The Carcinogenic Effect of Inhaled Asbestos Fibers

ANDREW L. REEVES, Ph.D.
Wayne State University, School of Medicine,
Department of Occupational and Environmental Health,
Detroit, MI 48201

ABSTRACT

Inhalation of asbestos fibers is associated with high incidence of lung cancers and pleural or peritoneal mesotheliomas in humans. All of these lesions were successfully reproduced in animal experiment, and it was shown that asbestos neoplasm may occur with or without accompanying asbestosis. Incidence of tumors from crocidolite was nearly three times as high as from chrysotile or amosite. It is possible that different carcinogenic entities are responsible for the causation of lung tumors and mesothelial tumors. Lung tumors seem to depend on the adsorptive capacity of asbestos fibers, allowing other carcinogens (heavy metals, polycyclic hydrocarbons, cigarette smoke) to attain a critical focal concentration. Mesothelial tumors, on the other hand, might arise in response to mechanical irritation by fibers which may become lodged during lymphatic spread. Tissues subject to constant respiratory movement (e.g., pleura or peritoneum) are specifically vulnerable to the latter action.

Introduction

Asbestos has been surrounded through the ages with nearly as much mystery, mysticism and even mythology as the noble metals. As a substance which has the characteristics of silk or cotton and at the same time will not burn, it became an early raw material of technology. The word asbestos in Greek means "unconsumed,"—a reference to one of the ancient applications of the mineral as wick in oil lamps not requiring periodic renewal. In Latin, the substance was called "amianthus" (undefined), referring to textiles which did not char. The story is told that early medieval potentates liked to astound their guests by serving meals on an asbestos tablecloth which was afterwards tossed into the fire and yet emerged unscathed. In the 17th century, attempts were made to make inc combustible books and inc combustible money from asbestos, but these items never became popular because of their easy tearability.

Marco Polo was told in the 13th century in China that asbestos was the shredded skin of salamanders, and ideas of this kind have continued into modern times. Gilson relates the anecdote of a major shareholder in one of the asbestos companies in South Africa, who came to visit the source of his supplies and demanded to be shown the plantations.

459
The well-informed layman today thinks that asbestos is a mineral with a definite chemical composition and crystalline structure; however, that is also a misconception. "Asbestos" as a single and unequivocal mineral species does not exist, and mineralogists prefer to talk about "asbestiform occurrences" of several different minerals. These are occurrences fibrous enough to be technically exploitable as asbestos. In fact, all these minerals also have nonfibrous occurrences, as well as a number of intermediate forms, which are distinguishable from each other only on the basis of their morphology but not chemical composition or crystal structure. "Asbestos" is, accordingly, a term of commerce and technology with no strict scientific definition.

The most important mineral with asbestiform occurrence is serpentine, $\text{Mg}_6\text{Si}_4\text{O}_{10-11}(\text{OH})_6-8 \cdot \text{H}_2\text{O}$. The asbestiform occurrence of serpentine, chrysotile (Greek for "golden flax"), forms molecular tubules of 100 to 200 Å diameter and several mm or even cm length. This structure renders chrysotile fibers soft, flexible and excellently spinnable. Chrysotile is most frequent among all asbestiform minerals and presently comprises about 93 percent of total world consumption.

The second important family of asbestos minerals are the amphiboles, with a general chemical formula of $\text{Me}_7[\text{Si}_8\text{O}_{22}(\text{OH})_4]$, with $\text{Me}$ being any combination of metallic ions such as $\text{Na}^+$, $\text{Ca}^{++}$, $\text{Mg}^{++}$, $\text{Fe}^{++}$, or $\text{Fe}^{+++}$ in almost any proportion. In view of this variability, there are numerous amphiboles. The most important asbestiform occurrences are crocidolite (Greek for "flaky stone") and amosite (named after the Asbestos Mining Organization of South Africa). Amphibole fibers are bundles of molecular chains, and they are generally harsher, shorter and more brittle than chrysotile fibers. They are also much less spinnable although more resistant to acid corrosion. They are used specifically where the latter property is of value (e.g. in filters) and presently comprise about 7 percent of world consumption.

In table I is shown the full classification of asbestiform materials.

Asbestos is used mostly as an ingredient of a cement for the building, heating, marine construction and furnace construction industries. A second impor-
tant application is as friction material in brake and clutch linings. Fire-resistant textiles and filters are in third and fourth places, respectively, and further quantities are used as asbestos paper, floor tiles, gaskets and coatings. Total world consumption in 1970 was about two million tons. During the past 50 years, asbestos production experienced a thousand-fold increase. This should be compared to the increase of petroleum production during the same interval which was only fifty-fold. It is perhaps not surprising that an expansion of this magnitude could not be achieved without an effect on public health.

The inhalation of asbestos fibers during mining and manufacture was viewed with concern since ancient times. The problem was recognized by Plutarchos and Strabo, as well as by Pliny the Younger, who recommended the use of respirators. Nonetheless, it took until the beginning of this century for asbestosis to become recognized as an occupational ailment.

Asbestosis is a diffuse interstitial pulmonary fibrosis which develops slowly (in the course of five to ten years) during occupational exposure. It is frequently accompanied by pleural calcification and is characterized by the presence of "asbestos bodies" in the lungs and in sputum. Asbestos bodies were first seen in 1906 by Marchand. In the beginning they were believed to be crystals or fungi. Gloyne first recognized that they were mineral fibers with iron-containing protein coating, and it was gradually assumed that these bodies arise as a result of interaction between inhaled asbestos fibers and certain pulmonary cells. It was also recognized that such interaction may take place between cells and non-asbestos fibers (e.g., fibrous glass) as well, and Gross et al in 1968 suggested the more general name "ferruginous bodies" for these structures, referring to their iron content.

In addition to fibrosis of the lungs and pleura, asbestos inhalation is also associated with malignant changes in these organs. Lynch and Smith suggested in 1935 that asbestosis may be accompanied by lung cancer, and later epidemiological studies have confirmed that the incidence of lung cancer among asbestos-exposed persons is much higher than expected. Interestingly, however, recent research tends to show that the higher-than-expected incidence of lung cancer among asbestos workers originates from the cigarette-smoking segment of the population, whereas if non-smoking asbestos workers are compared to non-smoking controls, the lung cancer mortality figures show no significant difference. It would appear, therefore, that the role of inhaled asbestos fibers with respect to lung cancer in humans is co-carcinogenic rather than carcinogenic.

An additional aspect was discovered in 1960 by Wagner et al who found 32 cases of pleural mesothelioma, otherwise a rare tumor, among persons exposed to crocidolite in South Africa. Subsequently, numerous other cases were discovered in all parts of the world and connected in some cases to chrysotile exposure as well. Mesothelial tumors were also discovered in the peritoneum of asbestos workers. The incidence of these tumors showed no relation to cigarette smoking and much less dose-dependence than the pulmonary tumors.

Experimental production of mesothelial tumors following implantation of dusts was accomplished by Wagner, Smith et al, Stanton et al and Reeves et al. These experiments involved various laboratory rodents and various dusts; Stanton and Wrench showed that positive results may be achieved even with fibrous glass. Size of the fibers appears to have been a governing parameter of
TABLE II
Inhalation Exposure of Rats to Three Different Varieties of Asbestos

<table>
<thead>
<tr>
<th>Dust</th>
<th>Chrysotile</th>
<th>Amosite</th>
<th>Crocidolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months in exposure</td>
<td>0</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Animal Investories</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st expt</td>
<td>1967/69</td>
<td>60</td>
<td>49</td>
</tr>
<tr>
<td>2nd expt</td>
<td>1970/72</td>
<td>69</td>
<td>62</td>
</tr>
<tr>
<td>Combined</td>
<td>129</td>
<td>111</td>
<td>105</td>
</tr>
<tr>
<td>Incidence of malignancy</td>
<td>Count</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Percent</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

tumorigenicity more than chemical composition, and about 3µ has been regarded as the lower threshold of pathogenic fiber length. Smaller fibers were apparently successfully removed by phagocytic mechanisms whereas the larger fibers were more prone to become enmeshed in pleural tissue during lymphatic drainage.

Pulmonary tumors after asbestos inhalation were experimentally produced in this laboratory.\textsuperscript{14,15} These experiments were successful thus far only in rats but tumors were produced by all three major types of asbestos dusts. The tumors were of the papillary, squamous cell or adenocarcinoma type. Fibrosarcoma or fibrous mesothelioma of the pleura or mediastinum were also observed. The total experience with rats is summarized in table II.

Inhalation Exposure
**CHRYSOTILE**
Chrysotile dust\textsuperscript{*} was disseminated with a hammer mill-blower system, resulting in a mean atmospheric concentration of 47.4 to 47.9 mg per m\textsuperscript{3}.\textsuperscript{3} The count of microscopically visible fibers was 54 million per m\textsuperscript{3},\textsuperscript{3} averaging 0.2 µ in diameter and 6 to 15 µ in length.

Two sets of rats were exposed to this atmosphere four hours per day, four days per week, for approximately two years each. The exposure yielded one squamous cell carcinoma of the lung, one papillary carcinoma of the lung and one fibrosarcoma of the mediastinum. These constitute a 5 percent incidence of malignancy among the survivors.

**AMOSITE**
Amosite dust† was disseminated similarly, with the animal exposure schedules identical. The mean atmospheric concentration in the amosite chamber was 48.2 to 48.6 mg per m\textsuperscript{3} with 864 million microscopically visible fibers per m\textsuperscript{3},\textsuperscript{3} averaging 0.2 to 0.5 µ in diameter and 3 to 5 µ in length.

Among the survivors, there was one papillary carcinoma of the lung, one fibrosarcoma of the lung and pleura, and one fibrous mesothelioma of the pleura. These constituted a malignancy incidence of 5 percent in this exposure group.

**CROCIDOLITE**
Crocidolite dust‡ was disseminated in a third chamber using identical technique, and two sets of rats were exposed to this dust also. Concentration of crocidolite in chamber air was 48.7 to 50.2 mg per m\textsuperscript{3} count of microscopically visible fibers was 1105 million per m\textsuperscript{3},\textsuperscript{3}

\textsuperscript{*} 3-T fibers of the Johns-Manville Corporation.

\textsuperscript{†} W-3 fibers of the Johns-Manville Corporation.

\textsuperscript{‡} 5-Blue fibers of the Johns-Manville Corporation.
average size of a fiber was 0.4 to 0.5 \( \mu \) diameter and 3 to 6 \( \mu \) length.

This exposure yielded five squamous cell carcinomas, one papillary carcinoma and one adenocarcinoma of the lung, constituting 14 percent malignancy incidence.

**Comparison of the Three Dusts**

The data in the previous sections show that the atmospheric concentration of the three dusts in terms of weight per volume was approximately the same, but the fiber counts were dissimilar. The dissemination procedure caused considerable destruction of fibrous structure at least in the microscopic size range, and the effect was much greater with chrysotile than with the amphiboles. Chrysotile is changed into forsterite at 810° and the amphiboles into pyroxenes at about 900°. These transformation products are non-fibrous, and it is possible that impact temperatures of this magnitude might have occurred during milling. However, the disseminated dusts also have fibrous component, and it may be assumed that the latter was responsible for the pathologic response.

All exposed animals had some degree of asbestosis, the extent and severity depending on the duration of exposure, with the response to chrysotile frequency very slight. This was probably a consequence of the sharply reduced fiber count (54 vs. 864 to 1105 million per m³). It may be noted that the shorter and harsher fibrils of the amphiboles have a better opportunity to penetrate into the deep lung than chrysotile, which, in view of its greater length and curved shape, is more likely to get arrested high in the respiratory tract.

**Discussion**

The carcinogenic effect of inhaled asbestos fibers is puzzling, because pure silica in any of its crystal forms is noncarcinogenic. Theories to account for the carcinogenicity of asbestos may be divided into physical and chemical. The physical hypotheses suggest that the mechanical irritation attributable to the embedded fibers or to the ensuing biological response (Oppenheimer effect) is the key factor in the etiology of asbestos cancers. This idea was not viewed with favor by the early investigators but received new support from the studies of Stanton and Wrench who obtained mesotheliomas with fibrous glass injected into the pleura. The latter authors concluded that carcinogenicity was primarily related to the structural shape of these dusts rather than to their chemical composition. The observation that the pleura and peritoneum are specifically vulnerable to the malignant effect of asbestos is reconcilable with this hypothesis because it is possible that the constant respiratory movements of these tissues subject them to a continuing mechanical irritation from imbedded fibers.

The chemical hypotheses suggest that a principle inherent either in the silicate core of asbestos fibers or in certain adventitious factors, is the ultimate carcinogenic entity. Thus far, the question of adventitious factors has received the most attention. Harington discovered in 1962 that certain virgin samples of asbestos contained cyclohexane-extractable oils composed of aromatic hydrocarbons, one of which was benzo-\( \alpha \)-pyrene. Furthermore, it was pointed out that beside natural trace constituents which apparently became adsorbed on asbestos fibers during their geological genesis, additional opportunities for contamination existed during commercial handling. Jute bags as well as polythene bags were shown to release aromatic compounds of possible or proven carcinogenic potential. Some researchers had the impression that asbestos specimens were more carcinogenic after transoceanic shipment.
**Figure 1.** Heavy metal content of Chrysotile. UICC: international standard; J-M: Johns-Manville.

**Figure 2.** Heavy metal content of Amosite. UICC: international standard; J-M: Johns-Manville.
than in the country of their origin. Systematic investigations, however, did not yield unequivocal results.

Metals present in asbestos include iron, aluminum, and magnesium as major constituents and chromium, nickel, cobalt, manganese and others as trace constituents. Several of the latter are suspected or proven carcinogens, although it was argued that their levels in asbestos are too small to be biologically significant. However, it was pointed out that during manufacture of asbestos textile products, the concentration of carcinogenic metals in asbestos increases substantially through contact with the weaving machinery. Similar increase in heavy metal content of asbestos was also experienced in the chamber dissemination procedures described here. In figures 1, 2 and 3, the relative concentrations of chromium, manganese, iron, cobalt and nickel are shown in each of the disseminated asbestos samples, as compared to their parent materials, and the international standard (UICC) specimens of each asbestos variety. It may be seen that chrysotile was not substantially contaminated with heavy metals during milling, while amosite became contaminated by chromium, and crocidolite by both chromium and nickel. Both of these metals are known respiratory carcinogens. They may have played a role especially in the causation of pulmonary carcinomas, where adsorptive capacity of the fibers seem to play an important role. In contrast to its effect on the pleura and peritoneum, asbestos in the lung is perhaps only a vehicle allowing other carcinogens (metals, aromatic hydrocarbons, cigarette smoke) to attain a high enough focal concentration. It is thus possible that different mechanisms are operative in the causation of mesotheliomas and of pulmonary carcinomas by inhaled asbestos dusts.

Conclusions
Inhalation exposure of rats to aerosols of chrysotile, amosite, and crocidolite caused squamous cell, papillary or
adenocarcinomas of the lung and fibrosarcomas of fibrous mesotheliomas of the pleura and mediastinum.

Light microscopic fiber counts of the amphibole dusts (amosite and crocidolite) were high enough to cause considerable asbestosis as well, where as with chrysotile, in view of a much lower fiber count, there was little asbestosis.

The incidence of tumors among the animals exposed to crocidolite was nearly three times as high as among those exposed to chrysotile or amosite.

The results show that asbestosis and asbestos cancers may develop independently from each other. The results also suggest that different oncogenic entities may be involved in the causation of pulmonary carcinoma and pleural mesothelioma from inhaled asbestos.

References