Is Short-Fibered Asbestos Dust a Biological Hazard?

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Contrary to the determination that the finer the quartz dust, the greater its pathogenicity; the pathogenicity of the finest asbestos dust has been shown to be negligible.

It has been the finding of research laboratories in Germany, England, South Africa, and the United States that short-fibered asbestos, dust, ie, less than 5μ in length, is incapable of causing fibrosis or cancer. This finding, in conjunction with the failure of different laboratories in the United Kingdom and in this country to discern abnormalities following prolonged asbestos feeding to rats, should lead to the abandonment of the present concept that maintains that mesotheliomas and gastrointestinal cancers arise from the ingestion of asbestos dust cleared from the lungs.

These negative results should also allay the alarm that has been raised as a result of the finding of ultramicroscopic mineral fibers in certain beverages and drinking water.

By short-fibered asbestos dust is meant that which has a fiber length of less than 5μ. Although fibers of this size usually constitute a very small fraction of the weight of a dust cloud, their numerical preponderance over the larger fibers may be manifold.

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Inasmuch as asbestos fibers smaller than 5μ tend to remain airborne longer than the larger ones, they have a greater chance of being inhaled. Furthermore, although the anatomy of the respiratory tract tends to prevent the intrusion into the airspaces of all but a few of the larger suspended particles, this deterrence does not extend to the smallest particles. The latter very readily enter the airspaces with the inspired air. Some of the short asbestos fibers may settle on the alveolar surface by sedimentation, whereas the smallest fibers, behaving almost like gas molecules, contact the alveolar membrane by diffusion.

What is the potential of these extremely fine submicronic fibers to produce disease? Is their potential greater than that of optically visible fibers? Is the behavior of submicronic asbestos fibers as opposed to that of larger fibers similar to that of the fibrogenic effect of very fine quartz dust as compared with that of the same weight of coarser quartz particles?[1-3]

These questions take on added importance in view of the commonly held hypothesis that mesotheliomas of the pleura and peritoneum arise by the transmigration of fibers to the pleura and peritoneum, respectively. In the case of abdominal mesotheliomas, it is assumed that the asbestos fibers cleared from the lungs are swallowed and then migrate through the intact intestinal wall to the peritoneum, there to initiate the development of mesotheliomas. So far as ability to penetrate into and transmigrate across the intact intestinal wall is concerned, once again it would appear that the submicronic fibers would be better able to accomplish this feat than would the coarser fibers.

Originally, the question of the pathogenicity of the short-fibered asbestos dust had relevance only to people occupationally exposed to asbestos; but more recently short asbestos fibers have been found in certain beverages and city water, in ambient community air, and in the lungs of city dwellers.[4-6] Consequently, the relevance of the above question must now extend to entire urban populations. However, lest undue alarm be raised by the last statement, it should be pointed out that in city dwellers no disease has been found that could be attributed to the presence of submicronic asbestos fibers in the pulmonary tissues. Neither has there been documentation of an increase in abdominal cancers in the general population, in spite of the fact that in many cities and smaller communities drinking water has been and is now transported in asbestos-cement pipes.

At the International Conference on the Biological Effects of Asbestos held in Dresden in 1968, Klosterkötter[4] found that both chrysotile and crocidolite, ground to an average fiber length of less than 5μ when injected intratracheally or intraabdominally, produced no fibrosis. The

pulmonary response consisted only of a macrophage reaction. In contrast, longer fibers of the same asbestos resulted in fibrosis in both regions. At the same conference Timbrell and Skidmore[4] reported the results obtained in rats and guinea pigs exposed to equal concentrations (by weight) of short-fibered amosite (90% of the fibers <4μ long) and long-fibered asbestos (45% of the fibers >4μ long). They concluded, "minimal reaction has been observed to short fibres but a marked reaction has been observed to the longer fibres." In the following year, Webster[5] reported that monkeys inhaling finely ground crocidolite (fiber length <3μ) also showed merely a macrophage reaction in the lungs. In 1970, Hilscher et al[6] showed the chrysotile or crocidolite, when ground to a fiber length of <3μ with a microtome and injected intraabdominally, produced no fibrous adhesions; whereas the same asbestos with greater fiber length did cause dense fibrous adhesions.

In 1971, the Johns-Manville Research Laboratory prepared for us chrysotile asbestos ground to a fiber length of <5μ. We injected this dust intratracheally into 10 rats and were able to confirm that such short-fibered asbestos could induce no more than a macrophage reaction (unpublished study). In 1973 Smith et al[7] reported that hamsters injected intrapleurally with chrysotile ground to a fiber length of <1μ developed no pleural cancer, whereas hamsters injected intrapleurally with longer chrysotile fibers did develop such cancers. Recently Wright (private communication) disclosed that in his laboratory short-fibered asbestos injected intratracheally also failed to elicit a fibrotic reaction. Maroudas et al[8] have concluded that, "Particles (mineral fibers) smaller than 20μ in length induce neither growth in vitro nor mesothelioma in vivo."

Thus, these reports from different laboratories are unanimous in finding asbestos that has an average length of <5μ is devoid of pathogenic potential. This included not only the fibrogenic potential[4-6] but also the cancerogenic potential.[7,8]

It may be argued that when asbestos is ground to a very small fiber size, either in a ball mill or a hammermill, much of the energy is converted into heat and the heat may change the chemical structure of the fibers. To continue this argument: since, strictly speaking, the fibers so altered may no longer be asbestos, the biologic "inertness" of such "altered" asbestos need not necessarily apply to fine asbestos dust that has not been heated to a high temperature.

This argument is rendered void by the following facts:

1. The short-fibered asbestos of Hilscher et al[6] was found to have maintained its fibrous structure after the grinding process.

2. Smith et al[7] prepared short-fibered asbestos as an aqueous slurry. This obviated excessive heat.

3. It has been concluded that the chemical structure of asbestos does not determine its pathogenicity since synthetic chrysotile is devoid of pathogenicity.[9] The latter has the same chemical and crystalline structure as the natural product. Therefore, the mere process of grinding with the associated heat production does not account for the lack of pathogenicity of the finely ground asbestos. However, by fitting together some newly derived experimental findings, a theory has recently been formulated regarding the locus of pathogenicity of asbestos dust that does offer a reasonable explanation for this lack of pathogenicity.[10]

There is, however, one laboratory that reported that short-fibered asbestos is tumorigenic. Pott and Friedrichs[11] and later, Pott et al[12] maintained that 100 mg of chrysotile with a fiber length <3μ injected into the abdomen of rats caused the development of cancers. Nearly 80% of the tumors were sarcomas—mostly fibrosarcomas.

The character of the tumors produced by this technique should have given the authors pause for reflection; not only because rats will produce fibrosarcomas secondary to injected or imbedded materials known to be biologically inert, but also because subcutaneous fibrosarcomas are very common spontaneous tumors in aging rats. An indication of the ease and nonspecificity of such tumor production in rats is demonstrated in the first[11] of the two above-mentioned papers when the authors list a better-than 60% tumor production with magnesium hydroxide and a 55% tumor production with fibrous glass! In contrast, they reported only a 40% tumor production with chrysotile. This lower tumor production was doubtlessly related to a high mortality caused, in turn, by the exceedingly high dosage of materials injected (100 mg).

The employment of unrealistic dosage, of inappropriate routes of administration, and of inappropriate animal species (all three "sins" were committed by the above authors) to achieve positive results has recently been adequately discussed by Dr. H. E. Stokinger.[13]

When asbestos is ingested, it is the ultramicroscopically-sized asbestos fibers that are assumed to be responsible for the development of mesothelioma by virtue of their alleged penetration and transmigration through the intact intestinal wall. The failure of short-fibered asbestos to induce mesotheliomas when injected intrapleurally[4-6] makes the above assumption highly questionable. Unpublished data from different laboratories (David B. Clayson, University of Leeds; L. M. Swinburne, St. James's Infirmary, Leeds, England; and John M. G. Davis, Institute of Occupational Medicine, Edinburgh) in which rats were fed asbestos intimately mixed in their food, indicate complete failure to induce tumors or any other kind of abnormality by these regimens. (A joint paper describing these investigations from the different laboratories is in preparation.)

As one example, the following experiment may be cited: ten weanling male rats were placed on a finely ground basal diet containing 5% by weight of chrysotile asbestos. Five litter mates were pair-fed with the same weight of food as the experimental rats had consumed on the previous day. This regimen was continued for 21 months. At the end of this time, the weight curve of the asbestos-fed animals was not significantly different from that of the pair-

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fed controls. The animals were killed 21 months after the initiation of the feeding period. At autopsy, no gross abnormality was found in either group of animals and microscopically no tumor or other gastrointestinal lesion was observed." It is to be noted that in previous studies, the first asbestotic lung cancer death occurred 16 months after the initiation of the dust exposure[17] and the first asbestotic pleural cancer death in rats occurred 17 months after the intrapleural injection of asbestos dust.[18]

It is of interest in this connection that the dose of fibers in the intestinal tract of the asbestos-fed rats was astronomical compared with the dose of fibers that is likely to be swallowed daily by a person occupationally exposed to asbestos dust—and he, in turn, would have an astronomically greater dose of fibers than the dose of fibers ingested daily by an urban dweller drinking a beverage or water containing mineral fibers.

The uniformly negative asbestos-feeding results should cast some doubts on the tenability of the concept that peritoneal mesotheliomas and an increased prevalence of gastrointestinal cancers arise in occupationally asbestos-exposed people from the ingestion of asbestos fibers cleared from their lungs. There must, of necessity, be some other explanation!

Although not an asbestos-feeding study, a recent report purports to demonstrate that the presence of asbestos in the intestinal lumen results in the penetration of asbestos fibers into the blood stream and organs throughout the body, inclusive of the brain.[18] The writers injected the asbestos into the stomach by means of a syringe and needle, thereby ignoring the probable opening of vessels in the path of the needle track and the presence of injection!

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Rebuttal

In looking through "Biological Effects of Asbestos" (*Ann NY Acad Sci* 136:37, 1965) I find one paper by Holt, Mills, and Young that says very small asbestos particles do cause fibrosis in the guinea pig lung. In the published discussion, no one challenges this result; one discussant, Ian Webster from South Africa agrees with it, and Gilson quotes it approvingly in his final wrap-up. At least in 1965, ultramicroscopic asbestos particles were believed to have fibrogenic potential for guinea pigs.

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I reply that Paul Holt used the same make hammermill to comminute his asbestos as I used. I fully agree with his statement that a high proportion of the particles to which he exposed his guinea pigs was too small to be seen by the light microscope.

The more important aspect of Holt's statement is the *long fibers were present* in the dust cloud. Having seen his set-up, I was impressed by the high density of the dust concentration (unmeasured!) to which his guinea pigs were exposed. The dosage of long-fibered (optically visible) particles must have been enormous whereas the dosage of submicronic fibers (those visible only with the electron microscope) must have been astronomical.

Holt's finding of many optically visible fibers in the lung sections of his animals as pictured in his illustrations and of many asbestos bodies attest to the plentiful dosage of long fibers. This undermines his claim that "Fine dust particles, too small to be seen under the light microscope, will produce asbestosis in the guinea pig."

The determinant(s) of asbestos toxicity is not known and I make no claim to such knowledge. However, in this article, I point to one aspect of asbestos dust which is not associated with pathogenicity.

By "submicronic" is meant something invisible with the light microscope but visible with the electron microscope. This generally means a particle $<0.25\mu$ in thickness. Although the vast bulk of fibers that have been ground to a length $<5\mu$ are submicronic, some would be thicker than 0.25μ and therefore, optically visible. Perhaps, it would be best not to specify "submicroscopic" and speak only of "short" fibers as defined in the opening sentence of the report.

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