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The Locus of Pathogenicity of Asbestos Dust

A Theory

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Documented experimental evidence, as well as the results of preliminary experiments, are presented which indicate a reduction in pathogenicity as the polyfilamentous arrangement of asbestos dust particles is replaced by a monofilamentous structure. On the basis of this evidence, it is proposed that the locus of pathogenicity of asbestos dust particles resides in their polyfilamentous structure.

Asbestos minerals are silicates, but the pathogenicity of their dusts is unmatched by that of any other silicate, and the fibrogenicity is equalled only by that of crystalline silica. There has been much speculation regarding the reason for this high degree of pathogenicity of the dust of the asbestos minerals, but today no satisfactory hypothesis remains.

Similar to the theories proposed for the pathogenic potential of silica dust, the first theory was a mechanical one based on the notion that inhaled asbestos particles tend to produce microtraumata by piercing and impaling delicate lung cells. This concept proved untenable when the dust of fibrous glass[1] and ceramic aluminum silicate fibers[2] were shown to be nonfibrogenic in the lungs.

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A theory based on chemical structure became unsatisfactory when synthetic chrysotile, which has the same chemical composition as the natural product, produced no fibrogenic response in the lungs.[3] This nonfibrogenic response in the lungs of rats to synthetic chrysotile also destroyed the validity of the theory that the crystalline character of the asbestos fibers determined their pathogenicity. It is to be noted that synthetic chrysotile has the same crystalline structure as the natural product since it yields the same roentgenographic and electron diffraction pattern; and, like natural chrysotile, it also exhibits a tubular crystalline structure under the electron microscope.[3]

The presence of trace metals on the asbestos particles has also been considered a possible cause for their pathogenicity.[4] However, in a recent investigation, when neither the removal nor the addition of trace metals altered the pathogenicity of asbestos dust, this theory had to be abandoned (P. Gross, MD and R.A. Harley, Jr., MD, unpublished data).

The discovery that, when asbestos is ground to a fiber size less than 5μ long its fibrogenicity for the lungs disappears,[5] astounded the scientific community. This finding, subsequently confirmed,[6,7] proved to be an enigma that ultimately resulted in a new concept of the locus of pathogenicity of asbestos dust.

Although the new concept rests

an embarrassingly obvious ...tural characteristic of asbestos. It is supported by uncontested documented experimental findings as well as by data from some promising preliminary experiments. The latter, however, require confirmation.

Theory and Supportive Data

The new theory is simply this: the locus of pathogenicity of asbestos dust resides in the polyfilamentous structure of its fibrous particles. Various data support this theory.

Man-made mineral fibers, in contrast to polyfilamentous asbestos fibers, are monofilamentous. The dust of those monofilamentous fibers (fibrous glass,[1] ceramic aluminum silicate,[2] and silicon carbide whiskers[3]) that have been studied have proved to be nonfibrogenic when inhaled or injected intratracheally.

Synthetic chrysotile is nonfibrogenic when it is injected intratracheally. It is monofilamentous. It differs from natural chrysotile in that ... tubular crystals are discrete and ... close parallel apposition to each other, as is the case with the natural product.

When a grinding force is applied to asbestos fibers, they tend to split longitudinally rather than to fracture transversely. Consequently, asbestos that has been ground to a fiber length of less than 5μ will consist largely of fibers that are monofilamentous. Those bundles of fibers still remaining will be greatly reduced in thickness and will approach the monofilamentous state. It is the fact that most of the fibers in such finely ground asbestos are either monofilamentous or nearly so, that offers a logical explanation of its nonfibrogenicity.

When asbestos is heated to 1,000 C, its pathogenicity is either lost or severely reduced (P. Gross, MD and L.A. Harley, Jr., MD, unpublished data). At this temperature, the fibrils composing the bundles tend to become fused into unitary structures, i.e, the fibers tend to become monofilamentous (Fig 1). Although chemical ... do occur as a result of the ... such changes have no bearing on the resulting loss of pathogenicity since it has been shown (with synthetic chrysotile) that the chemical composition of asbestos is not responsible for its pathogenicity.

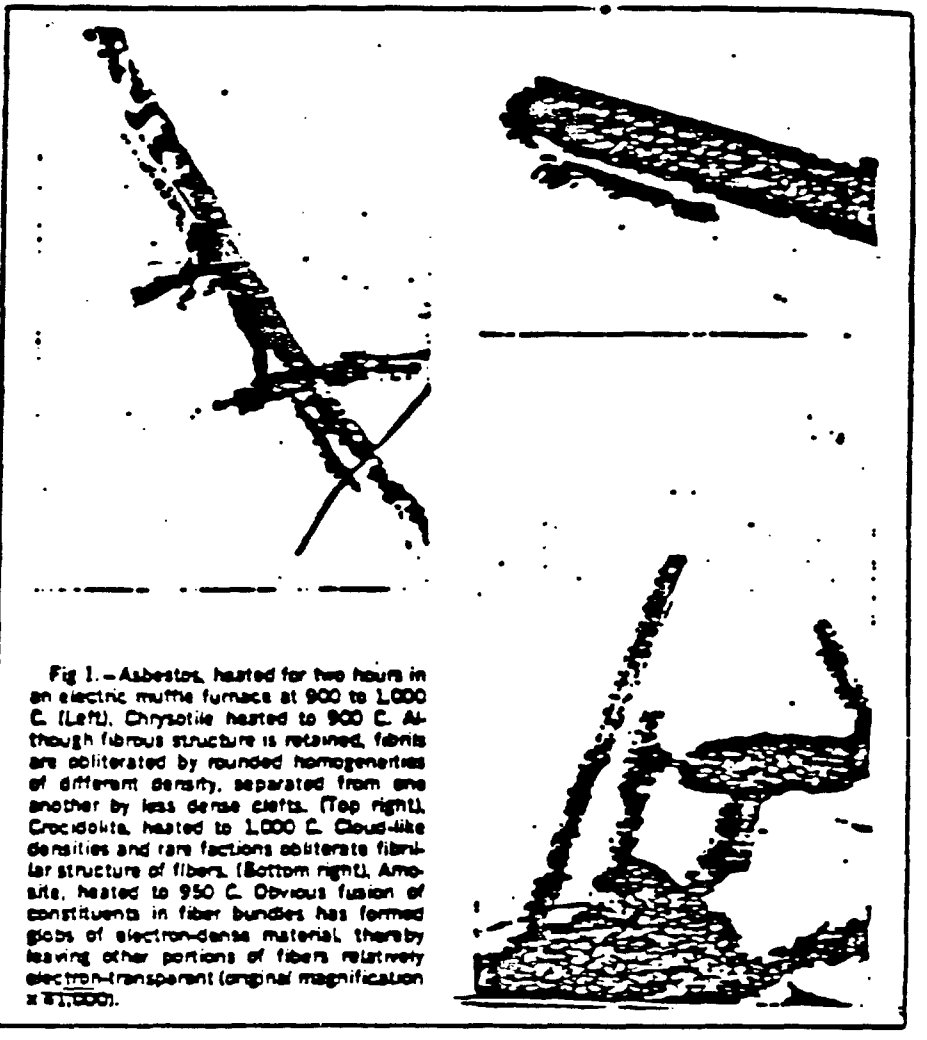

Fig 1.—Asbestos, heated for two hours in an electric muffle furnace at 900 to 1,000 C. (Left). Chrysotile heated to 900 C. Although fibrous structure is retained, fibrils are obliterated by rounded homogeneities of different density, separated from one another by less dense clefts. (Top right). Crocidolite, heated to 1,000 C. Cloud-like densities and rare factions obliterate fibrillar structure of fibers. (Bottom right). Amosite, heated to 950 C. Obvious fusion of constituents in fiber bundles has formed globs of electron-dense material, thereby leaving other portions of fibers relatively electron-transparent (original magnification x 81,000).

By cementing the fibrils of asbestos fiber bundles together chemically, it is possible to convert the polyfilamentous structures into monofilamentous ones. This has been successfully accomplished with various silicates such as those of lead, iron, and magnesium. The use of other water-insoluble cementing substances, such as those of magnesium and calcium pyrophosphate, calcium hypophosphate, and calcium metaphosphate, is contemplated.

The method has been to suspend finely ground asbestos in a dilute solution (1% to 5%) of an appropriate soluble metal salt (lead nitrate, iron chloride or magnesium chloride). After washing the asbestos free of all excess salt, it is suspended in a 1% solution of sodium silicate. The latter

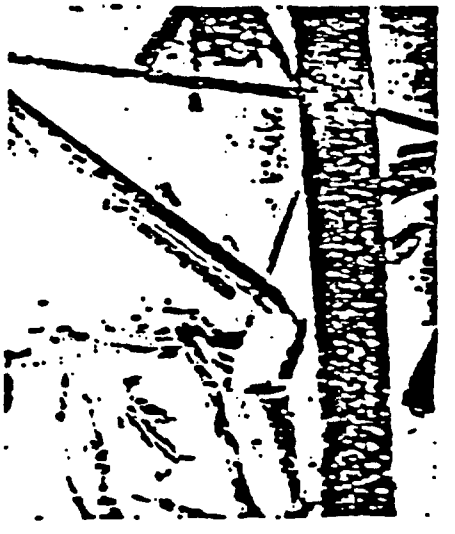

Fig 2.—Chrysotile fibers cemented with lead silicate. Presence of lead silicate indicated by electron-dense stippling within lumen of the fibrils and elsewhere (original magnification x 143,000).

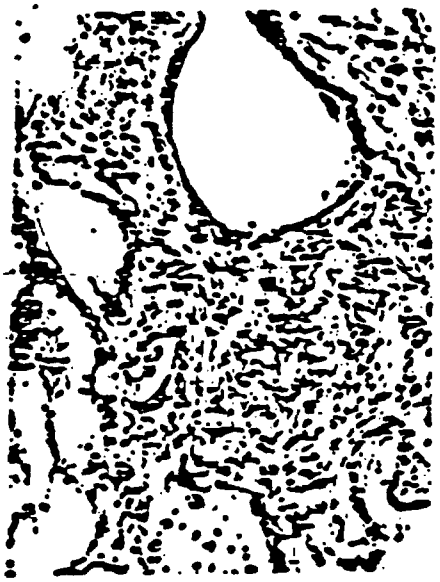

Fig 3.—Rat injected intratracheally with 10 mg iron silicate-cemented chrysotile, found dead six months later. Highly cellular inflammatory focus surrounds terminal bronchiole. An occasional giant cell is present, although in adjoining region many giant cells were observed. There is early fibrosis (hematoxylin-eosin, original magnification x 500).

Fig 4.—Rat died 6½ months after having been injected intratracheally with 7 mg unaltered chrysotile. Area of collagenous fibrosis is adjacent to respiratory bronchiole also involved in fibrosis. This fibrosis differs from that in Fig 3 as it is more collagenous and less cellular, ie, much more advanced. Granular material in collagen is brown pigment (hematoxylin-eosin, original magnification x 260).

reacts with the adsorbed metal salt to precipitate the insoluble silicate.

An electron photomicrographs (Fig appears that solutes are capable of penetrating not only between the fibrils but also within the tubular lumen of chrysotile crystals.

In a preliminary study, the lead silicate- and ferric silicate-cemented asbestos were injected intratracheally into a few rats. Their lungs were examined three months after the intratracheal injection. The predominant pulmonary lesion produced by the lead-cemented asbestos was minimal in character, consisting of prominent giant cells, few histiocytes, little reticulin, and no collagen fibers (Fig 3). In contrast, the lesions of the same age produced by the unaltered asbestos consisted of collagen as well as reticulin fibers and histiocytes. Foci consisting of the minimal reaction, as were noted secondary to the "cemented" asbestos, were not found in lungs injected with the unaltered asbestos (Fig 4).

In an in vitro study it was found that lead silicate-cemented crocidolite caused only 30% hemolysis of human red blood cells whereas, under identical conditions, the unaltered crocidolite caused 100% hemolysis.

Iron silicate was less effective in reducing the pathogenic potential of chrysotile than was lead silicate. The reason for this was a gradual disappearance of the iron from the asbestos stored in the lungs. However, as observed in a tall glass cylinder, the iron silicate-cemented chrysotile stains a deep blue color with acidic potassium ferricyanide and retains this blue color. It settles rapidly, leaving a colorless supernatant which remains colorless over many months.

Because of obvious inadequacies in these experiments with cemented asbestos, the results can be termed only suggestive. But in conjunction with the other findings, they tend to support the thesis that when polyfilamentous asbestos dust particles are converted toward a monofilamentous state, a reduction in their pathogenicity takes place.

An extensive inhalation study with cemented and unchanged asbestos will soon be initiated, as well as an investigation of the comparative fibrogenic and cancerogenic potential of the polyfilamentous, versus the cemented asbestos dust injected intrapleurally.

Thus, the documented evidence points to a sharp difference in pathogenicity between polyfilamentous dusts on the one hand and monofilamentous dusts on the other, and to a significant reduction in the pathogenicity of asbestos dust when its particles are rendered monofilamentous either by grinding or by thermal fusion of fibrils. Preliminary unconfirmed experiments suggest that a similar reduction in the pathogenicity of asbestos dust may be accomplished by chemical fusion of fibrils, ie, the deposition of insoluble cementing materials between the fibrils of the fiber bundles.

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Asbestos-Induced Intrathoracic Tissue Reactions

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Intrathoracic injection of different types of asbestos modified by different methods generally caused differentiated malignant chest tumors in rats and undifferentiated tumors in hamsters. Twenty-five malignant intrathoracic rat tumors were classified as fibrosarcomas; four as mesotheliomas; three as rhabdomyosarcomas; two as osteogenic sarcomas; and one as fibrolipoma. Tissues other than mesothelium rarely may also develop malignant tumors and all tumors arising from the chest wall are not necessarily mesotheliomas.

Asbestos dusts heated to 900 to 1,000 C were associated with only about 10% of the tumor production observed with the heated asbestos dusts. Since the removal of trace metals from or their addition to asbestos dust caused no significant difference in tumor production, the trace-metal hypothesis for the mechanism of asbestos-induced cancer was abandoned.

Although the development of lung cancer in man secondary to asbestos dust exposure is well established, only one laboratory reported the development of lung cancer in rats following exposure to asbestos dust.[1] Inasmuch as other laboratories had also exposed rats to asbestos without producing lung cancer, it was thought that there was something unusual about the asbestos exposure that gave rise to lung cancers. Chemical analysis disclosed that by hammer-milling, the asbestos fibers had acquired increased contents of nickel, cobalt, and manganese from the steel alloy of which the hammer mill was composed. A working hypothesis, therefore, was adopted in which it was assumed that the increased amount of nickel—a known pulmonary carcinogen, was responsible for the development of lung cancer in man and rats when exposed unduly to asbestos dust.

The report by Wagner et al[2] established that exposure to crocidolite asbestos was associated with the development of mesotheliomas of the pleura. This documentation was important, not only because it focused attention on an additional carcinogenic potential of asbestos, but also because it alerted the general pathologist to a hitherto very rare malignant tumor that within a relatively short period, was encountered with frightening frequency in regions where crocidolite asbestos exposures had occurred.

Since the publication of Wagner's report, the designation mesothelioma of pleura or peritoneum has become a "popular" diagnosis clinically as well as experimentally. The strictures and criteria for making the diagnosis of mesothelioma, as laid down by Willis,[3] largely have been ignored. For instance, in many of the cases of one reported series, the diagnosis was based only on biopsy material—often scanty, without substantiation by a complete autopsy.[4] Experimentally, a similar lack of critical judgment is evident where *all* tumors arising from the pleural cavity following the intrathoracic injection of asbestos have been classified as mesotheliomas.[5,6] This swing of the pendulum to the far left has reached the ultimate in the finding of "mesotheliomas" arising in association with ground glass.[7] Given the importance of experimental intrathoracic tumors needs to be accurate lest it cause undesirable alarm is illustrated by a recently published "expression of concern" with regard to fiber glass in which various types of fibrous glass, inclusive of glass wool, were tabulated as producing mesotheliomas.[8]

One purpose of this paper is to report the results of an attempt to test the trace-metal hypothesis for the development of asbestos-induced lung cancer. Another purpose is to document the occurrence of malignant intrathoracic tumors following intrapleural injections of different types of asbestos and to study whether some, if not the majority, of these intrathoracic tumors may arise from cells other than those of the mesothelial surface.

Methods and Materials

Samples of Canadian chrysotile, amosite, and crocidolite were each prepared by

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Fig 1.—Asbestos after having been heated to 900 to 1,000 C. Left, Amosite. Obscured fibrillar markings and blobs of dense material (original magnification × 70,000). Center, Chrysotile. Fibrous structure preserved, but no fibrillar markings (original magnification × 81,000). Right, Crocidolite. Translucencies and opacities associated with loss of fibrillar markings (original magnification × 81,000).

five different methods for intrapleural injection. One sample of each was hammer-milled for 12 hours (hammer mill described by Holt et al[7]). The purpose of the prolonged hammer-milling was to coat the asbestos with the nickel-containing alloy of which the hammer mill was composed. In a previous study, this hammer-milling resulted in the addition to the asbestos of 82% more nickel, 146% more cobalt, and 34% more chromium, all derived from the metal of the hammer mill.[1]

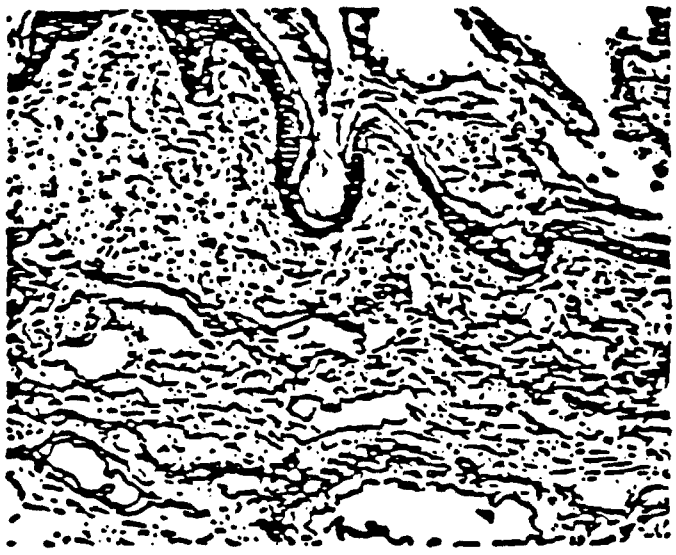
Another sample of each kind of asbestos was ball-milled for two hours and then heated in an electric muffle furnace for two hours at 900 C for chrysotile, at 980 C for crocidolite, and at 1,000 C for amosite. The heating did not destroy the fibrous structure, although it altered the chemical as well as the crystalline structure of the asbestos (Fig 1).

A third sample of each, after ball-milling, was treated with *aqua regia* for one hour, washed, treated with 2% acetic acid in 1M potassium hydroxide for another hour, and washed until the pH was 7.0. It was then milled in a shaking-type ball mill (Spex Mill[1]) for 3 to 15 minutes so that the material would easily pass through an 18-gauge needle. This chemical treatment was intended to remove trace metals, particularly nickel that is present within the mineral crystals.

The fourth sample of each type of asbestos was treated in a manner similar to the

Fig 2.—[illegible] in pleural inflammatory tissue. From a rat dead 11 months after an intrapleural injection of heated chrysotile (50 mg) (hematoxylin-eosin, original magnification × 250).

Fig 3.—Pleural surface is covered by keratinizing stratified squamous epithelium that rests on an inflammatory collagenous tissue. From a rat dead 16½ months after an intrapleural injection of 50 mg of treated crocidolite (hematoxylin-eosin, original magnification × 100).



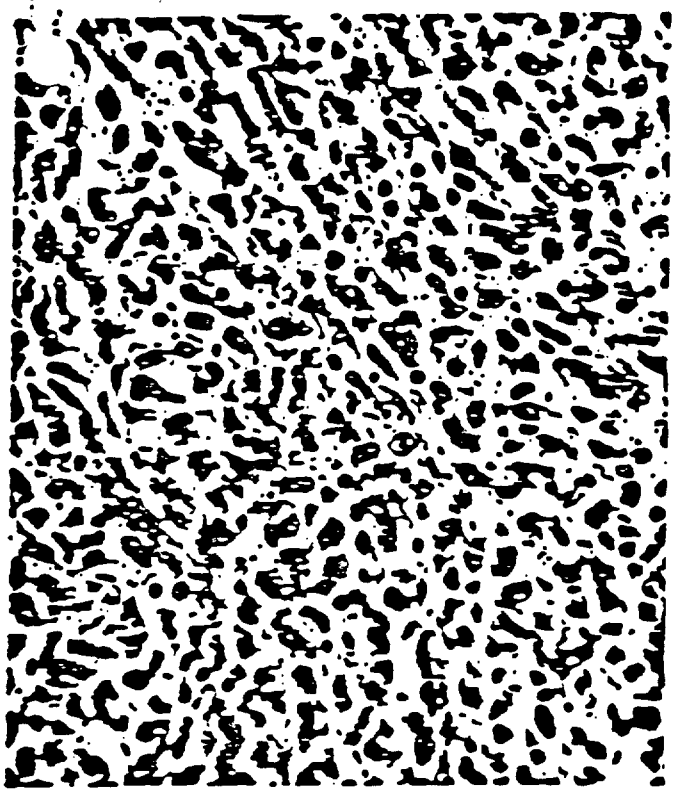


Fig 4.—Undifferentiated pleomorphic sarcoma involving chest wall and s of hamster dead 18½ months after an intrapleural injection of free amosite (hematoxylin-eosin, x 250).

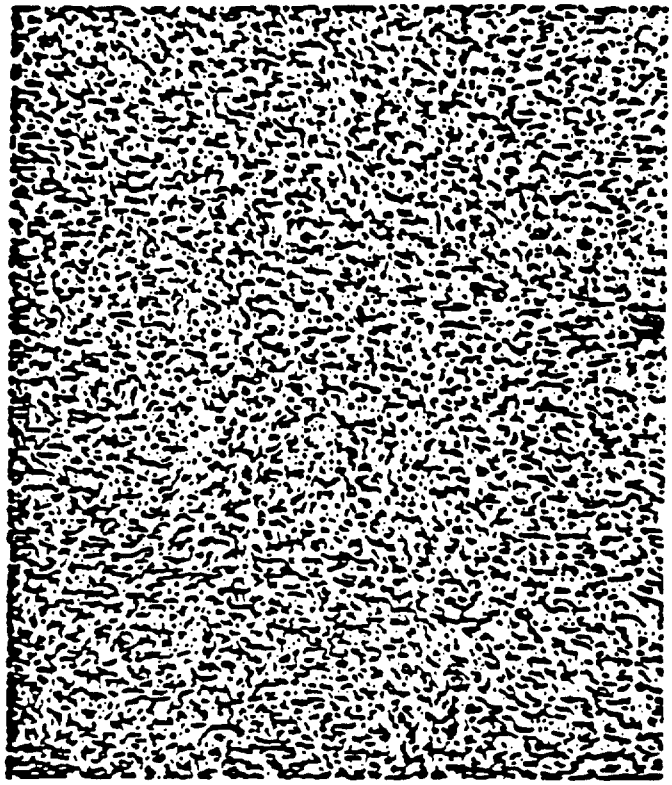


Fig 5.—Highly cellular spindle cell sarcoma involving pleura of rat that died 21½ months after intrapleural injection of 50 mg metal-free amosite (hematoxylin-eosin, original magnification x 250).

Fig 6.—Mesothelioma characterized by neoplastic fibrous stroma containing acinar structures. From rat injected intrapleurally with 50 mg hammer-milled chrysotile and dead 20 months thereafter (hematoxylin-eosin, original magnification x 250).

Fig 7.—Small portion of papillary mesothelioma that involved much of pleural surfaces. From rat dead 22 months after intrapleural injection of 50 mg hammer-milled amosite (hematoxylin-eosin, original magnification x 250).

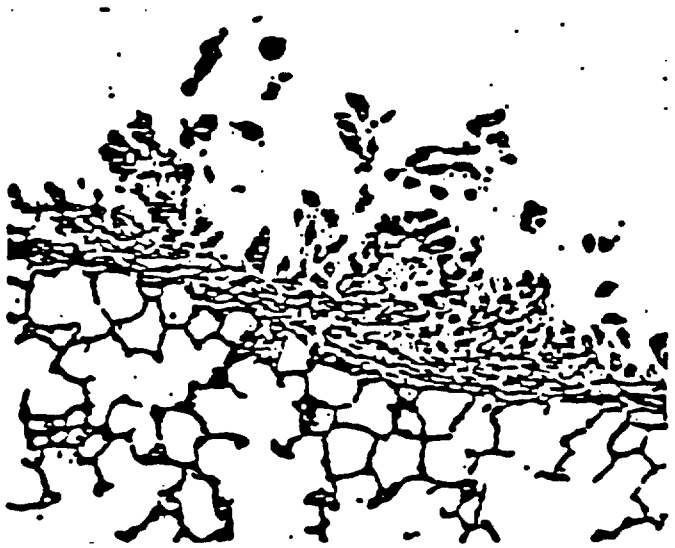


Table 1.—Incidence of Dust-Related Tumors in Animals

Method of Preparation	Amosite No.	Amosite %	Crocidolite No.	Crocidolite %	Chrysotile No.	Chrysotile %	Total (%*)
Rats							
Hammer-milled	4/12	33	5/16	31	2/6	33	11/34 (32)
Treated	2/11	18	7/17	41	4/14	29	13/42 (31)
Metal-free	5/10	50	3/9	33	1/6	16	9/25 (36)
Heated	0/15	0	0/17	0	1/16	6	1/48 (2)
Heated and treated	1/15	7	0/16	0	0/12	0	1/43 (2)
Total	12/63	19*	15/75	20*	8/54	15*	35/192 (18)
Hamsters							
Hammer-milled	2/15	13	0/7	0	0/0	0	2/22 (9)
Treated	1/8	13	1/8	13	0/3	0	2/19 (11)
Metal-free	7/14	50	2/6	33	0/0	0	9/20 (45)
Heated	1/15	7	0/18	0	0/13	0	1/46 (2)
Heated and treated	1/16	6	0/15	0	0/12	0	1/43 (2)
Total	12/68	18*	3/54	6*	0/28	0	15/150 (10)

*Overall percentage of tumor incidence.

Table 2.—Effect of Heating All Three Types of Asbestos Dust on Tumor Incidence

Method of Preparation	Rats No.	Rats %	Hamsters No.	Hamsters %
Heated	1/48	2	1/46	2
Heated and treated	1/43	2	1/43	2
Total	2/91	2*	2/89	2*
Hammer-milled	11/34	32	2/22	9
Treated	13/42	31	2/19	11
Metal-free	9/25	36	9/20	45
Total	33/101	33*	13/61	21*

*Overall percentage of tumor incidence.

third sample, but was subsequently also heated in the same manner as the second sample.

For the fifth sample, a chunk of the mineral ore of each type of asbestos was denuded of its superficial fibers on one surface with the use of a piece of broken glass. Additional deeper-lying fibers were then handpicked with the aid of sharp glass fragments to provide asbestos fibers that had no contact with a metal. These fibers were then Spex-milled for 20 to 30 minutes with the use of plastic containers and plastic balls. The samples are hereafter termed "metal-free."

Standard aqueous suspensions were made of each sample so that each contained 50 mg/ml.

With male rats weighing 150 to 200 gm under ether anesthesia, 1-ml amounts of the suspensions (50 mg each) were injected intrathoracically in the right axilla with the use of a 5-mm 18-gauge needle. Hamsters were similarly injected, but here the amount of dust was only 25 mg in 0.5 ml. Injections into the right thorax were administered to a total of 430 rats. Of these, were injected with amosite, 176 with crocidolite, and 139 with chrysotile. The number of rats per sample ranged from 20 to 45 because of early deaths, which were promptly replaced. Of a total of 239 hamsters similarly injected, only 157 survived 7½ months or longer. Of the hamsters injected with chrysotile, only 28 survived.

After the injections, the animals were pastured and allowed to live out their lives.

Results

There was a considerable early mortality at the dosage level employed in several groups so that in order to obtain a reasonable number of rats surviving at least six months, 45 rats were injected in the metal-free amosite group and 40 in the treated chrysotile group. Disregarding the deaths that occurred prior to six months, the average survival in the various groups ranged from 9 to 24.8 months, with an average of 16.7 months. However, the deaths of the animals were not necessarily related to the intrapleural injections of asbestos, since two separate epidemics of pneumonia occurred among the rats.

One of the more interesting observations pertains to the infrequency of obvious involvement of the visceral pleura as compared with the parietal pleura. In some animals when the surface of the lungs seemed uninvolved, interlobar lesions were often noted. In its most severe form, the tissue reaction consisted of ovoid nodules of dense collagenous tissue bordered by a vascular and highly cellular granulation tissue containing asbestos as well as multinucleated giant cells and histiocytes. In many animals, large centers of aggregated asbestos and necrotic material were surrounded by vascular and cellular granulation tissue continuous with that surrounding the previously mentioned ovoid nodular collagen masses.

The visceral pleura was often slightly thickened by edematous fibrillar tissue poor in cells. The parietal pleural involvement frequently extended into the skeletal muscle as a histiocytic and collagenous inflammation. In the superficial portions of the chest wall, it was often apparent that proliferation of the mesothelial cells had occurred. This was demonstrable as a surface covering of crowded plump cells—occasionally arranged in two or more layers. The pleural involvement was also seen as gland-like structures within the inflammatory tissue (Fig 2). Another very interesting finding (noted in only two rats) was squamous metaplasia of the proliferated surface cells—even with the formation of keratin (Fig 3). These mesothelial changes were found predominantly on the chest wall. The animals injected with the heated, or the treated and heated, varieties of asbestos generally showed less severe and less extensive inflammation than the animals injected with asbestos treated in other ways.

In some animals there was a transition from the cellular granulation tissue to tissue that was manifestly neoplastic. A total of 35 and 15 malignant tumors in rats and hamsters, respectively, originated from the inflammatory tissue associated with the injected asbestos. The earliest tumor was seen in a rat that survived 13 months and in a hamster that survived 7½ months after the injection. Consequently, in considering the incidence of these tumors, only those animals were counted that survived the number of months at which the

ea[illegible]t tumor was found.

bulation of the tumors found in the various groups (Tables 1 and 2) suggests that the animals can be arranged in two contrasting series: one in which the asbestos had been heated, or treated and heated, and the other that included all the remaining animals. The animals injected with the dusts that had been heated—whether treated additionally with *aqua regia* or not—had a low tumor incidence, around 2%, whereas the tumor incidence of the combined animals injected with dusts treated differently was approximately ten times greater—21% and 33% for hamsters and rats, respectively.

The tumors found in the rats were, with few exceptions, well-differentiated. Those in the hamsters were undifferentiated sarcomas (Fig 4). Of the 35 tumors in the rats, 25 were fibrosarcomas (Fig 5); four were mesotheliomas (Fig 6 and 7); three were rhabdomyosarcomas (Fig 8 and 9); two were osteogenic sarcomas or [illegible]sarcomas with bone formation [illegible]10); and one was a fibroliposarcoma (Fig 11).

The mesotheliomas were identified on the basis of discrete papillary structures covered by mesothelium-like cells or the presence of plump cells resembling those of mesothelium, associated with otherwise well-differentiated fibrous tissue. Gland-like structures were also found (Fig 7).

The tumors diagnosed as fibrosarcoma admittedly may also include a few mesotheliomas. We do not know how to discriminate between a well-differentiated fibrous mesothelioma and an equally well-differentiated fibrosarcoma in the absence of tissue suitable for electron microscopic study or tissue culture.

The incidence of tumors in both species of animals was least with chrysotile. So far as the other two types of asbestos are concerned, they tended to produce about the same incidence of tumors in the chests of rats, but in hamsters amosite caused a higher incidence of tumors than crocidolite.

Comment

It is apparent from the results obtained that no significant difference exists in the incidence of tumors produced in the chests of rats or hamsters injected intrapleurally with the different modifications of unheated asbestos. This lack of difference in the incidence of tumors held whether more trace metals had been added to the asbestos dusts by hammer-milling, whether metals had been removed by *aqua regia* and edetic acid or trace metals had neither been added nor subtracted. The trace-metal hypothesis must therefore be abandoned.

Another conclusion that is readily apparent from these results is that prolonged heating of the three most commonly used types of asbestos will diminish their pathogenic potential inasmuch as the tumor incidence associated with the heated asbestos is about one tenth of that associated with the unheated types. The fibrogenicity of the former also seemed less, since the inflammation was noted to be less severe and less extensive than that seen with the latter.

The present results also have relevance to the tendency to make the diagnosis of mesothelioma without excluding the possibility that the tumor in question is metastatic or, in case of experimental intrathoracic tumors, without considering a possible origin of the tumor from the submesothelial or the inflammatory connective tissue. The occurrence in this series of rhabdomyosarcomas, osteogenic sarcomas, and fibroliposarcomas suggests that the tissues of the chest wall other than mesothelium also have the potential to give rise to malignant tumors when stimulated by intrapleurally injected asbestos dust. It is therefore likely that some, if not many, of the reported nonpapillary fibrous tumors designated as mesotheliomas were in reality fibrosarcomas. This is also a probability with respect to the "mesotheliomas" observed in association with fibrous glass.[7]

In contrast to the usually well-differentiated tumors in the rat's chest cavity, the intrathoracic tumors in hamsters are highly cellular, undifferentiated sarcomas. It is presumptuous to designate such undifferentiated tumors as mesotheliomas.

The relative resistance of the visceral pleura to the damage caused by the injected asbestos represents interesting incidental information secondary to the results obtained. An explanation for the phenomenon is not available, but it seems to have its clinical counterpart in the hyaline plaques observed with increased frequency in people exposed to asbestos dust.[10] These hyaline plaques also occur preponderantly on the parietal pleura.

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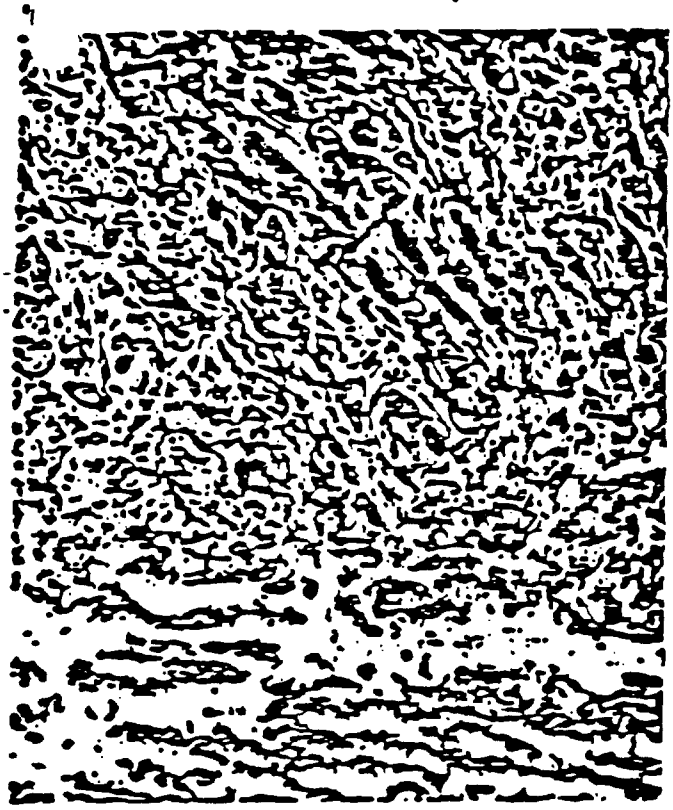

Fig 8.—Rhabdomyosarcoma extending into subpleural alveolar tissue. rat dead 19 months after intrapleural injection of 50 mg hammer-amosite (hematoxylin-eosin, x 125).

Fig 9.—Selected high-power field of tumor in Fig 7 demonstrating cross-striations in some neoplastic muscle fibers (hematoxylin-eosin, original magnification x 450).

Fig 10.—Early bone formation in an otherwise poorly differentiated sarcoma. From pleural cavity of rat dead 19½ months after intrapleural injection of 50 mg hammer-milled amosite (hematoxylin-eosin, x 125).

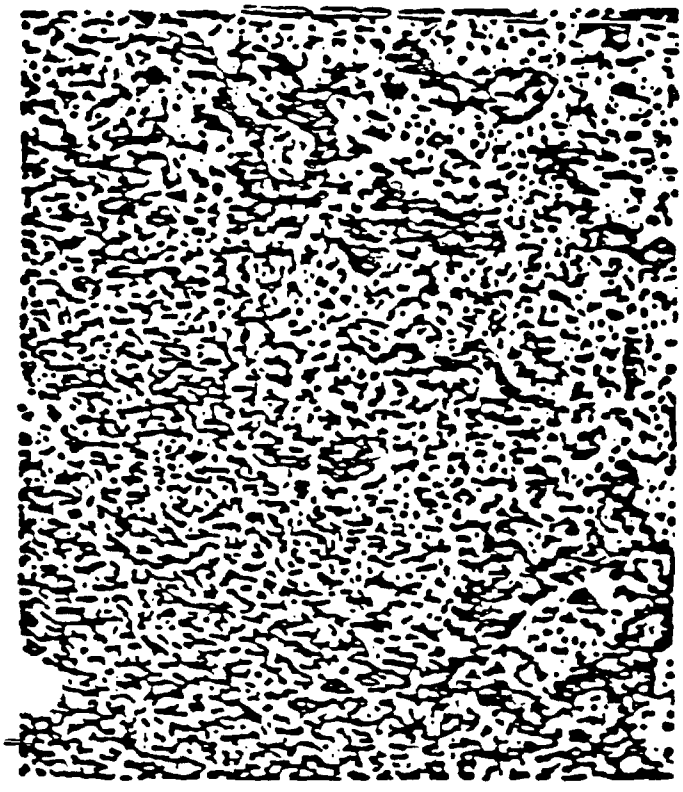

Fig 11.—Neoplastic pleural tissue of well-differentiated fibroadipose tissue extends into air spaces. From rat dead 23½ months after intrapleural injection of 50 mg hammer-milled amosite (hematoxylin-eosin, x 250).