Diffuse Infiltrative Lung Disease
## Including Selected Pneumoconioses

Introduction

In this topic, we will deal with conditions that tend to 1) involve both the lungs diffusely, and 2) primarily produce abnormalities of the pulmonary parenchyma (as opposed to the airways and blood vessels, which are dealt with elsewhere). All diseases may be classified by anatomic, physiologic, and clinical schemes. In pathology, we tend to work from anatomic classifications in understanding the physiologic and clinical manifestations of diseases. We will start with a discussion of the anatomic patterns of diffuse infiltrative lung disease, and then move on to specific conditions.

Anatomic patterns in parenchymatous lung disease

Normal pattern. In routine histologic section of the normal lung, the alveolar walls are a delicate filigree, with the only visible parenchymal components being the diaphanous pneumocytes (types 1 and 2 not being distinguishable) and occasional intracapillary blood cells. Capillary endothelial cells are not distinguishable from the pneumocytes. Stromal elements such as fibroblasts, elastic, and collagen, are not discernible. The alveolar basement membrane is so thin as to be submicroscopic. Bronchi and bronchioles are easily made out because of their columnar cell lining, but distinguishing pulmonary artery branches from pulmonary vein tributaries occasionally gives students problems. A rule of thumb is that arteries (A) tend to course with bronchi (B), while veins (V) eschew this pulmonary pipe-chase.
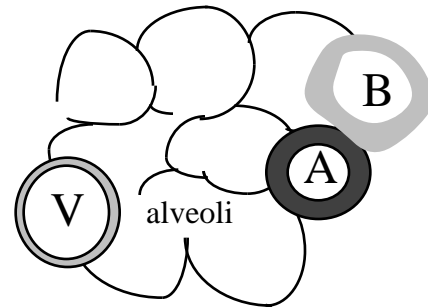

Intra-alveolar pattern. This is the classic pattern of bacterial lobar and lobular pneumonias. It is also seen in aspiration pneumonia and in uncommon conditions such as pulmonary alveolar proteinosis, Goodpasture's syndrome, and idiopathic pulmonary hemosiderosis. In this pattern, the alveolar spaces are occupied by materials that give the water-density opacities referred to as "infiltrates" by radiologists. These materials may be **neutrophils** (in bacterial pneumonias), **thin serous fluid** (as in pulmonary edema and Pneumocystis pneumonia), **viscous gelatinous substance** (pulmonary alveolar proteinosis), **blood** (as in Goodpasture's syndrome), **eosinophils** (Loeffler's syndrome, etc), **macrophages** (hemosiderosis) or **fibrous connective tissue** (organizing bacterial and aspiration pneumonias). In fact, of all the inflammatory/hematopoietic cell types, lymphocytes and plasma cells are notable in that they tend **not** to accumulate in the alveolar spaces, instead preferring the interstitium as a locus for their inflammatory activities.
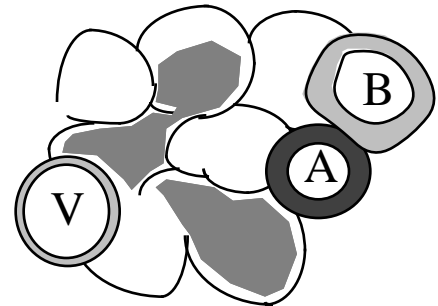

In terms of pulmonary functional effects, intra-alveolar lesions tend to affect pulmonary venous blood oxygen tension due to shunting produced by abnormal ventilation/perfusion balance. Because CO_2 is more readily diffusable through water than O_2, one would expect hypoxemia to dominate the results of clinical arterial blood gas measurements. Hypercapnia should then be considered a dire message that the disease process is *in extremis.* Some potentially fatal intra-alveolar diseases, notably acute bacterial pneumonia, produce death more through the systemic toxic effects of microbial and inflammatory byproducts than through specific embarrassment of pulmonary function.

Interstitial pattern. In this pattern, substances remain confined to the interstitium rather than proceeding into the alveoli. Because the interstitium is intrinsically much less voluminous than the alveolar spaces, much less fluid, exudate, or other abnormal materials may accumulate there to produce an equivalent pathophysiologic effect on gas exchange. Therefore, the radiographic

expression for a given level of functional embarrassment may be less severe for interstitial than for intra-alveolar lesions. Abnormal substances found in the interstitium include **serous fluid** (diffuse alveolar damage [DAD], equivalent to the clinical adult respiratory distress syndrome [ARDS]), **lymphocytes** (viral pneumonias, usual interstitial pneumonia, lymphocytic interstitial pneumonia), **plasma cells** (often associated with collagen vascular diseases), **macrophages** (sarcoidosis), and **fibrous connective tissue** (interstitial fibrosis, "honeycomb lung"). Neutrophils, so prominent in intra-alveolar responses to acute injury, tend to play a minor rôle in interstitial reactions.
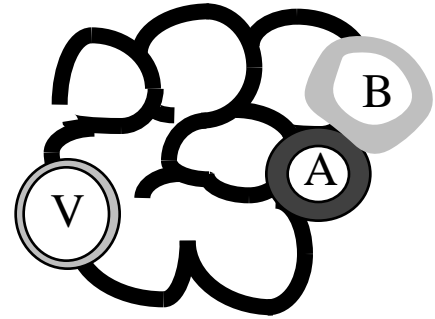
When an interstitial process involves only fluid and inflammatory cells, shunting of unoxygenated blood through the abnormal areas results in hypoxemia without significant hypercapnia. When, however, the interstitium becomes fibrotic through ingrowth of fibroblasts and collagen, the lung becomes less deformable and may not expand normally in inspiration. In such a case, the result is a *ventilatory* deficit due to a *restrictive* (rather than obstructive) mechanism. Here, hypercapnia would be expected to accompany hypoxemia.
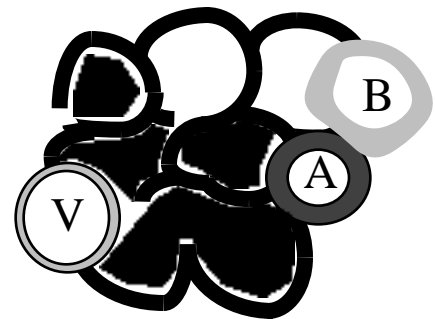
Combination intra-alveolar/interstitial pattern. As you have probably come to expect, few concepts in medicine adhere to pristine purity in actual observation and practice. Anatomic patterns of lung disease are no exception. There are some conditions which tend to demonstrate a mixture of the intra-alveolar and interstitial patterns. The most important of these is **diffuse alveolar damage** (DAD), the anatomic correlate of clinical **adult respiratory distress syndrome** (ARDS). Less common conditions with a similar pattern are **desquamative interstitial pneumonia** (DIP), in which macrophages fill the alveoli, and **eosinophilic pneumonia**, in which eosinophils predominate.

Diffuse alveolar damage (DAD)

DAD is an anatomic pathology term referring to a specific constellation of histologic findings in the lung parenchyma. For all practical purposes, it is congruent to ARDS, which is a clinical term. DAD is the lesion which is seen in most acute lung injury and may, through episodic expression and/or misfortuitous resolution, lead to many of the chronic interstitial lung diseases.

Etiology. A large number of causative agents are known to produce DAD. The most important are:

Shock (especially septic)	Oxygen in high concentration	Smoke
Cancer chemotherapeutic agents	Heroin	Radiation
Uremia	High altitude	Acute pancreatitis
Viruses	*Mycoplasma*	Unknown

Although this may seem a hodgepodge of unrelated trouble-makers, perhaps one common thread is the concept of *toxicity*. While this may seem straightforward in the case of etiologic agents like chemotherapeutic drugs and radiation, toxicity may also be invoked in conditions which produce an inflammatory response, in which the body's own products may act as toxins. Theorists on the nature of pulmonary toxicity often invoke that oft maligned villain, the free radical (such as hydroxyl, OH·) and other oxygen-based highly reactive molecular species, including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and singlet oxygen (O_2·). These substances are able to inactivate sulfhydryl-containing enzymes, disrupt DNA, destroy cell membrane integrity, and generally contribute to the total entropy of the universe with great enthusiasm.

In the end, the molecular basis of acute alveolar injury remains unproved speculation. Whatever the toxin(s), the targets are the type 1 pneumocytes and alveolar capillary endothelial cells. The type 2

pneumocytes are hardier and are the cells responsible for regeneration of the alveolar lining — if the patient survives.

Pathologic   anatomy. Two stages are described, with all cases demonstrating the first stage, and selected cases proceeding into the second.

Stage 1. All cases of DAD begin with the acute or **exudative stage**, which lasts for about a week. The earliest change is intra-alveolar *and* interstitial edema. This is followed by elaboration of the characteristic hyaline membranes, which are eosinophilic blankets that line the alveolar spaces. These appear homogeneous by light microscopy, but ultrastructurally are shown to consist of the cellular debris of sloughed pneumocytes embedded in a matrix of fibrin. After about one week, the interstitium becomes prominently infiltrated with lymphocytes, histiocytes, and plasma cells. Since the architectural skeleton of the lung is not destroyed, it is possible for this stage to resolve without permanent alteration of the pulmonary anatomy; consequently, no permanent loss of respiratory function results. Resolution is followed by the proliferation of type 2 pneumocytes, which repave the alveolar wall and (at least as is shown in animal experiments) differentiate into type 1 pneumocytes.

Stage 2. In selected cases, the exudative stage is followed by the **proliferative** stage (also called the **organizing** stage). In this stage, permanent alteration of the lung anatomy results, due to the deposition of collagen and elastin by fibroblasts proliferating in the interstitium. The final product of the proliferative stage is the "honeycomb lung," where broad fibrous trabeculae traversing the vacuous wasteland of destroyed alveoli results in a lung that is a gross caricature of alveolar microarchitecture. The honeycomb lung has a strikingly dramatic gross and radiographic appearance.

Pathophysiologic consequences. In the exudative stage pulmonary function is compromised due to 1) increased gas diffusion path due to edema fluid and inflammatory cells within the interstitium and alveoli, 2) decreased lung compliance[1], and 3) (as is postulated) increased surface tension of the alveolar walls due to the presence of the hyaline membranes, making it more difficult to re-expand any collapsed alveoli on inspiration. All of these result in an imbalance of ventilation and perfusion, producing local shunting of underoxygenated pulmonary arterial blood through the abnormal portions of the lung. Admixture of this shunted blood with the rest of the pulmonary venous return produces a decreased P_{O_2} in the blood serving the systemic arterial circulation.

It is a generally held rule that fibrous tissue, once deposited in the body, does not go away. Therefore, the proliferative stage is a one-way street to thickened, fibrotic alveolar walls, with resulting continuation and/or accentuation of the first two of the pathophysiologic consequences cited above. Although we often think of fibrosis as a chronic, months-long process, an unfortunate individual, who, previously healthy before developing DAD/ARDS, may develop end stage honeycomb lung in just 10 days.

Chronic Interstitial Pneumonias

Chronic interstitial pneumonia (CIP) is a classical term with little utility in modern nosology. The term implies a chronic, progressive abnormal alteration in the interstitium in which the interstitium is infiltrated by cells typically associated with the inflammatory response (*e.g.*, lymphocytes, histiocytes, plasma cells). If this sounds like a squishy, evasive definition, it probably is because the term "inflammation" is purposely left out, even though we have learned generally to equate the term "pneumonia" with inflammation of the lung. To see why we cannot consider all CIP's as inflammations, let us look at the classic categorization of CIP by A. A. Liebow in 1968.

---

[1] "Compliance" is a physical term, defined essentially as the change in volume per unit increment in applied pressure. Decreased compliance means that more pressure need be exerted to expand the lungs to a given volume. Since *work = pressure* x *change in volume*, decreased pulmonary compliance results in increased work of breathing. The subsequent increased caloric demand may have profound effects on the nutritional status of the patient.

Usual interstitial pneumonia (UIP)　　　　　Desquamative interstitial pneumonia (DIP)

Lymphocytic interstitial pneumonia (LIP)　　　Giant cell interstitial pneumonia (GIP)

Bronchiolitis with interstitial pneumonia (BIP)

Liebow attempted to categorize cases of a mysterious lung disease described clinically in 1944 by Hamman and Rich. The "Hamman-Rich syndrome" came to be considered any idiopathic condition that produced end-stage honeycomb lung, typically very rapidly. The term is best not used today, as it has no pathologic relevance.[4]

Let us first dispense with some of the cull-outs and curiosities. **Lymphocytic interstitial pneumonia** (LIP) is really a low grade malignant lymphoma of the lung. Therefore it is not an "-itis" at all, as the lymphocytes presumably are in the interstitium because they are neoplastic rather than as a part of the chronic inflammatory response. LIP is an uncommon complication of AIDS and may actually be due to HIV infection itself, rather than an opportunistic pathogen. **Giant cell interstitial pneumonia** (GIP) is so rare that Liebow himself had seen only two cases by the time of his 1968 monograph. Recent studies have suggested that GIP may be related to exposure to "hard metal," an alloy of tungsten carbide and one or more metals. **Bronchiolitis with interstitial pneumonia** (BIP) is now basically classed as **bronchiolitis obliterans with organizing pneumonia** (BOOP!). This is principally an airway disease and will not be considered further here. This leaves UIP and DIP. There is some clinical relevance in distinguishing each from the other in patients with interstitial lung disease, as will be discussed below.[5]

Usual interstitial pneumonia. So named because this is the most commonly encountered of all the idiopathic CIP's of Liebow, UIP is characterized histologically by the infiltration of the interstitium by lymphocytes and histiocytes, and occasionally by plasma cells and/or eosinophils. These are replaced gradually by fibroblasts who lay down collagen and eventually produce a fibrotic, honeycomb lung.

Desquamative interstitial pneumonia. DIP is so named because of the prominent feature of large numbers of large, mononuclear cells lying within the alveolar spaces (making this a combination interstitial/intra-alveolar lesion). The name is somewhat misleading, since "desquamate" would seem to imply some kind of flat cell (like a pneumocyte) which is "scaling off" into the alveoli. Actually, the "desquamated" cells are not flat but ellipsoidal and are not pneumocytes but histiocytes. In the interstitium, the inflammatory infiltrate consists of a mixture of cells similar to those seen in UIP.

Both UIP and DIP have unknown etiology and pathogenesis. Most patients are older than age 40 at time of diagnosis, with DIP patients being slightly younger than those with UIP. About 20% of UIP patients have evidence of collagen-vascular disease (such as lupus); with DIP, this proportion is much smaller. Simply by observation, it has been shown that DIP is a milder disease than UIP and responds better to the use of the anti-inflammatory pharmacologic properties of steroids (see table, below).

	UIP	**DIP**
Mean years to death.	6.2 y	16.8 y
Percent showing improvement with steroids.	8%	68%

Still, both of these diseases are fatal after a prolonged course, often of years, and no "cure" is available.

Pneumoconiosis

---

[4] But don't say that if your attending uses the term first! (Whether or not to throw around eponyms on ward rounds is a tough decision. Generally surgeons love them, but some internists, especially the more scientific ones, may react violently)

[5] However, it should be noted that, although the distinction of UIP from DIP is demanded widely by American and Canadian pulmonologists, British physicians rarely make the distinction. This is just one small, insignificant example of the sometimes profound disparity in medical nosology and philosophy between anglophonic colleagues across the Atlantic.

This term describes conditions caused by the **reaction of the lung to inhaled dusts**. These conditions are conveniently discussed as interstitial lung diseases in that they tend to produce interstitial fibrosis, which may be nodular and/or diffuse with honeycombing. They are peculiar clinically in that they tend to affect certain occupations as a group, such that a physician who practices in certain areas may by experience become expert in a particular pneumoconiosis, while one who practices elsewhere may never see a single case in his/her career. The pneumoconioses also are peculiar pathologically in that usually the inciting dust remains in the lung (and occasionally other tissues) where it may be detected by various means (including routine microscopy) available to the pathologist.

The dusts involved must be of the correct physical dimension to be deposited in the alveolar walls and respiratory bronchioles. Generally, particles >10μm are not respirable; those <0.5μm will be inhaled and then exhaled without being deposited in tissue. Particles 1 to 2 μm in diameter are mathematically most likely to be deposited. After the dusts are impaled on the alveolar walls, macrophages respond to the presence of a foreign substance by phagocytosing and attempting to destroy the invaders. Since human enzymes were designed to reek havoc on organic molecules rather than inorganic minerals, about all the macrophages can do is destroy themselves (thus releasing the dust particle again, for more sports action, coming right up!) and any innocently bystanding host pulmonary tissue that happens to be part of the scenery. This is a very glib and convenient explanation of the pathogenesis of pneumoconioses but unfortunately does not explain why some dusts (in particular, calcium minerals) are not fibrogenic but others (such as silica and silicates) are extremely so. At any rate, macrophages seem to be the pivotal factor in producing the clinical disease and are capable of elaborating a substance, **macrophage fibrogenic factor**, which has been shown to stimulate fibroblasts to produce collagen. We will consider the important pneumoconioses separately:

Silicosis. Classical silicosis is caused by inhalation of dusts composed of silica (SiO_2), the second most common class of minerals in the earth's crust (after the feldspars). This term *excludes* disorders produced by other silicon compounds, such as talc and asbestos, which produce their own specific pneumoconioses. Mineralogical distinction of the various forms of silica is based upon the crystalline structure of the specific mineral. Quartz, cristobalite, and tridymite are all crystalline forms of silica, while diatomite is an amorphous form.[6] Occupations at risk for silicosis include gold mining, quarrying for sandstone, granite, and slate, cleaning of castings in foundries, and boiler scaling. Sandblasting, once considered a prime occupation at risk for silicosis[7] , now properly employs non-siliceous abrasives, such as metal grit (boy, that sounds a *lot* safer, doesn't it?) However, despite these gains in workplace safety, 1993 brought an alarming report of numerous cases, apparently of *acute* silicosis (see below), in Mexican nationals working sandblasting jobs in Central Texas.

Anatomically, **chronic silicosis** manifests itself as discrete fibrous nodules situated around respiratory bronchioles. These nodules contain silica which may or may not be detectable by polarized light microscopy. **Acute silicosis**, an unusual form of the disease, results from heavy dust exposure over a relatively short period of time (1 to 3 years, as opposed to 20 to 40 years for chronic silicosis) and produces a pathologic picture resembling **pulmonary alveolar proteinosis**, with intra-alveolar deposition of gelatinous proteinaceous material.

An interesting observation is the well-documented association between silicosis and **pulmonary tuberculosis**. Experimentally it has been shown that silica interferes with the ability of macrophages to inhibit the growth of *Mycobacterium tuberculosis*.

Talcosis. Talc, a silicate($3MgO \cdot 4SiO_2 \cdot H_2O$) may enter the lungs through inhalation or through the bloodstream, the latter circumstance occurring when talc used as a pharmaceutical filler is

---

[6] But I would certainly not memorize this mineralogical information; this is about as far off the mainstream of Houston medical practice as you can get. It *is* something nice to get into if you would like to become a expert in an area where there would be minimal local competition.

[7] A notice chalked up in a foundry in Coventry, England, in 1934 read, "Join the navy and see the world; become a sandblaster and see the next."

inappropriately injected by an intravenous drug abuser.[8] Talcosis has occurred in talc miners and millers, but pathologists in our geographic area most often find this condition serendipitously (and subclinically) in autopsies of intravenous drug users who just couldn't say no to the allure of a soft, greasy, white mineral *(…pssst!…hey kid! Try* my *stuff. It's got the lowest Mohs in town. Just try to scratch gypsum with this!)*

Talcosis is manifested anatomically by focal or diffuse interstitial fibrosis, sometimes with foreign body granulomas. The most dramatic finding is the presence of large numbers of highly birefringent talc particles easily seen by even the most untalented morphologist by microscopically examining routine histologic lung sections between crossed polarizers.

Coal Workers' Pneumoconiosis. This disease is so weasily named because no one really knows just what foreign substance or substances produce the disease. Coal miners are exposed to a mixture of dusts, including carbon, quartz (which is silica, remember), kaolin and mica (both silicates), and mineral carbonates of iron, calcium, and magnesium. It may be convenient, in this etiologic vacuum, to consider CWP as a reaction to the synergistic stimulation of the lungs by some permutation of these various dusts. It is important to remember that CWP is *not* nosologically congruent to silicosis (discussed above), *nor* is it a simple reaction to elemental carbon, as the lay term "black lung disease" would seem to imply. CWP occurs in two forms:

Simple CWP. This is generally clinically undetected. Morphologically the condition features the presence of **dust macules** and **coal nodules** in the interstitium. Both are grossly visible as black spots on the cut surface of the lung, but nodules are palpable, while macules are not. The macules may be seen in urban dwellers with no mining exposure, but the nodules are considered specific features of CWP. In simple CWP, there is little if any pulmonary functional deficit, and the chest x-ray may be normal.

Complicated CWP. This is characterized by the development of large areas of interstitial fibrosis, referred to as **progressive massive fibrosis**.[9] Grossly, there are large black masses, often with central cavitation, distributed throughout both lungs. As one might expect, there is compromise of pulmonary function with shunting and obstructive/restrictive ventilatory effects.

Other observations concerning CWP. **Caplan's syndrome** denotes the presence of fibrotic nodules (up to 5 cm. diameter) occurring in coal workers with **rheumatoid arthritis**. **Tuberculosis** is also strongly associated with CWP, and some believe that TB has an important rôle in the development of the pneumoconiosis.

Asbestosis. Asbestos (referred to by Pliny the Elder, AD 23–79, as "the only flax which is not consumed by fire"[10]) is a term used to denote a group of fibrous silicates. The most prevalent in nature and industry is chrysotile ($Mg_6Si_4O_{10}(OH)_8$), which consists of curved fibers. Less abundant are the amphiboles, which are chemically diverse and consist of much larger straight fibers. All forms of asbestos produce disease. Although chrysotile is the major culprit in the pathogenesis if interstitial fibrosis (due to its abundance), its fibers are so small that the morphologic "giveaway" under the microscope is the less prevalent but larger, straight amphibole fibers, which are admixed with the essentially submicroscopic chrysotile. The amphiboles, through the action of host

---

[8] But this is not really a pneumoconiosis, since, by definition, the term is limited to a condition that is the result of *inhaled* dusts.

[9] I really don't think that naming diseases like this is a good idea. The very name of the condition could frighten the patient to death. In this regard, the only disease name I know of that is worse is "lethal midline granuloma," as in "Mr. Jones, the tests have shown that you have *lethal midline granuloma* ; but don't worry, I have these sample pills I'd like you to take…" Fortunately, perhaps partly as beneficial fallout from the politically correct euphemism movement, this term has fallen into disuse.

[10] Pliny was an encyclopedic student of natural history whose works shaped scientific thought for centuries. His last lesson was in the field of geology. Lured to shore by a "strange cloud formation" over Mt. Vesuvius, Pliny asphyxiated from the gaseous emissions belched by the volcano during the famous eruption that iced the cities of Pompeii and Herculaneum.

macrophages, become coated with micelles of hemosiderin, producing the characteristic beaded appearance of the coated fiber, which is then called a "ferruginous body," even though the iron coating has nothing to do with the development of disease. The diagram on the next page shows the relative sizes of a large ferruginous body, typical chrysotile fibers, and, for a sense of scale, typical staphylococci and an erythrocyte.
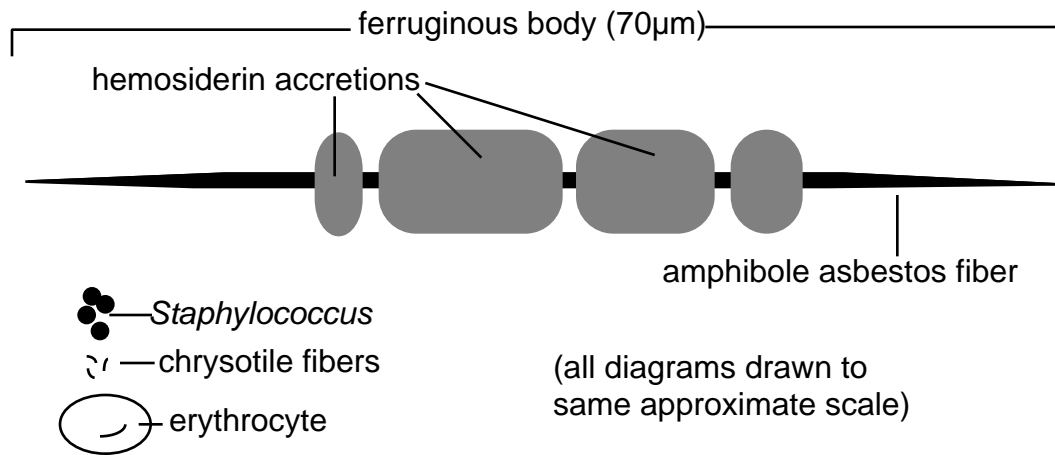
Asbestos exposure has been associated with a number of pathologic changes in the lungs and pleura, as listed below:

Interstitial fibrosis   Benign serous pleural effusion
Bronchogenic carcinoma   Malignant mesothelioma
Fibrous plaques of the parietal pleura

Much has been made in the lay press of the observation that even brief, casual exposure to low levels of asbestos dust may produce fatal asbestosis or one of the associated malignant neoplasms. While this is not inaccurate, it should be kept in mind that the great majority of cases of asbestos-related disease occurs in individuals who have had heavy occupational exposure over a long period of time. Also, while we are demythologizing, it should be noted that while many conceive of mesothelioma as *the* asbestos-related cancer, actually bronchogenic carcinoma is much more common among asbestos-exposed individuals. Moreover, the carcinogenic potential of asbestos is markedly synergized by cigarette smoking. Male asbestos workers who smoke have a risk of lung cancer mortality *92 times* that of nonsmokers with no asbestos exposure.

Mesothelioma, which has been shown to be induced by amphibole asbestos only (not chrysotile), is a morphologically very interesting neoplasm. Although it is a true cancer in the sense that it can invade and metastasize, it tends to grow so as to line the pleural cavity and may completely encase the lungs in its unyielding embrace. Asbestos-induced mesotheliomas may also occur in the peritoneal cavity, where they exhibit a similar growth pattern.

Currently, asbestosis is the subject of a veritable medicolegal subindustry that has evolved as a result of alleged disability and other damage ascribed to asbestos. Large-scale endeavors aimed at removing the fire-resistant mineral from existing older buildings have generated dubious benefit to the general welfare, with at least one cost-benefit study indicating that the cost per life saved is about US$250,000,000. With so much money at stake on both sides of the issue, and in light of the observation that scientific investigators must rely on external sources, often partisan ones, for research funding, it seems unlikely that truly unbiased information on asbestosis will be forthcoming in the foreseeable future. So, until the polemic tenor subsides, *caveat lector.*