Asbestos-induced disease is one of the major areas of current interest in occupational medicine. The magnitude of the problems caused by asbestos can be appreciated from the fact that some 4 million people in the United States were exposed to asbestos dust in shipyards in World War II\(^1\) and from the 16,000 lawsuits relating to asbestos-induced disease currently pending against the Manville Corp.\(^2\) Excellent long and short reviews of the clinical manifestations of asbestos-related disease have been published recently.\(^3,4\) Diseases induced by asbestos include the following:

Established:
- Asbestosis (interstitial fibrosis)
- Asbestos Airways disease
- Pleural effusions
- Pleural fibrosis
- Pleural plaques
- Carcinoma of the lung
- Pleural and peritoneal mesothelioma

Questioned:
- Carcinoma of the colon, kidney, ovary, and larynx

In this article, I wish to consider the usefulness and limitations of the pathologic diagnosis of these conditions, and in particular new areas such as asbestos airways disease, the significance of the asbestos body and the value of mineralogic analysis. More comprehensive pathologic reviews can be found in Craighead et al\(^6\) and in Churg and Golden.\(^7\)

**Asbestos Fibers and Asbestos Bodies**

Asbestos is a generic term for a variety of fibrous silicate minerals. The bulk (90 percent) of asbestos used commercially is chrysotile, much of which comes from Quebec. The remaining types are members of the amphibole group of minerals; of these, amosite and crocidolite are of commercial importance, while tremolite, anthophyllite, and actinolite are encountered as contaminants of other minerals such as chrysotile ore or talc.

Asbestos is inhaled as the bare mineral fiber. Once in the lung, a portion of these fibers acquire an iron protein coat. Microscopically, this structure, which is the familiar asbestos body, appears as a transparent fiber encrusted with a golden yellow coat which may be sheath-like or segmented and knobbled. The nature and significance of asbestos bodies and nonasbestos ferruginous bodies have been a source of largely unwarranted controversy and confusion. In 1963, Thomson et al\(^8\) first reported that asbestos bodies could be found in a substantial fraction of an autopsied population who had no known exposure to asbestos; subsequent reports from western Europe and North America have made it clear that asbestos bodies can be recovered from the lungs of virtually everyone in the population if suitable methods of digestion are employed.\(^9\)

These observations were the first evidence that the entire population was being exposed to asbestos. Gross et al\(^10\) countered this argument by demonstrating that in experimental animals, similar appearing bodies could be formed on nonasbestos minerals such as fine fiber glass. On the basis of these experiments, Gross et al\(^10\) concluded that the "ferruginous bodies" (a general term for mineral fibers of any sort with an iron protein coat) found in human lung from nonoccupationally exposed individuals were not formed on asbestos; however, more recent work\(^1\) has demonstrated clearly that the hypothesis of Gross and associates\(^10\) is wrong and that, as a practical matter, any structure which looks like an asbestos body does contain asbestos, whether or not there is a history of exposure (the one possible exception in humans is the formation of ferruginous bodies on erionite; these bodies are identical to asbestos bodies morphologically, but so far have only been demonstrated in the population of a restricted area in Turkey\(^11\)). In the general population the cores of these bodies are almost always amphibole asbestos; in workers with a history of exposure, bodies formed on chrysotile may also be found.
Other types of ferruginous bodies are also occasionally seen in human lung; some have black cores of carbon or yellow cores of talc or mica; however, these ferruginous bodies do not look like asbestos bodies in the light microscope and usually present no source of confusion.

Not only do lungs from the general population contain asbestos bodies (generally at a level of fewer than 1,000/g of dry lung, but they also contain numerous uncoated asbestos fibers. In this population the total burden of fibers outnumbers the bodies by a factor of about 10,000. Most of the uncoated fibers are short pieces of chrysotile, tremolite, and anthophyllite, with only about 1 percent of the total on average represented by the commercial amphiboles, amosite and crocidolite. Detailed values have been reported, and these values must be borne in mind when interpreting any mineralogic analysis which purports to show special exposure to asbestos. Except for the few commercial amphibole fibers, the source (commercial use vs natural contamination of air and water supplies) of these asbestos fibers is unclear.

The fact that asbestos bodies can be recovered from every lung by techniques of digestion and concentration has led to concern about overdiagnosing asbestosis in patients with interstitial fibrosis; however, Roggli and Pratt have calculated, using the known concentration of asbestos bodies in the general population, that one should not observe an asbestos body in more than one in 100 sections from someone who has only background exposure to asbestos. The implication of this calculation is that the observation of an asbestos body in a section of tissue is a reasonably good indication of some special (usually occupational) exposure to asbestos. The converse of this proposition is equally important; the finding of an asbestos body in histologic section implies only exposure. Asbestos bodies are not by themselves manifestations of disease, and, especially, they are not "asbestosis."

ASBESTOSIS

The features of asbestosis have been well defined since the beginning of the century. Clinically, functionally, radiographically, and, to a great extent, pathologically, asbestosis resembles idopathic interstitial fibrosis (usual interstitial pneumonia [UIP]; fibrosing alveolitis). It should be appreciated that given a good history of exposure to asbestos and compatible symptoms, findings, pulmonary function, and radiographic pattern, the disease can be regarded as established without histologic examination. A biopsy should be reserved for cases in which either the history of exposure or the nature of the pathologic process is obscure.

The diagnostic pathologic features of asbestosis are the combination of diffuse interstitial fibrosis and inflammation in the pattern of UIP, accompanied by asbestos bodies in histologic section (Fig 1). Certain features bear emphasis. For one thing the combination just stated must be present; interstitial fibrosis by itself allows only the diagnosis of interstitial fibrosis, cause unknown (as discussed hereafter). Asbestos bodies by themselves signify exposure only. An expert committee has recommended that at least two asbestos bodies be seen in histologic section before the diagnosis is made; however, given the calculation of Roggli and Pratt mentioned previously, this stipulation, which is meant to avoid diagnosing interstitial fibrosis of some other cause as asbestosis, may be too stringent. Interstitial fibrosis in any population is a rare disease; if one combines this fact with the one in 100 chance of finding an asbestos body as a result of mere background exposure to asbestos, then the likelihood of accidentally overdiagnosing asbestosis seems rather remote.

If a biopsy is performed, then open biopsy is the procedure of choice. Transbronchial biopsy is totally inadequate; Wall et al have carefully demonstrated that the finding of "fibrosis" in a transbronchial biopsy is a poor predictor of the presence of diffuse interstitial fibrosis. Because of the nature of the pathologic process, this conclusion must apply equally well to asbestosis. It should be remembered that the diagnosis
of asbestosis requires diffuse fibrosis and that agents such as radiation or desmoplastic reaction to carcinoma may produce local fibrosis which might mimic asbestosis; both pathologist and clinician should be sure that diffuse disease is present before making this diagnosis.

Do cases of asbestosis exist in which asbestos bodies cannot be documented in histologic sections? Studies in animals show that asbestos bodies fragment with time and conceivably could not be found in a patient with fairly remote exposure. This is particularly likely to be true in chrysotile workers, since chrysotile forms bodies poorly compared to amphiboles, and the bodies appear to be quite fragile. An additional factor which may be of importance is that asbestos bodies are not evenly distributed in pulmonary tissue, and it is conceivable that a biopsy might by chance sample an area which is poor in such bodies. Rare cases of apparently "occult" asbestosis have been reported; however, this is clearly an unusual situation, and the absence of bodies should mitigate strongly against the diagnosis. Mineralogic analysis to determine actual asbestos content is potentially of value in such a situation.

**Small Airways Disease**

It has been known for more than 30 years that when animals are exposed to asbestos, a pathologic reaction occurs in the region of the respiratory bronchioles and alveolar ducts. A number of these experimental reports have concluded that the fibrosing process then "spreads" to the interstitium, producing the classic pattern of asbestosis. Documentation of the existence of such lesions in humans has been scanty. An expert committee has recently examined a large number of cases of asbestosis and concluded that airway lesions of this sort do exist in humans. I believe that the committee's description of the lesions as a fibrotic process affecting initially the walls of respiratory bronchioles and alveolar ducts (Fig 2) is correct; however, the following three factors suggest that this process should be not be called "asbestosis;" (1) it has been shown both in humans and animals (references in Churg and Wright) that identical lesions can be produced by a wide variety of nonasbestos mineral dusts (for example, silica, mica, brucite, and potassium octatitanate), none of which cause interstitial fibrosis; (2) recent carefully performed studies in animals have suggested that both alveolitis and lesions of the airways appear more or less concomitantly soon after asbestos dusting; these observations imply that the changes in the airways seen with asbestos and these other dusts may be a fairly nonspecific response to inorganic minerals and may not, in fact, be related to interstitial fibrosis at all; and (3) the implication of the term, "asbestosis," for airway lesions, whether or not they give rise to interstitial fibrosis, is unfortunate. Classic asbestosis is an interstitial disease which radiographically shows a pattern of reticulonodular infiltrates and functionally is characterized by restrictive changes. The disease frequently produces functional impairment. By contrast, airway disease due to asbestos, although probably detectable with some difficulty over the background of airway disease caused by cigarette smoke, is of questionable functional significance and clearly is not a radiographically visible lesion. In this context, calling the airways disease "asbestosis" is equivalent to calling cervical dysplasia "cancer." Clearly, cancer may arise in the setting of dysplasia, but this is not invariably true, and dysplasia is not in itself functionally important. For this reason, I prefer to call these lesions "asbestos airways disease" and to save the term, "asbestosis" for the classic type of interstitial fibrosis.

These comments should not be taken to imply that asbestos airways disease is unimportant. On the contrary, airways disease may be an extremely valuable marker of early parenchymal pulmonary damage caused by asbestos. If such disease can be detected either functionally or pathologically, it is possible that removal of the patient from exposure at that point would prevent or slow down the appearance of the
disabling interstitial fibrosis. This is clearly an area for further investigation.

**Benign Pleural Disease**

Asbestos causes pleural effusions, pleural fibrosis, and pleural plaques. The pathologist has little to offer diagnostically with regard to these lesions, except to rule out the presence of malignant neoplasm; however, terminology is again important: none of these pleural diseases is "asbestosis," and the term, "pleural asbestosis," is unfortunate, since it serves to sow confusion between a process which has usually little functional consequence and one which is disabling.

**Carcinoma of the Lung**

Statistically, asbestos-related lung cancers are the most important current problem in the area of asbestos-induced disease. Numerous studies have documented that asbestos is carcinogenic, particularly when combined with cigarette smoke.2-4,21 and Doll and Peto22 estimate that asbestos contributes to the development of some 5,000 to 10,000 cases of lung cancer per year in the United States. The major issue which confronts clinicians and pathologists alike, for purposes of compensation, is determining which lung cancers can be reasonably ascribed to asbestos exposure. When a carcinoma occurs in an asbestos-exposed individual who does not smoke, the issue is straightforward. Unfortunately, in the much more common situation in which a cigarette-smoking worker develops a lung cancer, I know of no pathologic method of ascribing part or all of the injury to asbestos (see following discussion). Although there may be minor differences in the frequency with which different histologic types of lung cancer are seen in asbestos workers, as opposed to pure cigarette smokers (a point not agreed upon by everyone),5-6,66 all histologic types of cancer are, in fact, common in asbestos workers. The histologic demonstration of asbestos bodies in conjunction with a cancer again implies only exposure.

One practical solution is the method used at present in the United Kingdom, where the cancer is ascribed to asbestos if there is accompanying interstitial fibrosis of a sort seen in asbestosis.6 The pathologist should take care in such instances to be sure that the fibrosing process is diffuse and not a local reaction around the tumor or a result of irradiation or chemotherapy. In this context, I believe that the finding of asbestos airways disease is very useful, since it indicates the presence of asbestos-induced parenchymal damage, even in the absence of diffuse fibrosis.

**Malignant Mesothelioma**

Malignant mesothelioma of the pleura and peritoneum are strongly associated with exposure to asbestos and are extremely rare (one to two per million persons per year) in the general population. *Cigarette smoke does not appear to be implicated in the genesis of this tumor, and, with the disputed exception of erionite in Turkey,27 no other etiologic agent for mesothelioma has yet been documented in humans. A careful occupational history should therefore be obtained in all cases of mesothelioma; published series suggest that such a history can be obtained overall in about 50 percent of cases in males.28,29*

The major problem in regard to mesothelioma is not ascribing cause but establishing the diagnosis pathologically. Carcinoma and sarcoma metastatic to the pleura or peritoneum frequently mimic mesothelioma, and even in the reports with the highest incidence of mesothelioma in asbestos workers, bronchogenic carcinoma is still two to three times more common. The pathologic requirements for the diagnosis of mesothelioma are set out in detail in reports by Kannerstein et al.28,30 these include a set of distinctive histologic appearances, a set of histochemical reactions to demonstrate the presence of neutral or acidic mucins, and a consistent gross appearance, particularly the presence of tumor encasing viscera.

Making the diagnosis of mesothelioma during life requires a proper biopsy. Needle biopsy of pleura is generally inadequate, and either an open pleural biopsy or an extensive pleuroscopic biopsy should be used. Autopsy may be required to demonstrate the absence of another primary site. Mesothelioma reference panels exist in both the United States and Canada and are available to review problem cases.

**Other Cancers**

Asbestos has been associated in some series with carcinoma of the larynx, gastrointestinal tract, and possibly the kidney and ovary.3-5 These associations are not strong and are not universally agreed upon. Given that all of these cancers are common and that some are strongly associated with cigarette smoke, all of the comments made previously concerning carcinoma of the lung in asbestos-exposed individuals also apply here. There is certainly no gross or microscopic finding which permits the pathologist to determine that any of these tumors has occurred as a result of exposure to asbestos.

**Mineralogic Analysis**

Techniques are now available which allow quantitation of both asbestos bodies and fibers from pulmonary tissue and specific identification of the types of asbestos present. This topic is reviewed in another report.* The techniques have largely been used for research purposes but do have some applications in regard to diagnosis and compensation for asbestos-induced injury; the uses for mineralogic analysis in the evaluation of asbestos-related disease are listed in the
following tabulation:

Asbestos body count (light microscopy)
Uses: Quick screening test to rapidly confirm high asbestos burden
Advantages: (1) High value indicates definite exposure
(2) Relatively inexpensive and quick to perform
(3) Any laboratory can perform test provided standards are set up
Disadvantages: (1) Measures only a fraction of total asbestos load
(2) Low count does not necessarily indicate lack of exposure
(3) Yields no information about type of asbestos present

Examination of uncoated fibers (electron microscopy)
Uses: Measure total asbestos burden
Advantages: (1) Measures total number of fibers
(2) Provides information on fiber type and size
(3) May provide indication of source of exposure
Disadvantages: Procedure is slow, expensive, and requires specialized equipment and extensive standards

These applications can be broken down into several categories:
(1) Documentation of exposure in the absence of either a good history or of asbestos bodies in histologic sections. An example is the demonstration of high levels of asbestos in cases of interstitial fibrosis where no asbestos bodies are present in histologic section. Another area is household-contact asbestos disease. For example, we analyzed the lungs of a woman who gave a history of washing her husband’s asbestos-laden work clothes and 30 years later developed a malignant mesothelioma. Analysis revealed a 30-fold increase in the pulmonary burden of commercial amphiboles, thus confirming the asbestos etiology of this tumor (Table 1).

(2) Documentation of the magnitude of exposure. Certainly, a stronger case can be made, even in the face of biologic variability, for asbestos causation of a given disease when a marked increase in fiber content over background is present. Obviously, for this purpose, it is critical that a set of standard values documenting in detail the types, numbers, and sizes of fibers found in the background population be available from the laboratory which performs the analysis; it cannot be overemphasized that the mere presence of asbestos in pulmonary tissue is, by itself, of no value. It is also important that not only number of fibers present, but the type of fibers be determined; for example, a lung containing a million fibers of chrysotile per gram of dry tissue is entirely consistent with the background exposure of the general population; a lung containing a million fibers of amosite or crocidolite per gram almost certainly indicates a fairly substantial occupational exposure to asbestos dust. At present there are no set guidelines for determining what number of fibers may be etiologically associated with given diseases, although with time, analysis of large series of cases may permit some guidelines to be developed.

(3) Documentation of exposure to a specific type of fiber. Epidemiologically, the amphiboles, amosite and crocidolite, are strongly associated with the development of mesothelioma, whereas mesothelioma after pure chrysotile exposure is relatively rare. On the other hand, all types of asbestos fibers appear to be relatively equally dangerous from the point of view of carcinoma or asbestosis. Documentation of fiber type is also useful in compensation cases when it is desired to demonstrate exposure to a specific product made by a certain manufacturer or used by a certain employer.

Quantitation of bodies is faster and less expensive than examination of fibers. When high values are obtained, the former procedure is useful for proving high pulmonary asbestos loads, but negative results do not entirely rule out such loads; examination of fibers in the electron microscope is slower and more expensive but gives definitive values both for numbers of fibers and for types of fibers. In any of these applications, only analysis of pulmonary tissue is of value. Tumor tissue and pleural plaques may or may not contain fibers or bodies, and the few published studies in this area suggest that the relationship of fibers or bodies seen in plaques or tumors to the actual pulmonary concentration is quite variable and may not be at all representative. In this regard also, experience in my laboratory indicates that the larger the sample, the more accurate the results are likely to be, in part because of the error inherent in measuring small weights and multiplying by large numbers, and in part

| Table 1—Analysis of Lung for Asbestos in a Household-Contact Case of Mesothelioma* |
|-----------------------------------------------|-----------------------|---------------------|
| Data                                          | Control Group (n = 9) | Mesothelioma Case   |
| Asbestos Bodies                               | 280                   | 2500                |
| Uncoated Fibers                               |                       |                     |
| Chrysotile                                    | 1.0 x 10⁶             | 0.2 x 10⁶           |
| Noncommercial amphiboles†                     | 0.2 x 10⁶             | 0.2 x 10⁶           |
| Commercial amphiboles‡                        | 0.01 x 10⁶            | 0.3 x 10⁶           |

*All values are per gram of dry lung.
†Tremolite, actinolite, and anthophyllite.
‡Asbestos and crocidolite.
because of variations in fiber concentration within the lung. The difficulties posed by transbronchial biopsies in this context are obvious, and for the same reason a large piece of fixed wet pulmonary tissue is far preferable to paraffin blocks. Incidentally, there are no published reference values for analyses performed on paraffin blocks, and until such analyses are performed, there is no reason to assume that values determined from wet tissue can be applied.

CONCLUSION

This article has briefly reviewed a number of issues in asbestos-related disease. The application of mineralogic analysis to diagnosis, although established, will benefit greatly from extensive background data on various exposed populations. For some other problems, particularly attribution of etiology of asbestos-induced cancers, there does not at present appear to be any easy scientific solution, and some legislated or administrative remedy may be needed; however, most of the conditions which have been discussed here are reasonably well defined. What their diagnosis does require is close cooperation and exchange of information between clinicians and pathologists.

REFERENCES

12. Roggli VL, Pratt PC. Relationship of numbers of asbestos bodies on iron-stained tissue sections and asbestos body counts in lung tissue digests. Hum Pathol (in press)