-4. Marked intimal fibrosis is visible in this muscular pulmonary artery. The artery is entering an area of dense fibrosis in a case of asbestosis (aldehyde fuchsin, X360).

Figure X-5. A small muscular pulmonary artery is invested by a mantle of coal dust in coal workers' pneumoconiosis (trichrome, X200).

lesions as the sole cause of pulmonary arterial hypertension and cor pulmonale in silicosis. Airways obstruction as well as pericicatricial and other forms of emphysema are common in the disorder, so alveolar hypoxia may make a contribution to the cor pulmonale (11)(44)(48)(56).

Silicates

Talc is not a uniform commercial product. Some commercial talc is mixed with other silicates such as serpentine, tremolite and anthrophyllite as well as other ingredients such as carbonates. The extent to which each of these contributes to the granulomatous process characteristic of talcosis is not precisely known. In addition, the length of some fibers in talc mixes (such as tremolite) reportedly affects the fibrogenic properties of the product (23). Commercial talc may also contain traces of quartz. Usually the amount of reticulum and collagen in talc granulomas is somewhat less than that found in strictly silicotic lesions. The extensive arterial obliteration found in silicosis is not so often encountered in talcosis (56). However, endarteritis with vascular obliteration is common at the edge of granulomas and many cases of chronic cor pulmonale have been reported in workers exposed to talc (23)(24). Other studies have reported no cor pulmonale in talc workers despite long exposures to the agent (21).

Asbestos

Asbestos belongs to a group of silicate minerals known as amphiboles. The production and use of asbestos has increased greatly throughout the world in the last two decades. When inhaled, the needle-like fibers mainly pass to the lower lobes where the greatest damage occurs. In severe cases the lower lobes are largely replaced by a mass of grey fibrous tissue. The granulomas may start in bronchioles, alveolar ducts, or alveoli. A diffuse, interstitial, alveolar fibrosis develops in some cases when the asbestos particles are very small (Figures X-3 and X-4). Severe airways obstruction and emphysema are not usually a prominant feature in asbestosis, so alveolar hypoxia and cor pulmonale are not as common as in silicosis. Clinically, signs of right sided cardiac failure are usually a very late feature of the disease (1)(12). More specific information about

Figure X-6. Progressive massive fibrosis (PMF) in a 40-year-old coal miner. Blood vessels are usually completely obliterated in such lesions. (Gough section).

vascular lesions and cor pulmonale is absent from the literature.

Beryllium

Chronic beryllium disease of the lungs is characterized by a chronic interstitial pneumonitis, often accompanied by focal granulomatous lesions which resemble sarcoid (15). The chronic disease has an immunologic origin. There is no doubt that a portion of the victims develop cor pulmonale, but published accounts have little to say about pulmonary vessels (15)(19). Seventeen of 124 patients with chronic beryllium disease in one series had pulmonary emboli or infarcts at autopsy (15). This is not a large number considering many of these individuals had protracted cardiac failure prior to death (15). It has been reported that some pulmonary arteries are obliterated by the granulomas in the disorder, but their relative number is unknown. Published information is not adequate to estimate the frequency of cor pulmonale or to speculate on its exact causes when present.

Coal Workers' Pneumoconiosis

Far more is known about the frequency and causes of cor pulmonale in coal workers' pneumoconiosis than about cor pulmonale in any other occupational lung disease. Several types of pulmonary vascular abnormalities are found in the lungs of coal workers with pneumoconiosis: A) lesions related to the primary dust macule; B) lesions related to fibrotic nodules and progressive massive fibrosis (PMF); C) lesions related to other pulmonary disease processes. Only one of these lesions (A) is relatively specific for coal workers, and its functional significance may be small. Coal dust macules evolve by the incorporation of dust-filled macrophages into the walls of respiratory bronchioles and adjacent alveoli. In this process the associated small muscular artery is invested by the mantle or cuff of coal dust (Figure X-5). It has been postulated that such mantles lead to a perfusion derangement. Quantitative analysis has shown that arterial medial muscle mass increases significantly in those artery segments inside the dust macules (40). The increase is mainly due to hypertrophy of individual arterial medial muscle fibers. In young miners, this muscular hypertrophy is not associated with cor pulmonale, an indication that by itself, the hypertrophy does not have great functional significance.

Obliterative vascular lesions are often associated with fibrotic nodules and progressive massive fibrosis in coal workers' pneumoconiosis. Occluded and destroyed blood vessels are common in completely collagenized nodules and in areas of progressive massive fibrosis (Figures X-6, X-7). These vascular lesions are most frequent in anthracite workers (17)(18).

Most of the cor pulmonale in coal workers appears related to airways disease and emphysema (40). The emphysema is of several types: focal, centrilobular, pericicatricial, and mixed. The predominant vascular lesion in miners who develop cor pulmonale is an increase of circularly-oriented muscle in the media of muscular pulmonary arteries (40). This is presumably due to alveolar hypoxia (39). Although studies show overall correlations between degrees of emphysema and chronic cor pulmonale, such correlations are often poor in individual patients. This may be due to genetic differences between in-

Figure X-7. Collagen has replaced most other constituents in a coal dust macule. Blood vessels are obliterated in such lesions (trichrome, X130).

dividual miners which appear to significantly influence the pulmonary vascular pressor response to alveolar hypoxia (35). Individual variations in this pressor response seem to influence the clinical course of emphysema. In individuals with severe emphysema, cardiac failure develops later and survival is longer in those who have only a small pulmonary arterial pressor response to alveolar hypoxia (27).

Tungsten Carbide

Two forms of disease are produced by exposure to cobalt which is a contaminant in tungsten carbide. One resembles berylliosis in that it has both an interstitial and a granulomatous component. The other is a disorder that produces airways constriction. A few cases of cor pulmonale have been reported in individuals with the diffuse, interstitial form of the disorder in which many capillaries and small arteries are presumably replaced by fibrous tissue (8)(14). Published information is so sketchy that the exact nature of the pulmonary vascular lesions responsible for the cor pulmonale is not known.

Allergic Alveolitis

This describes a series of disorders produced by the inhalation of antigenic materials which produces an inflammatory process in the alveolar wall. The lesions are often complex which may explain why the vascular lesions responsible for occasional cases of cor pulmonale have not been described. Inflammation often involves the bronchioles as well as the alveoli, and sometimes appears in the form of noncaseating granulomas that resemble sarcoid. In rare instances, lesions progress to severe interstitial fibrosis and even honeycomb lung. Patients tend to hyperventilate during the acute phase of the disease and may have a slight increase in pulmonary vascular resistance and pulmonary arterial pressure. Severe pulmonary arterial hypertension and cor pulmonale develop only in advanced cases with severe interstitial fibrosis. It is likely that combinations of airways obstruction and vascular obliteration are responsible for the right ventricular hypertrophy and failure.

Cadmium

An acute exposure to high concentrations of cadmium fumes results in acute pulmonary edema and acute cor pulmonale (16). Workers chronically exposed to cadmium fumes may develop a mild interstitial fibrosis and perhaps emphysema, without much obstructive airways dis-

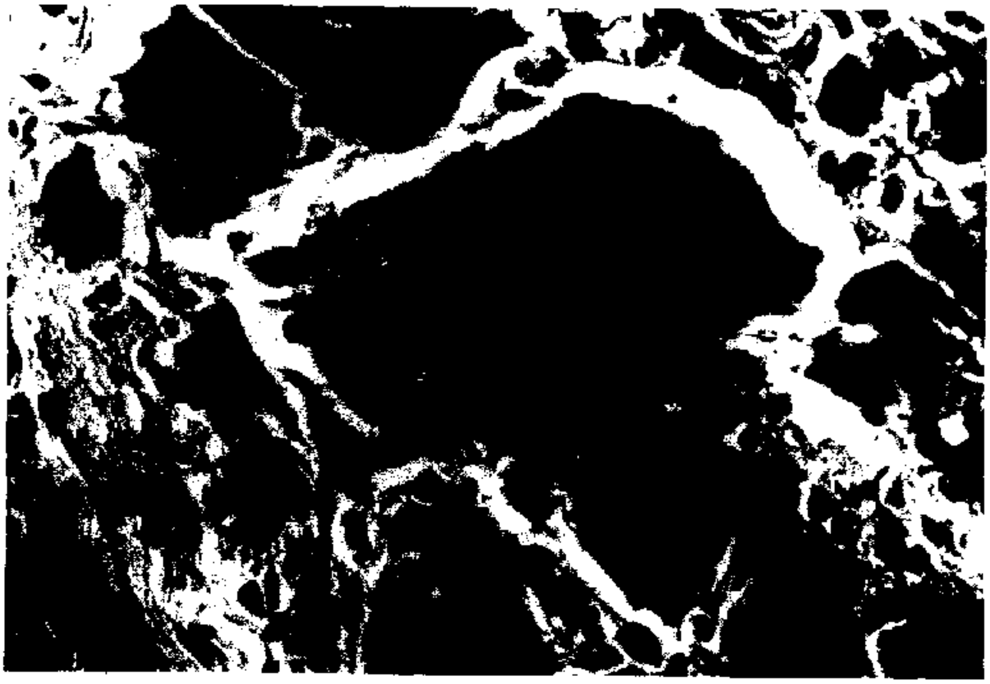

Figure X-8. This lung section from a graphite worker shows giant cells with enclosed graphite crystals (H&E,X1075).

ease. Cor pulmonale has not been reported in these latter cases.

Graphite

Synthetic or naturally occurring graphite can cause remarkable granulomatous lesions in the lungs, often perivascular in location (22)(28). A few workers have developed cor pulmonale (28). Not enough information has been published to identify the nature of the vascular lesions responsible for the cor pulmonale (Figure X-8).

Byssinosis

Cotton, flax, and hemp workers sometimes develop byssinosis. Many workers are involved and large epidemiologic studies have been published (29)(30)(59). The disease is usually characterized by a reversible airways obstruction accompanied by signs and symptoms of bronchitis. An increased mortality has been reported in workers heavily exposed to such dusts for long periods (49). A few reportedly develop chronic airways obstruction and some hemp workers have reportedly died with cor pulmonale (4). Nothing has been reported on the nature of the pulmonary vascular abnormalities in these fatal cases.

Nitrogen Oxides

Nitrogen dioxide can produce acute pulmonary edema with consequent acute cor pulmonale.

CLINICAL DESCRIPTION OF COR PULMONALE

"Of the many disease entities that affect the heart, the internist and even the cardiologist is least familiar with the entity of cor pulmonale... there is a definite lack of prevalence data because of the lack of uniform diagnostic criteria and reporting" (13).

Symptoms

Acute cor pulmonale is usually produced by embolism or acute pulmonary edema. A number of occupational exposures produce such edema. The symptoms referable to cor pulmonale are obscured in such cases by the dyspnea and discomfort associated with the edema.

Chronic cor pulmonale—An early diagnosis is made only when it is recognized that a pulmonary disorder in a patient can culminate in pulmonary hypertension. Overt right sided cardiac failure if often a late feature of chronic cor pulmonale. When it develops, such failure is often insidious in onset unless it appears during the course of an acute respiratory tract infection. Frequently, diagnosis is made only when shortness of breath fails to resolve after an acute infection is controlled. Patients with marked pulmonary ventilation/perfusion imbalances and gas diffusion defects may also experience somnolence due to hypercapnia.

Signs

The signs of right venticular hypertrophy are a cardiac thrust along the left sternal border or just below the sternum and a fourth heart sound, arising in the hypertrophied right ventricle at the same site. Pulmonary hypertension is often accompanied by a loud second heart sound in the second left interspace adjacent to the sternum and a cardiac thrust in the same area. Sometimes the pulmonic valvular ring dilates and the murmur of pulmonic valvular insufficiency can be heard. If the right ventricle fails, a right ventricular gallop and tricuspid valvular insufficiency murmur may appear. Hydrothorax is rare but dependent edema is commonly present. Systemic venous congestion is often evident.

Natural History Including a Consideration of Reversibility and Progression

Since overt signs and symptoms of cor pulmonale frequently appear during the course of an acute respiratory infection, improvement often follows successful treatment of the infection. More fundamental questions relate to the causes of increased pulmonary vascular resistance and its reversibility. Pulmonary hypertension whose main cause is alveolar hypoxia, is potentially reversible, because structural changes in the pulmonary arteries involve only a hypertrophy of medial smooth muscle. This potential reversibility is confirmed by the finding that some individuals with hypoxia-induced pulmonary arterial hypertension have a decrease in pulmonary vascular resistance following the sustained administration of oxygen (7). In general, cardiotonic drugs are not effective in relieving right-sided cardiac failure unless oxygenation is improved. If adequate arterial blood oxygen tension is restored, it is often possible to discontinue diuretics and digitalis.

Since airways obstruction is the most common cause of low aveolar and arterial blood oxygen tension, the course of pulmonary hypertension and the resultant cor pulmonale depends on the reversibility of the obstruction. The fundamental causes of the obstruction are at least partially irreversible, i.e., destruction of airways and loss of the radial traction that keeps them open. Respiratory tract infections add to the obstruction by narrowing or plugging the airways with mucus and inflammatory debris. Treating the infections often partially alleviates the obstruction. Usual treatment measures are hydration, antibiotics, and bronchodilators. When respiratory failure supervenes, mechanical aids to respiration are often needed.

Treatment for cardiac failure is usually instituted when there is evidence of right-sided failure. Methods include digitalis, diuretics, low salt diet, and phlebotomies to bring hematocrits and blood volumes to more normal levels. Diuretics have to be carefully administered because potent diuretics (like ethacrynic acid) may cause metabolic alkalosis which depresses the CO_2 stimulus to the respiratory center. The most important therapeutic measure in a patient with severe hypoxemia is the administration of supplemental oxygen.

Complications of cor pulmonale are difficult to treat when the increase in pulmonary vascular resistance is mainly due to blood vessel destruction. This applies particularly to cases of silicosis in which silica-bearing macrophages have invaded the adventitia of arteries and led to widespread fibrous obliteration of vessels.

Appropriate Laboratory Investigations

The diagnosis of cor pulmonale can be made with certainty by right-sided cardiac catheterization. Typically such catheterization shows pulmonary arterial hypertension, a normal pulmonary arterial wedge pressure, and an increased right ventricular diastolic filling pressure—when ventricular failure is present. Roentgenographic analyses have value in diagnosing cor pulmonale, but they are often not definitive. A pruned peripheral pulmonary arterial tree is perhaps the most definitive diagnostic finding when the pulmonary arteries are obstructed. Enlarged central pulmonary arteries coupled with a known pulmonary disorder raise the suspicion of pulmonary arterial hypertension. Selective right-sided cardiac enlargement is difficult to recognize on roentgenographic examinations, but should be suspected in cases where heart size increases during bouts of acute respiratory insufficiency.

The electrocardiogram is sometimes helpful in making a diagnosis of cor pulmonale, mainly when it is advanced. It is not as useful in many occupational disorders as in those of nonoccupational origin. A high proportion of individuals with cor pulmonale due to occupational lung disease have chronic airways obstruction. Reportedly, the diagnosis of cor pulmonale can be made by ECG on only about one quarter of the patients who have the disorder secondary to obstructive airways disease (13). This is apparently due to hyperinflated lungs and to the episodic nature of the pulmonary hypertension in many patients with airways obstruction. The ECG is somewhat more useful in diagnosing cor pulmonale due predominantly to obliterative pulmonary vascular disease. ECG patterns that suggest chronic cor pulmonale include P-pulmonale in leads II, III, IV; AVF, right axis deviation; R:S ratio in $V_1>1$, in V_5,1, and in right chest leads; and partial or complete right bundle branch block (13)(54). These criteria are moderately specific but insensitive. Recently introduced radionuclide technology can also be used to demonstrate cor pulmonale. Patients with cor pulmonale reportedly have a reduced right ventricular ejection fraction (3).

The echocardiograph can detect some cases of cor pulmonale. Both hypertrophy and dilatation can sometimes be detected in the right ventricle by this means. Such patients often have abnormal motion in the pulmonic valve, i.e., an absent or decreased alpha dip and a rapid systolic opening velocity of the valve. Most echocardiographers have difficulty making the diagnosis of chronic cor pulmonale unless right ventricular hypertrophy is moderate or severe. Thus, the technique is not suitable for screening programs designed to detect early thickening of the right ventricular wall.

DIAGNOSTIC CRITERIA

The post mortem diagnosis of acute cor pulmonale rests on finding a dilated right ventricle. Flattening of the trabeculae carneae usually makes this diagnosis easy. Chronic cor pulmonale is recognized by finding myocardial hypertrophy in the right ventricle wall. This latter diagnosis is not easy to make when the hypertrophy is mild or when the ventricular wall is dilated. Comparisons with the left ventricular wall are not always helpful because left ventricular hypertrophy and failure are common in cor pulmonale (31). A more certain diagnosis can be made by separately dissecting and weighing the two cardiac ventricles and then comparing them with body weight (31)(43). Such dissections are rarely undertaken and are one reason there is so little prevalence data on cor pulmonale for occupational pulmonary disorders. Finally, many pathologists do not recognize mild or even moderate degrees of right ventricular hypertrophy because they do not consider a diagnosis of cor pulmonale. Or when they do recognize the abnormality, they do not connect it with the occupationally related pulmonary parenchymal disorder. This accounts for the many reports in the literature of advanced occupational lung disease without any recognition of abnormalities in the right heart.

Even greater problems are posed by the inadequate methods available for making the diagnosis of cor pulmonale in living patients. Cardiac catheterization is the most definitive method for detecting cor pulmonale, but it is expensive and involves risks to the patient. It is therefore unsuitable for mass screening and prevalence studies. Echocardiography is noninvasive but as used by most cardiologists detects only advanced right ventricular hypertrophy. Its use in surveys would greatly underestimate the prevalence of chronic cor pulmonale. Physical examination evidences of chronic cor pulmonale are usually late manifestations of the disorder and are usually absent when patients die of nonpulmonary disorders. Chest radiographs are unreliable in recognizing most mild and many moderate cases of chronic cor pulmonale. The diagnosis can reliably be based on the ECG only when obstructive airways disease is absent and the cor pulmonale advanced. The true prevalence of cor pulmonale will not be known for any occupational disease until inexpensive, sensitive, practicable, and noninvasive techniques are developed to make the diagnosis in life.

METHODS OF PREVENTION

Methods for preventing acute cor pulmonale depend entirely on avoiding contact with toxic fumes and gases that produce acute pulmonary edema and on avoiding the trauma that results in fat and bone marrow emboli. Because obstructive airways disease is the most common cause of chronic cor pulmonale in most occupational lung disease, methods for preventing chronic cor pulmonale are largely those required to prevent individual occupational pulmonary disorders. A public health program that delays the appearance and reduces the frequency of chronic airways obstruction—through enforcement of air pollution standards; anti-smoking education; a monitored system of pulmonary function testing; etc.,—should reduce the prevalence of chronic cor pulmonale in occupational lung disease.

RESEARCH NEEDS

1. The most obvious need is for prevalence data. This will be both expensive and difficult to obtain. To obtain postmortem data, a program of sponsored autopsies like that operated by ALOSH for coal workers is needed. Hearts would probably have to be collected and examined at one central location to insure uniform dissections and weighing. Obtaining clinical prevalence data on cor pulmonale presents formidable problems. The only definitive available method for making the diagnosis is cardiac catheterization, and it is unsuitable for epidemiologic studies because of its expense and risk to patients. Studies should be undertaken to determine if ECG, in combination with echocardiography and x-ray, would be suitable epidemiologic tools. The recently introduced radionuclide techniques are another possible diagnostic tool.
2. The most common mechanism responsible for cor pulmonale in occupational lung disease is alveolar hypoxia. Possible biochemical mediators and mechanisms of hypoxia-induced pulmonary hypertension, such as prostaglandins, histamine receptors, calcium transport, etc., need further investigation.
3. New drugs are needed to dilate pulmonary arteries. All currently effective drugs have side effects that are too serious to permit long-term use. Some dilate systemic as well as pulmonary arteries. All have the inherent limitation that they permit perfusion of poorly ventilated areas of the lung and thereby cause hypoxemia. Despite these limitations, there are substantial numbers of patients whose high levels of pulmonary vascular resistance are a prime threat to their survival. More effective, safe pharmacologic vasodilator agents would likely benefit many of these individuals.
4. There are almost no data in the literature quantitating the individual pulmonary vascular lesions responsible for cor pulmonale in occupational lung diseases. Coal workers' pneumoconiosis is a partial exception; CWP data confirmed that alveolar hypoxia, rather than fibrotic and obliterative lesions, was primary responsible for cor pulmonale. Similar studies are needed for other occupational lung diseases.
5. In the first section of this report there is an outline of pulmonary vascular changes related to aging and cigarette smoking. These changes in themselves do not significantly increase pulmonary vascular resistance and cause cor pulmonale. They might, however, potentiate vascular damage due to occupational agents and thereby accelerate the development of cor pulmonale. Postmortem material for this line of research is readily available and should be studied.
6. No systematic studies have been published detailing specific effects—on human pulmonary arteries and veins—of common air pollutants in our industrial environments. Not only should such studies be undertaken, but possible interactions between these air pollutants and occupational agents need to be examined.
7. The list of documented occupational lung disorders involving cor pulmonale is short. The actual incidence of occupational disorders involving cor pulmonale is undoubtedly substantial. Systematic studies should be undertaken to search for these associations. Most such (currently unrecognized) associations are likely to be found in occupational disorders in which airways obstruction is a major feature.
8. Quantitative studies have shown that the microcirculation of the left ventricle is affected by cigarette smoking. Smoking accelerates the replacement of normal, circularly oriented, smooth muscle in small artery walls by collagen and longitudinally oriented muscle (42). There is strong evidence that these small artery lesions impair ventricular contractility when a severe pressure load is imposed on the ventricle (41). Such studies should be repeated on the right ventricle to determine if lesions in the small intramyo-

cardial arteries contribute to the development of right-sided cardiac failure in patients with chronic pulmonary arterial hypertension.

REFERENCES

1. Bader, M. E., Bader, R. A. et al.: Pulmonary function in asbestosis: serial tests in a long-term prospective study. Ann NY Acad Sci *132:*391-405, 1965.
2. Bates, D. V.: The prevention of emphysema. Chest *65:*437-441, 1974.
3. Berger, H. J., Matthay, R. A., et al.: Assessment of cardiac performance with quantitative radionuclide angiocardiography: right ventricular ejection fraction with references to findings in chronic obstructive pulmonary disease. Am J Cardiol *41:*897-905, 1978.
4. Bouhuys, A. and Zuskin, E.: Chronic respiratory disease in hemp workers. Ann Intern Med *84:*398-405, 1976.
5. Brody, J. S., Stemmler, E. J., and DuBois, A. B.: Longitudinal distribution of vascular resistance in the pulmonary arteries, capillaries and veins. J Clin Invest *47:*783-799, 1968.
6. Bruecke, P., Burk, J. F., et al.: The pathophysiology of pulmonary fat embolism. J Thorac Cardiovasc Surg *61:*949-955, 1971.
7. Burrows, B.: Arterial oxygenation and pulmonary hemodynamics in patients with chronic airways obstruction. Am Rev Respir Dis *110:*65-70, 1974.
8. Coates, E. O., Jr., and Watson, J. H. L.: Diffuse interstitial lung disease in tungsten carbide workers. Ann Intern Med *75:*709-716, 1971.
9. Cox, M. A., Schiebler, G. L., et al.: Reversible pulmonary hypertension in a child with respiratory obstruction and cor pulmonale. J Pediatr *67:*192-197, 1965.
10. Daoud, F. S., Reeves, J. T., and Schaefer, J. W.: Failure of hypoxic pulmonary vasoconstriction in patients with liver cirrhosis. J Clin Invest *51:*1075-1080, 1972.
11. Dutra, F. R.: Diatomaceous earth pneumoconiosis. Arch Environ Health *11:* 613-619, 1965.
12. Elmes, P. C.: The epidemiology and clinical features of asbestosis and related diseases. Postgrad Med *42:*623-636, 1966.
13. Fishman, A. P.: *Principles of Internal Medicine,* editors M. W. Wintrobe, G.W. Thorn, et al., New York, McGraw-Hill Book Company, 7th edition, 1974.
14. Forrest, M. E., Skerker, L. B., and Meniroff, M. J.: Hard metal pneumoconiosis, another cause of diffuse interstitial fibrosis. Radiology *128:*609-612, 1978.
15. Freiman, D. G.: Beryllium disease, the relation of pulmonary pathology to clinical course and prognosis based on a study of 130 cases from the U.S. beryllium case registry. Hum Pathol *1:*25-44, 1970.
16. Friberg, L., Piscotor, M., and Mordberg, G. F.: Cadmium in the environment. Cleveland, C. R. C. Press Inc., 1974.
17. Gough, J.: Pneumoconiosis in coal workers in Wales. JOM *4:*86-97, 1947.
18. Gough, J.: Pneumoconiosis of coal trimmers. J Path Bact *51:*277-285, 1940.
19. Hansan, F. M. and Kazema, H.: Chronic beryllium disease, a continuing epidemiologic hazard. Chest *84:*398-405, 1974.
20. Haslcton, P. S., Heath, D., and Brewer, D. B.: Hypertensive pulmonary vascular disease in states of chronic hypoxia. J Pathol Bacteriol *95:*431-440, 1968.
21. Hildick-Smith, G. Y.: The biology of talc. Br J Ind Med *33:*217-229, 1976.
22. Jaffe, F. A.: Graphite pneumoconiosis. Am J Pathol *27:*909-924, 1951.
23. Kleinfeld, M., Messite, J., et al.: Mortality experienced among talc workers, a follow-up study. JOM *16:*345-349, 1974.
24. Kleinfeld, M., Messite, J., et al.: Mortality among talc miners and millers in New York State. Arch Environ Health *14:*663-667, 1967.
25. Kok-Jensen, A., Sorensen, E., and Damsgaard, T.: Prognosis in severe chronic obstructive pulmonary disease. Scand J Respir Dis *55:*120-128, 1974.
26. Kremer, R.: Pulmonary hemodynamics in coal workers' pneumoconiosis. Ann NY Acad Sci *200:*413-432, 1972.
27. Lindsay, D. A. and Read, J.: Pulmonary vascular responsiveness in the prognosis of chronic obstructive lung disease. Am Rev Respir Dis *105:*242-250, 1972.
28. Lister, W. B. and Wimborne, D.: Carbon pneumoconiosis in a synthetic graphite worker. Br J Ind Med *29:*108-110, 1972.

29. Martin, C. F. and Higgins, J. E.: Byssinosis and other respiratory ailments, a survey of 6,631 cotton textile employees. JOM *18:*455-472, 1976.
30. Merchant, J. A., Kilburn, K. H., et al.: Byssinosis and chronic bronchitis among cotton textile workers. Ann Intern Med *76:*423-433, 1972.
31. Mitchell, R. S., and Stanford, R. E.: The right ventricle in chronic airway obstruction, a clinicopathologic study. Am Rev Respir Dis *114:*147-154, 1976.
32. Mitchell, R. S., Standord, R. E., et al.: The morphologic features of the bronchi, bronchioles and alveoli in chronic airway obstruction: a clinicopathologic study. Am Rev Respir Dis *114:*137-145, 1976.
33. Morgan, W. K. C. and Seaton, A.: Occupational lung disease. Philadelphia, W. B. Saunders Company, pp. 291, 301, 1975.
34. Mountain R., Zqillich, C., and Weil, J.: Hypoventilation in obstructive lung disease. N Engl J Med *298:*521-525, 1978.
35. Naeye, R. L.: Children at high altitude; pulmonary and renal abnormalities. Circ Res *16:*33-38, 1965.
36. Naeye, R. L.: Polycythemia and hypoxia, individual effect on heart and pulmonary arteries. Am J Pathol *50:*1027-1033, 1967.
37. Naeye, R. L.(unpublished data).
38. Naeye, R. L., and Dellinger, W. S.: Pulmonary arterial changes with age and smoking. Arch Pathol *92:*284-288, 1971.
39. Naeye, R. L., Greenberg, S. C., and Valdivia, E.: Small pulmonary vessels in advanced pulmonary emphysema. Arch Pathol *97:*216-220, 1974.
40. Naeye, R. L., and Laqueur, W. A.: Chronic cor pulmonale, its pathogenesis in Appalachian bituminous coal workers. Arch Pathol *90:*487-493, 1970.
41. Naeye, R. L. and Liedtke, A. J.: Consequences of intramyocardial arterial lesions in aortic valvular stenosis. Am J Pathol *35:*569-580, 1976.
42. Naeye, R. L. and Truong, L. D.: Effects of cigarette smoking on intramyocardial arteries and arterioles in man. Am J Clin Pathol *68:*493-498, 1977.
43. Naeye, R. L., Whalen, P., et al.: Cardiac and other abnormalities in the sudden infant death syndrome. Am J Pathol *82:* 1-8, 1976.
44. Nicod, J.: Les lesions vasculaires dans le poumon silocotique et leurs relations avec la tuberculose. Schwiez Z Pathol Bakteriol *12:*157-160, 1949.
45. Noonan, J. A.: Reversible cor pulmonale due to hypertrophied tonsils and adenoids; studies in two cases. Circulation *32:*II-164, 1965.
46. Pimentel, J. C., and Avila, R.: Respiratory disease in cork workers (suberosis). Thorax *28:*409-423, 1973.
47. Ranasinha, K. W. and Uragoda, C. G.: Graphite pneumoconiosis. Br J Ind Med *29:*178-183, 1972.
48. Ruttner, J. R., and Gassman, R.: Lungengefassveranderungen bei Silikose. Schweiz Z Allg Path *20:*737-744, 1959.
49. Schilling, R. S. F.: Byssinosis in cotton and other textile workers. Lancet *2:*261-265, 1956.
50. Scott, E. G. and Hunt, W. B., Jr.: Silo filler's disease. Chest *63:*701-706, 1973.
51. Scott, K. M.: An autopsy study of bronchial mucous gland hypertrophy in Glasgow. Am Rev Respir Dis *107:*239-245, 1973.
52. Scott, K. M.: A pathological study of the lungs and heart in fatal and non-fatal chronic airways obstruction. Thorax *31:*70-79, 1976.
53. Scott, K. M. and Steiner, G. M.: Post mortem assessment of chronic airways obstruction by tantalum bronchography. Thorax *30:*405-414, 1975.
54. Schmock, C. L., Pemerantz, B., et al.: The electrocardiogram in emphysema with and without chronic airways obstruction. Chest *60:*328-334, 1971.
55. Simons, P. and Reid, L.: Muscularity of pulmonary artery branches in the upper and lower lobes of the normal young and aged lung. Br J Dis Chest *63:*38-44, 1969.
56. Spencer, H.: Pathology of the Lung, Philadelphia, Pergamon Press, 1977.
57. Trapp, E., Tenzetti, A. D., et al.: Cardiopulmonary function in uranium miners. Am Rev Respir Dis *101:*27-43, 1970.
58. Vaage, J. and Hauge, A.: Prostaglandins and the pulmonary vasoconstrictor response to alveolar hypoxia. Science *189:*899-900, 1975.

59. Valic, F. and Zuskin, E.: Effects of different vegetable dust exposures. Br J Ind Med *29*:293-297, 1972.
60. Vogel, M. H. K., Pryor, R., and Blount, S. G., Jr.: The cardiovascular system in children from high altitude. J Pediatr *64*:315-322, 1964.
61. Warraki, S. and Herant, Y.: Pneumoconiosis in china-clay workers. Br J Ind Med *20*:226-230, 1963.
62. Wood, P.: Diseases of the Heart and Circulation, 2nd edition, London, Eure & Spottiswoode, p. 850, 1956.

APPENDIX

THE U.S. POPULATION AT RISK TO OCCUPATIONAL RESPIRATORY DISEASES

APPENDIX

The U.S. Population-At-Risk to Occupational Respiratory Diseases

Wayne T. Sanderson

In the assessment of agents associated with occupational diseases, the *population-at-risk* indicates the enormity of the problem in the workplace that future research and health needs must address.

This table juxtaposes hazardous agents with diseases they cause or provoke; conjoins these agents with involved occupations; and estimates the number of workers in these occupations potentially at risk to exposure from the associated agents. This approach provides a quick reference to the causes of each disease; the occupations where a prevalence of disease might be expected; and a ranking based on the number of people exposed. The reader should bear in mind that the agents listed may not constitute all factors contributing to the diseases (other etiologic factors may be equally weighty), nor will all workers involved in the listed occupations be exposed to the associated agents. Additionally, only the major industries and occupations in which the agents are used are included in this table; therefore, a particular disease may be exhibited in a job not delineated.

The *population-at-risk* estimate should be taken as an approximation of the number of workers who work closely with an agent and not the number of people who should be considered probable *cases* of disease. *Agents* listed are those which have been noted to contribute to or cause particular diseases. *Industries or Occupations* associated with the agents listed are revised lists from the National Institute for Occupational Safety and Health (NIOSH) criteria documents, NIOSH publication No. 77-181, and epidemiological studies. *Estimates of population-at-risk* are from the NIOSH criteria documents, the National Occupational Hazard Survey (NOHS), and revised estimates based on census data and prevalence studies. Behind each number of estimated people exposed is a letter designation, indicating the source of that estimate:

- **C** = estimates from NIOSH criteria documents addressed to the various agents.
- **H** = estimates from the National Occupational Hazard Survey (NOHS) conducted by NIOSH in 1972-74.
- **R** = estimates from census data and disease prevalence studies.

To simply state that an estimated number of people are occupationally exposed to a particular agent does not solve the complex problem of determining the true magnitude of the hazard. For this, an in-depth look at the concentrations, modes of exposure, and trends in use (among other things) should be considered. The value of these estimates is to indicate (1) where in the work force these toxic agents appear, and (2) the numbers of workers who *may* be exposed to hazardous agents.

Disease	*Agents*	*Industry or Occupation*	*Number*
Aluminosis	Aluminum (powdered metal) [Exposure to aluminum and aluminum oxide is frequently associated with exposure to silica and dusts also]	aluminum alloy grinding aluminum smelting aluminum workers ammunition makers fireworks makers foundry workers petroleum refining plastic making rubber making	575,000 H
	Aluminum oxide	abrasive manufacturing catalyst makers metal grinders potteries refractories	500,000 H
Antimony Pneumoconiosis	Antimony Stibnite (antimony sulfide)	alloy manufacturing ceramic making drug manufacturing fireworks manufacturing leather mordanting mining and milling of antimony paint manufacturing pewter manufacturing pharmaceuticals rubber production textile manufacturing typesetting	1,350,000 H
Argyria	Silver and compounds silver cyanide silver fulminate silver nitrate	alloy manufacturing ceramics coin production chemical laboratory workers dental alloy makers drug manufacturing electrical equipment manufacturing food product equipment manufacturing glass making hair dye manufacturing hard solder makers ivory etching mirror making organic chemical manufacturing photographic workers water treatment	60,000 R
Asbestosis	Asbestos actinolite	brake and clutch lining manufacture and	1,500,000 R

Disease	Agents	Industry or Occupation	Number
	anthophyllite asmosite crocidolite tremolite	installation cement (asbestos) production and application demolition workers furnace and kiln lining insulation and fireproofing manufacture and installation mining and milling of asbestos paint production paper manufacturing plastic manufacturing plumbing power station workers roofing tile production and installation shipbuilding	
Asthma-like Illness "Pneumoconiosis"	Cobalt	alloy manufacturing catalyst workers ceramic manufacturing drug manufacturing electroplaters glass colorers nickel workers paint dryer manufacturing porcelain coloring rubber coloring synthetic ink manufacturing	250,000 H
Baritosis	Barium sulfate	animal oil refining baryta mining brick manufacturing ceramic manufacturing glass making ink manufacturing linoleum production lithopone making paint manufacturing plastic manufacturing soap making textile manufacturing tile manufacturing wax processors	800,000 H
Berylliosis	Beryllium and compounds ammonium beryllium fluoride beryllium carbide beryllium copper alloys beryllium fluoride	aerospace equipment manufacturing alloy manufacturing beneficiation of beryllium minerals beryllium ceramic products beryllium processing and	800,000 R

Disease	Agents	Industry or Occupation	Number
	beryllium hydroxide beryllium oxide beryllium oxyfluoride beryllium phosphors beryllium sulfate zinc beryllium silicate	refining cathode ray tube manufacturers chemical manufacturing electronic equipment manufacturing gas mantle makers metallurgical operations missile technicians nonferrous foundry production nuclear reactor workers phosphor manufacturing refractory material makers tool and die manufacturing welding and torch cutting beryllium alloys	
Bird Breeders' Lung	Avian droppings	bird keepers	100,000 R
Bird Fanciers' Lung	Avian proteins		
Pigeon Breeders' Lung		pigeon breeders	
Byssinosis	Cotton dust	cotton classifiers cotton processing carding drawing & roving ginning growing & harvesting opening, cleaning, picking spinning, winding, twisting spooling, beaming, slashing weaving cottonseed oil mill workers cotton waste reclaimers garnetting	800,000 C
	Flax	flax carders flax mixers flax workers yarn makers	2,000 H
	Jute	jute workers	3,000 H
	Hemp	hemp workers	1,000 H
	Sisal	carpet makers combers of sisal	2,000 H

Disease	*Agents*	*Industry or Occupation*	*Number*
		drawers of sisal rope makers sisal workers twine spinners	
Cer-pneumoconiosis	Ceria (cerium oxide)	alloy manufacturing ammonia production enamel manufacturing glass making graphic art workers ink manufacturing lighter flint makers metal refining mining and milling of cerium optical lens production phosphor production rocket fuel manufacturing textile manufacturing	7,000 H
Coal Workers' Pneumoconiosis due to Carbon	Carbon black	battery manufacturing carbon electrode makers carburization workers cement workers ceramics food processing ink manufacturing paint manufacturing paper production plastic manufacturing printing production, collection, and handling of carbon black rubber manufacturing	35,000 C
	Coal dust anthracite bituminous coal lignite seacoal	loading and transporting of coal mining and milling of coal	150,000 R
	Graphite	brake lining manufacturing cathode ray tube manufacturing commutator brush manufacturing crushing and milling of graphite crucible production electrode making explosive manufacturing foundries lubricant production	250,000 H

Disease	Agents	Industry or Occupation	Number
		match production nuclear reactor workers paint manufacturing pencil lead making pigment manufacturing refractory material makers steel workers stove polish manufacturing	
	Lamp black	cement workers ceramic ware manufacture lamp black production and handling liquid-air explosive manufacture lubricating composition manufacturing steel making	UK
Coffee Workers' Lung	Coffee dust	coffee bean processors	12,900 R
Enzyme Workers' Lung	Bacillus subtilis (detergent enzymes)	detergent workers housewives laundry workers	175,000+ H
Epoxy Resin Workers' Lung	Phthalic anhydride	alizarin dye manufacture alkyd resin manufacture automobile finish makers cellulose acetate plastizers dacron fiber production epoxy resin workers erythrosin manufacture insecticide manufacture mylar plastic manufacture organic chemical synthesis phthalein manufacture plastics manufacture resin making vat dye makers vinyl plasticizer manufacture	54,000 R
Furriers' Lung	Hair dust (animal proteins)	furriers	4,700 R
Hard Metal Disease Tungsten Carbide Pneumoconiosis	Tungsten Carbon plus Cobalt	arc cutting hard metal manufacturing metal cutting milling of tungsten carbide with cobalt	60,000 H

Disease	Agents	Industry or Occupation	Number
	Metallurgical blending of tungsten and carbon with cobalt used as a binder		
Hypersensitivity Pneumonitis			
Farmers' Lung	Micropolyspora faeni (moldy compost) or hay	farmers, especially dairy farmers	2,800,000 R
Mushroom Workers' Lung	Thermoactinomyces vulgaris Thermoactinomyces viridis	clean out crews of mushroom bed houses	<1,000
Bagassosis	Thermoactinomyces sacharii (moldy sugar cane)	sugar cane workers	5,000 R
Maple Bark Strippers' Disease	Cryptostroma Corticale (moldy maple bark)	bark strippers loggers pulp mills sawmill workers	80,000 R
Malt Workers' Lung	Aspergillus claratus (moldy malt)	malt house workers	1,800 R 1,700 R
Suberosis	Penicillium frequentans (moldy cork dust)	cork workers	7,000 H
Cheese Washers' Lung	Penicillium caseii (cheese mold)	cheese workers	25,000 R
Woodworkers' Lung	Alternaria sp. (moldy wood chips)	carpenters construction workers joiners sawmill workers wood pulp workers	10,000 R
Sequoiosis	Pullalaria (moldy redwood dust)	loggers sawmills	<1,000 R
Paprika Splitters' Lung	Mucor sp. (paprika dust)	paprika splitters	
Wheat Weevil Disease	Sitophilus grainarius (wheat weevil) (infested wheat)		
Infectious Disease			
Anthrax	Bacillus anthracis	agricultural workers goat hide handlers renderies	>10,000 R

Disease	Agents	Industry or Occupation	Number
		veterinarians wool handlers	
Brucellosis	Brucella sp.	agricultural workers consumers of unpasteurized milk or milk products meat packers slaughterhouse workers veterinarians	>10,000 R
Histoplasmosis	Histoplasma capsulatum	farm workers endemic in certain areas	
Tuberculosis	Mycobacterium tuberculosis	coal workers foundry workers hard rock miners medical laboratory workers nurses physicians saloon workers	UK (30,000 cases per year)
Metal Fume Fever	Antimony Cadmium Copper 1° agents Iron Magnesium Manganese Nickel Selenium Tin Zinc	brass founders copper and zinc melters welders zinc galvanizers zinc smelters	40,000 R
Neoplasms Nasopharyngeal Neoplasms	Chromium salts	alloy makers chemical laboratory workers electroplaters miners and millers pigment makers tanners	1,000,000 H
	Nickel	battery makers ceramic makers chemists dyers electroplaters enamelers ink makers magnet makers oil hydrogenators paint makers pen point makers spark plug makers stainless steel workers textile dryers	250,000 H

Disease	Agents	Industry or Occupation	Number
		varnish makers welders	
	Nickel salts	nickel mining, smelting, refining	250,000 H
	Wood dust	carpenters furniture makers loggers plywood & structural wood producers sawmill workers woodworkers	775,000 H
No known pneumoconiosis demonstrated to be caused by fibrous glass alone.	Fibrous glass	aircraft workers construction workers glass workers glass fiber manufacturers insulation manufacturers laundry workers refrigeration workers shipyard workers	300,000 H
	Mineral wool	mineral wool manufacturers	3,000 H
No specific respiratory disease associated with the inhalation of Zirconium or its compounds	Zirconium or zirconium compounds	abrasive makers ceramic makers ceramic manufacturing crucible manufacturing deodorant manufacturing enamel manufacturing explosive manufacturing foundry workers glass makers incandescent lamp manufacturing metallurgists pigment manufacturing rayon spinneret makers refractory material makers textile waterproofers vaccuum tube manufacturing	150,000 H
Occupational Asthma and Rhinitis		See chapter: Occupational Asthma & Rhinitis	
Polymer Fume Fever	Polytetrafluorethylene (teflon, fluon) (PTFE)	polytetrafluoroethylene producers and handlers cutters of metal welders	100,000 H

Disease	Agents	Industry or Occupation	Number
Porcelain Refinishers' Lung Isocyanate Disease	Hexa methylene diisocyanate	rubber workers ship burners textile processors wire coating workers	3,000 H
	Toluene diisocyanate (paint catalyst)	adhesive workers foam insulation workers isocyanate resin workers lacquer workers organic chemical synthesizers paint sprayers polyurethane manufacture	6,000 H
Pulmonary Neoplasms	Arsenic	alloy makers aniline color makers arsenic workers babbitt metal workers brass makers bronze makers ceramic enamel makers ceramic makers copper smelters drug makers dye makers enamelers fireworks makers gold refiners herbicide makers hide preservers insecticide makers lead shot makers painters paint makers petroleum refinery workers pigment makers printing ink workers rodenticide makers semiconductor compound makers silver refiners taxidermists tree sprayers type metal workers water weed controllers weed sprayers	150,000 C
	Bischloromethyl ether	ion exchange resin makers laboratory workers organic chemical synthesizers polymer makers	UK
	Coal tar & pitch volatiles	artificial stone makers asbestos goods workers	250,000 H

Disease	*Agents*	*Industry or Occupation*	*Number*
		asphalt workers	
		battery workers	
		boatbuilders	
		brick workers	
		briquette makers	
		brush makers	
		coal tar workers	
		creosoters	
		coke oven workers	
		electrode makers	
		electric equipment makers	
		gas house workers	
		glass blowers	
		insulators	
		linemen	
		miners	
		painters	
		pavers/road workers	
		pipeline workers	
		railroad track workers	
		roofers	
		rubber workers	
		shingle makers	
		water proffers	
		shipyard workers	
		wood preservers	
	Chromium	alloymakers	175,000 C
		catalyst workers	
		ceramic workers	
		drug makers	
		electroplaters	
		glass colorers	
		nickel workers	
		paint dryer makers	
		porcelain colorers	
		rubber colorers	
		synthetic ink makers	
	Radon daughters	uranium miners	5,900 R
Pulmonary Reactions to Man-made Fibers and Miscellaneous Pneumoconioses, Including "Mixed Dust" Pneumoconioses			
Respiratory Effects of Inhaled Toxic Agents	Ammonia	aluminum workers	3,100,000 H
		amine workers	
		ammonia workers	
		annealing	

Disease	Agents	Industry or Occupation	Number
		bronzers	
		chemical workers	
		coal tar workers	
		coke production	
		compressed gas workers	
		drug manufacturing	
		dye manufacturing	
		electroplating	
		electrotypers	
		explosive manufacturing	
		farming	
		fertilizer manufacturing	
		galvanizing	
		glue making	
		lacquer/latex workers	
		metal extraction	
		metal powder processing	
		mirror silvering	
		paper production	
		perfume manufacturing	
		pesticide manufacturing	
		petroleum refinery workers	
		photographic film makers	
		rayon manufacturing	
		refrigeration workers	
		resin makers	
		rubber workers	
		sewer workers	
		steel workers	
		sugar refiners	
		sulfuric acid manufacturing	
		tanneries	
		transportation workers	
		water treatment	
	Cadmium and Cadmium containing compounds	alloy manufacturing	150,000 H
		auto mechanics	
		battery manufacturing	
		braziers	
		cadmium smelting, refining, processing	
		ceramics	
		copper refining	
		dental amalgam makers	
		electroplating	
		engravers	
		glass making	
		lead refining	
		metalizers	
		paint manufacturing	
		pesticide manufacturing	
		pigment makers	
		solderers	

Disease	Agents	Industry or Occupation	Number
		textile printing welders zinc smelting and refining	
	Cadmium Chloride		18,000 R
	Cadmium Oxide		20,000 R
	Cadmium Sulfide		25,000 R
	Chlorine	aerosol propellant makers alkali salt manufacturing aluminum purification bleaching carpet makers chemical manufacturing chlorinated solvent manufacturing chlorine workers disinfectant manufacturing dye manufacturing flour bleachers gold extraction ink manufacturing iron workers laundry workers paper/pulp bleaching pesticide manufacturing petroleum refinery workers plastic manufacturing rayon manufacturing refrigeration workers rubber production sewage treatment silver extraction submarine workers sugar refining tin recovery transportation workers water treatment	75,000 R
	Hydrogen sulfide	barium carbonate makers brewery workers caisson workers cellophane makers citrus root fumigation coke oven workers depilatory makers dye makers farmers fat renderers felt makers fermentation process workers	25,000 H

Disease	Agents	Industry or Occupation	Number
		fertilizer manufacture	
		fish processing	
		lithographers	
		miners	
		natural gas makers	
		paper pulp makers	
		petroleum/gas refining & processing	
		photo engravers	
		rayon makers	
		sewage treatment plant workers	
		sewer workers	
		silk makers	
		slaughterhouse workers	
		smelting of metallic ore	
		soap makers	
		sugar beet processors	
		sulfuric acid purifiers	
		sulfur makers	
		synthetic fiber makers	
		tannery workers	
		tunnel workers	
		well diggers	
	Mercury (and its compounds)	amalgam makers	150,000 R
		bacteriocide manufacturing	
		battery makers	
		boiler makers	
		bronzers	
		cap loaders, percussion	
		caustic sode makers	
		ceramic workers	
		chlorine makers	
		dentists	
		drug makers	
		explosive manufacturing	
		fireworks manufacturing	
		fungicide manufacturing	
		fur preserving/processing	
		gold/silver extraction	
		histology technicians	
		insecticide manufacturing	
		jewelers	
		mercury workers/ mining/refining	

Disease	Agents	Industry or Occupation	Number
		paint making paper manufacturing pesticide workers photographers tanneries taxidermists thermometer/barometer makers	
	Osmium tetroxide	alloy manufacturing drug manufacturing histology technicians organic chemical synthetization osmium tetroxide production platinum hardening synthetic ammonia manufacturing	3,000 R
	Oxides of Nitrogen Nitric oxide--NO Nitrogen dioxide--NO_2	braziers dentists diesel engine maintenance and mechanic workers dye makers fertilizer manufacturing fire fighters food and textile bleachers explosive workers garage workers gas and electric arc welders jewelers medical technicians metal cleaners miners nurses organic chemical synthesizers physicians silo fillers sulfuric acid manufacturing welders	950,000 H
	Oxides of Sulfur Sulfur dioxide--SO_2 Sulfur trioxide--SO_3	beet sugar bleachers bleachers boiler water treatment brewery workers diesel engine operators and repair disinfectant makers firemen food bleaching foundry workers fumigant manufacturing	125,000 H

Disease	*Agents*	*Industry or Occupation*	*Number*
		furnace operators gelatin bleaching glass manufacturing ice making ore smelting paper manufacturing petroleum refining preservative makers protein processing refrigeration workers sodium sulfite manufacturing sulfuric acid manufacturing tanneries thermometer manufacturing (vapor) wine makers wood bleaching	
	Ozone	air treaters arc welding cold storage food preservers industrial waste treatment liquor agers odor controllers oil bleaching organic chemical synthesis sewage treatment textile bleaching water treatment wax bleaching wood aging	750,000 R
	Phosgene	chlorinated compound manufacturing drug manufacturing dye manufacturing firemen isocyanate manufacturing insecticide manufacturing metallurgists organic chemical synthesis phosgene workers plastics production resin manufacturing welding/brazing	6,000 H
	Sulfuric acid	aluminum sulfate synthesis battery manufacturing cellulose workers chemical manufacturing copper sulfate synthesis	200,000 C

Disease	Agents	Industry or Occupation	Number
		detergent manufacturing dye manufacturing explosive manufacturing food processing glue making jewelers leather workers metal cleaners paint makers paper production phenol manufacturing	
	Vanadium and Vanadium containing compounds		174,000 R
	Vanadium pentoxide	alloy manufacturing catalysts manufacturing ceramics cleaning of oil fired boilers dye manufacturing ferrovanadium workers glass manufacturing organic chemical synthesization petroleum refining photographic chemical makers printing textile dye workers vanadium smelting, refining, processing welding	3,000 R
	Other Vanadium oxides halides salts of vanadium sulfates vanadates		
Siderosis	Iron and iron oxides	arc welders boiler scalers friction saw operators grinders metal workers mining, milling and transporting iron ores oxyacetylene cutters polishers production and refining of metal and alloys containing iron	1,775,000 R

Disease	Agents	Industry or Occupation	Number
		silver finishers stainless steel makers steel foundry workers welding	
	Fibrous		
Silicate Pneumoconioses	Attapulgite clay (Fuller's earth)	mining and milling of attapulgite	120,000 H
	Fibrous talc	agricultural chemical manufacturing candy molding ceramics chalk making cosmetics crayon manufacturing dusting powder manufacturing foundries (ferrous and nonferrous) insecticide manufacturing lubricant production mining and milling of talc paint manufacturing paper production pharmaceutical manufacturing pigment production polishing peanuts and rice rubber making roofing material manufacturing salami dusting soap filler addition textile manufacturing white shoe cleaners	1,800,000 H
	Sericite	of no commercial importance; was implicated in the 1930's as a cause of silicosis. Subsequent work has not supported this hypothesis.	UK
	Sillimanite	furnace patching mining and milling of sillimanite porcelain manufacturing for electrical equipment refractories	UK

Disease	Agents	Industry or Occupation	Number
	Wollastonite	cements production ceramics mining and milling of wollastonite plastics manufacturing	67,000 H
	Non-fibrous		
	Bentonite	decolorizing oil production making refractory linings mining and milling of bentonite preparing fine grouting fluids thickening drilling muds water softener production and addition	250,000 H
	Kaolin	bagging and loading of kaolin cements production ceramics paint making paper manufacturing pharmaceutical manufacturing mining and milling of kaolin	1,450,000 H
	Mica	electrical industry insulation production and installation mining and milling of mica or feldspar paint production paper production wallpaper manufacturing	300,000 H
	Portland cement	brick masons bridge building building construction burial vault builders cement plant production (milling) cement workers concrete workers drain tile makers heat insulation makers oil well builders silo builders storage tank builders tunnel builders water pipe makers	500,000 H

Disease	Agents	Industry or Occupation	Number
Silico-antimoniosis	Antimony plus Crystalline Silica	Antimony miners	50R
Silicosiderosis	Iron ore Iron oxides plus Crystalline silica	boiler scalers foundry workers iron mining iron and steel workers ochre mining welding	UK
Silicosis	Crystalline silica diatomaceous earth flint granite quartz sand sandstone slate	cement production workers coal mining and milling foundries (ferrous and nonferrous) glass making insulation production and installation metal mining and milling nonmetallic mining and milling plastic manufacturing porcelain production pottery making refractories road working rubber manufacturing sandblasting scouring soap manufacturing stone cutting stone masons tile and clay production tunneling wood filler making	2,300,000 R
Silver Polishers' Lung	Silver plus Iron oxide	jewelers silver polishing silversmiths	13,000 R
Stannosis	Tin Tin oxide	babbitt metal manufacturing brass founding brittania metal making bronze founding dye manufacturing fungicide manufacturing	225,000 H

Disease	*Agents*	*Industry or Occupation*	*Number*
		pewter makers pigment manufacturing plastic manufacturing solder manufacturing textile manufacturing tin miners and millers tin refiners and smelters type metal making	
Trimellitic Anhydride Lung Disease TMA Disease	Trimellitic anhydride	chemical manufacturers dye and pigment manufacturing epoxy resin workers paint manufacture pharmaceutical manufacturing resin manufacturing vinyl plasticizing	11,000 H 10,000 H