

PLAINTIFF'S EXHIBIT

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EDITORIAL

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Fiber Carcinogenesis: Is Asbestos the Only Hazard?

DATA FROM several laboratories as well as my own indicate that asbestos causes cancer, not because it is asbestos, but because of the unique physical structure it can attain (1). Asbestos causes cancer when it separates into fibers with exceptionally small diameters that retain substantial lengths. This concept may explain many differences in cancer risk during various occupational exposures to asbestos. It is particularly supported by the correlation shown by Tompkins et al. between differing mesothelioma risk and differing fiber diameters of amphibole asbestos from the Nor-west Cape and Transvaal mining regions of South Africa (2). However, the basis for this premise is evidence gained from our work and that of others in which various types of fibers were implanted in the pleura of rats and yielded carcinomas essentially the same as the mesotheliomas induced by asbestos in man (3, 4). This procedure circumvents the variables dependent on the ability of a fiber to reach the target organ and thus becomes an initial step to understanding mechanisms of cancer induction by fibers. These studies indicate that neither the hydrations and trisaccharide complexes naturally associated with asbestos nor those associated with the processing of asbestos are sufficient to account for asbestos carcinogenicity. Further, the studies indicate little difference in the carcinogenicity of types of asbestos that vary widely in physicochemical structure if they are tested in similar ranges of size.

The most convincing evidence of a structural relationship to carcinogenicity is that fine, long fibers of durable materials completely unrelated to asbestos, i.e., glass and aluminum oxide, are similarly carcinogenic in the pleura of the rat. On the other hand, nonfibrous particles of asbestos, glass, or aluminum oxide, as well as exceptionally short fibers of these materials, are far less carcinogenic in the pleura of the rat. In fact, the degree of carcinogenicity of the fibrous materials correlates with the dimensional range of the fibers implanted. Because fibers in the samples vary widely in size, carcinogenicity cannot be confined to an absolute dimensional range. But a conservative

estimate indicates that in the pleura of the rat, durable fibers of 3 μ m diameter and 10 μ m in length are at least as carcinogenic as other fibers of various lengths with diameters of 3 μ m. Fibers with diameters of 3 μ m and lengths of 10 μ m. Some of our preliminary data indicate that exceptionally long glass fibers with diameters of 3 μ m are highly carcinogenic in the pleura of the rat. We are now testing sized samples of durable fibers of many types to improve our estimates of which dimensions are the most hazardous.

These parameters need not be defined to appreciate that carcinogenicity can depend on the structure rather than the physicochemical composition of a particle. The most important corollary to this conclusion is that any type of durable fiber falling into the broadly defined dimensional range of low, fine fibers may be carcinogenic. Certainly this seems true for the pleura of the rat, and it is unlikely that different mechanisms are operative in man. If we consider the conventional definition of a fiber as any particle with a length ≥ 5 times its diameter, minute fibers are abundant in our environment, and the list of fibers used by man increases daily. Durable fibers are used not only as insulation materials and binders of high tensile strength, but also as excellent filters, abrasives, refractory emulsifiers, and chemically inert fibers that can be found in everyday household products, i.e., cleaners, paints, cosmetics, and even fibers, foods, and medications. Furthermore, air and water samples are frequently contaminated with mineral fibers from natural sources as well as with pollution by man. The point of man's exposure to fibers lies in the fact that fibers of a variety of types can be isolated from nearly all human lungs.

The question raised is the risk that such fibers may hold currently or with the increasing use of fibers that may occur in the future. A great deal of speculation already made is perhaps relevant to this question (5, 6). I mention here only a few. The fibrous materials to which we are most continually exposed consist for the most part of particles too large or too small to be consistently inhaled. Glass fibers, for example,

dimensional fibers we have estimated in the rat are used as criteria. For example, most insulation materials, as well as many other than asbestos, are composed entirely of fibers with diameters $< 0.5 \mu$. Emission and friction wastes of asbestos and other fibrous products are, for the most part, short fibers of submicron size, which in rats seem far less hazardous than fibers in the lowest range of optical visibility. Were it not for these fortunate circumstances, the problem of fiber carcinogenicity might be more obvious today. The most hazardous fibers may be those of exceptional length, with diameters of $< 0.5 \mu$; such fibers are near the limits of optical visibility and are to some extent in nearly all fibrous materials. Our present systems of assessing carcinogenicity in animals can at best only detect response to large numbers of fibers; therefore, materials containing only a few exceptionally fine fibers could easily escape detection as a hazard in simply designed animal tests. Even with the most sophisticated test, it would be difficult to establish an absolute threshold of safety, since each small exposure possibly adds to the total hazard and represents a fiber, albeit small, asbestos risk.

The ultimate risk of fibers is, of course, a complex problem. In addition to the level of exposure and physical properties of fibers, one must take into account factors of inherent resistance, mechanisms of elimination and environment, the properties and opportunities that enable particular types of fibers to reach tissues, and the contributions of other carcinogens such as cigarette smoke. From our experiences with asbestos, it is apparent that fibers can be most subtle carcinogens that deviate from simple dose-response relationships and that require long latent periods before showing carcinogenic activity. For these reasons alone, it would be unwise to ignore a potential problem of greater range than asbestos.

There is perhaps one way to determine the hazards of fibers without waiting the many years necessary for the effects of even massive exposure to become evident. Unlike most carcinogens, fibers that are a threat are sufficiently durable to remain in the tissues from which cancers are derived. Since carcinogenic responses can

be related to doses of sized fibers in experimental animals, it may be possible to equate the number and size distribution of fibers in human tissues to cancer in man. Although much has been accomplished in assessing large, protein-coated fibers in human lungs, surprisingly little has been done in assessing the size distribution and total quantity of all fibers in human tissues. This would be a tedious job, but it might determine the true significance of fibers as carcinogens in man.

Further, we need clues to the intimate events between cell and fiber that lead to cancer. Not all cells penetrated by fibers die. Conceivably these transiting fibers could irreversibly alter intracellular replicative processes either directly, through activation of repressed oncogenes, through alteration of cell membranes, or through initiation of a unique, precancerous fibrosis. Short, fine fibers may be less carcinogenic, simply because they are more effectively removed by acute or intracellular phagocytic activity. However, a more complex explanation is suggested by recent studies showing that in vitro groups of cells on minute glass fibers is related to the length of the fiber (6). Whatever the mechanism of fiber carcinogenesis is, I believe that the following guidelines must be taken into account. Durable fibers, perhaps at the extreme range of dimension, cause cancer simply because they are fibers and irrespective of their physicochemical nature. Vigilance in detecting the presence of such fibers in the environment and implications of man may well profit on all.

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