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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 Timbrell et al. between differing mesothelioma risk and differing fiber diameters of amphibole asbestos from the Northwest Cape and Transvaal mining regions of South Africa (*1*). 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 sarcomas essentially the same as the mesotheliomas induced by asbestos in man (*1–3*). 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 hydrocarbons and metal-mineral 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 milled to 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 3 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 $<3\mu$ in diameter and $>20\mu$ in length are far more carcinogenic than either fibers of various lengths with diameters $>3\mu$ or fibers with diameters $<3\mu$ and lengths $<20\mu$. Some of our preliminary data indicate that exceptionally long glass fibers with diameters $<0.5\mu$ 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.

Precise 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 observation is that any type of durable fiber falling into the broadly defined dimensional range of long, 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 >3 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, lubricants, emollients, and chemically inert fillers that can be found in everyday household products, e.g., cleansers, paints, cosmetics, and even fabrics, foods, and medications. Furthermore, air and water supplies are frequently contaminated with mineral fibers from natural sources as well as with pollution by man. The proof 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 number of observations already made are perhaps relevant to this question (*1–3*); I mention here only a few. The fibrous materials to which we are most commonly exposed consist for the most part of particles too large or too small to be considered potent carcinogens, if the

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ional ranges we have estimated in the rat are
ia. For example, most insulation mate-
day, other than asbestos, are composed
of fibers with diameters $>5\mu$. Erosion and
on wastes of asbestos and other fibrous products
for the most part, short fibers of submicroscopic
which in rats seem far less hazardous than fibers
the lowest range of optical visibility. Were it not
these fortunate circumstances, the problem of fiber
cinogenicity might be more obvious today. The
ost hazardous fibers may be those of exceptional
igth, with diameters of $<0.5\mu$; such fibers are near
he limits of optical visibility and are to some extent
n nearly all fibrous materials. Our present systems of
ssessing 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
finite, albeit small, ultimate 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 containment, 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 response can be related to doses of sized fi
animals, it may be possible to equate the
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 transfixing 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 contained by overt or intracellular phagocytic activity. However, a more complex explanation is suggested by recent studies showing that in vitro growth of cells on minute glass fibers is related to the length of the fiber (*4*). Whatever the mechanism of fiber carcinogenesis is, I believe that the following premise must be taken into account. Durable fibers, perhaps at the extreme ranges 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 in the tissues of man may well profit us all.

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