Fiber Toxicology

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It is beyond our normal experience to comprehend how a very durable, non-reactive material such as asbestos can play a role in the complex biological process that leads to malignant growth. The objectives of this discussion are to show that the factors involved can be reduced to three major determinants and to consider how these determinants can be used to evaluate the possible risk associated with occupational exposure to a wide variety of fibrous materials, both natural and man-made.

Our current knowledge regarding asbestos-related diseases has been derived from both epidemiological and animal studies. In certain limited areas confirmatory evidence has been obtained from in-vitro cell culture studies. All of this information indicates that the important determinants for the biological activity, and, therefore, the disease-producing potential, of fibers are the *dimensions* of the fibers, the *dose* and the *durability* of the fibers in the biological system.

Dimensions of Biological Activity

The information available on this subject is primarily a result of animal experimentation by Stanton,[1] Pott,[2] Wagner,[3] and Davis.[4] These investigators used a variety of techniques to implant fibers of various types and differing dimensions into the pleural or the peritoneal cavities of animals. The development of tumors and the relationship of these findings to the dimensions of fibers were observed and analyzed. Stanton, for example, reported that fibers which had lengths in excess of 8 micrometers and diameters less than 1.5 micrometers have the greatest biological activity. Pott's most recent data are in close agreement with those of Stanton. He points out that the fiber diameter for maximal biological activity is approximately 0.25 micrometers. These studies provided the foundation for the "long, thin" hypothesis for the pathogenesis of malignant fibrous neoplasms. Of special note is the fact that this hypothesis is supported by essentially all of the experiments which have been reported to date. Even though these experiments have produced tumors in animal models using very artificial means to bring the fiber in contact with the target tissue, these non-physiological exposures have contributed significantly to elucidating the mechanism of the biological activity of fibers. There are unfortunately, no data relating to bronchogenic cancer and there are only scant data on fibrogenesis.

In contrast to the above studies, Wright and Kuschner[5] introduced well-characterized fibers into the lungs of guinea pigs by intratracheal injection. Although this mode of exposure also can be considered artificial, it is certainly not as artificial as intrapleural implantation. The circumstances for the development of fibrosis in their experiment very clearly support the long, thin hypothesis of biological activity.

Table 1 lists those fibrous materials which have been demonstrated to produce malignant fibrous neoplasms following implantation in the pleural or the peritoneal cavities of animals. This listing clearly illustrates the fact that such materials cover an extremely broad range of chemical composition, structural types, and surface characteristics. Careful analysis of all the available data fails to show any other consistent underlying cause for the biological activity other than the fiber dimensions. If the bulk composition, surface chemistry or other factors do play a role, it must be secondary. Hypotheses relating the carcinogenicity of fibers to contamination by trace metals or organic materials have not been substantiated by animal experiments.[3,4]

Dose and Dose-Response

An extremely important factor governing the incidence of disease from any cause is the dose of the agent which has been received by the subject. It is not necessary to discuss the basic concept of dose-response except to emphasize that fibers are known to comply with the accepted principles of pharmacology and toxicology in their interaction with tissue. Concentration and dimensions *in the environment* play a major role in determining host entry or availability to target tissues.

In a theoretical sense, dose is best defined in terms of host entry and the biological availability of the fibers multiplied by the duration of the exposure to the target organ, tissue or cell. At the present time these parameters cannot be quantified. Among the factors which will influence the dose are: (1) the concentration of respirable

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Table 1. — Fibers Which Have Shown Biological Activity in Animals.	
Amosite	Mineral wool
Anthophyllite	Aluminum oxide
Chrysotile	Potassium titanate
Crocidolite	Silicon carbide
Tremolite	Sodium aluminum carbonate
Borosilicate glass	Wollastonite
Aluminum silicate glass	Attapulgite

fibers in the breathing zone; (2) penetration into the respiratory system; and (3) the efficiency of the clearance mechanisms. The concentration of fibers in the breathing zone is very dependent upon the physical and chemical properties of the material under consideration. Since this characteristic is also associated with other important factors, it will be discussed in more detail later in this paper.

Much of our practical knowledge regarding the deposition of fibers in the respiratory system comes from the work of Timbrell and co-workers.[7] Starting in 1965, they studied the problem of fiber deposition from both the theoretical and experimental standpoints, demonstrating that fibers falling with their long axes oriented normal to the direction of fall behave much the same as spheres having equivalent aerodynamic diameters. The inertial characteristics of fibers are governed by essentially the same parameters as the sedimentation.

When considering how fibers are deposited within the respiratory system, it became necessary to place considerable significance on the length of the fiber as well as its aerodynamic diameter. Timbrell was able to show that fibers as long as 200μ had a finite probability of penetrating to the distal portions of the lung and being deposited in the alveoli. The limiting factor for fiber respirability was determined to be a diameter of approximately 3μ; thus a fiber with this or lesser diameter can be regarded as respirable, even with a length in excess of 100μ. It has also been demonstrated that the most probable sites for the capture of fibers would be at the branch points in the bronchial system. Equidimensional particles, such as quartz and coal dust, are considered respirable only if the diameters are considerably less than 10μ. The aerodynamic behavior is probably the most important factor in determining the deposition within the lung.

In 1977 Harris and Timbrell[8] studied the deposition of fibers in the human lung as a function of fiber dimensions, using the model developed by Harris and Fraser[9] as the basis for their calculations. Prior to the appearance of this work, the only detailed models available were used to represent the deposition of equidimensional particles, such as quartz or coal, in the respiratory system. The Harris-Fraser model is based upon a lung architecture devised by Weibel.[10] In general, Harris and Timbrell predicted that the probability for penetration to the alveoli would decrease with increasing equivalent diameter, with increasing length and with random rather than ordered orientation of the fibers.

The length of time the fibers may remain in the various portions of the respiratory system is a function of the clearance mechanism. There are two mechanisms which are involved: the muco-ciliary system and the alveolar macrophages. The muco-ciliary system is quite effective in removing particulates from the bronchial system in a very short period of time. Lung clearance by this path is not particularly sensitive either to the size or shape of the particles. Since the alveoli do not contain ciliated cells, the removal of foreign material from this region of the lung is accomplished predominantly by the alveolar macrophages. It is also possible that free particles can be swept out of the alveoli by the natural movement of surfactant film which is produced in this region. It has been suggested that fibers which are longer than 10μ in length cannot be removed by the macrophages and that, therefore, if they become lodged in an alveolar space they may become permanent residents.[1]

The foregoing discussion shows that the fiber dimensions are extremely important, not only from the standpoint of tissue response, but in controlling the concentration reaching the tissue as well.

Particle Dimensions, Structure and Composition

In very general terms, fibers encountered in the occupational environment can be placed in one or more of the following categories: (1) natural or man-made; (2) crystalline or amorphous; or (3) virgin or process fragments. The portion of any fibrous material which can exist in respirable or biologically active size ranges depends on a variety of factors including the conditions of formation or crystal growth, the internal structure and, to a certain extent, the chemical composition.

Information relating to the physics and chemistry of asbestos and related minerals can be obtained from a number of sources.[11-15] In simple terms, asbestos minerals are naturally occurring crystalline materials which are very readily separated into fine diameter fibers of considerable commercial value. Since they are so easily separated into finer fibers, there is also a high probability that when they are used under uncontrolled conditions in the workplace high concentrations of respirable fibers can be generated.

There are a number of minerals in the amphibole family which can be considered to be close relatives of the commercial asbestos minerals. These minerals have the same general internal crystalline structure. This structure possesses natural cleavage planes which encourage fracture into long, thin fragments. However, subtle variations in composition or in growth conditions lead to a broad range of physical properties and their behavior on milling can vary considerably. Some specimens will fracture into thin, fibrous fragments almost as readily as the asbestiform variety, while others will behave as a solid mass and fracture into more equidimensional fragments.

In addition to the asbestos minerals and their amphibole cousins, there are literally dozens of other minerals which occur in fibrous form. Only a very few, however, are worth consideration because of their widespread occurrence or commercial importance. The most widely publicized of these have been the zeolites which have been implicated with mesothelioma in Turkey. The clay minerals attapulgite, halloysite, and sepiolite also occur in fibrous form. All of these latter minerals can be classified as naturally occurring, crystalline, virgin fibers. Even though these minerals have grown with a fibrous habit, their internal structure is not conducive to fracture parallel to the fiber axis. Milling or grinding will produce shorter rather than thinner fibers.

Man-made vitreous fibers have become important commercially over the past several decades. This category includes glass fiber, mineral wool, aluminum silicate refractory fibers, and glass Micro-Fibers!™ They are produced by blowing, spinning, pulling, or other means from a molten mass. In the general classification scheme they are man-made, amorphous, and virgin fibers. It is desirable to reemphasize the fact that the internal structure of vitreous fibers is not consistent with the tendency to fracture parallel to the fiber axis. Any input of mechanical energy will result in the production of shorter fibers.

The final category of commercially significant fibers to be included in this discussion is the group of high-performance reinforcing fibers used for specialized applications. These man-made, crystalline, virgin fibers include alumina whiskers, silicon carbide whiskers, carbon fibers, and others. Because of their very high cost they are only used in small amounts for special applications. The populations exposed are only a small fraction of those in the asbestos or the vitreous fiber industries. The majority of fibers in this category have internal structures which preclude the formation of smaller diameters on grinding.

Biological Durability

The last determinant of the biological activity of fibrous materials which was presented earlier is the durability of the fibers in tissues, organs, or organ systems. If a sufficient quantity of fibers is received and if their dimensions are in the biologically active range, it can be presumed that they must remain in contact with target tissue for a considerable period of time in order to cause disease. If the body fluids can attack the fiber so that in some way it is rendered harmless, it would not then be considered biologically active even though two of the three determinants had been satisfied. The process of rendering a fiber harmless would involve one of two situations. The first and most obvious would be for the fiber to go completely into solution with non-toxic end products. The second mechanism could involve the changing of the dimensions of the fiber (particularly the length) so that the normal clearance mechanisms within the respiratory system could function more effectively. Very little is known about the biological durability of fibers.

Wright and Kuschner[5] suggest that the reduced activity that they noted for the long and very thin glass fibers could be due to the fact that the fibers were less durable. The etching and pitting and resultant overall weakening of glass fibers by aqueous solutions is not unknown. There is a great need for well-developed information on this particular subject. In the laboratory at Johns-Manville a study has been initiated to determine the relative durability of fibers by long-term continuous extraction with simulated biological fluids.

At Tulane University Dr. Hammad has started an experiment in which he is attempting to measure the biological durability of man-made mineral fibers in the whole animal. This will be accomplished by making serial sacrifices of the animals after an initial exposure period. The fibers will be recovered from the animals and examined for signs of etching, pitting, or other indications of chemical attack.

The Semantic Properties of Fibers

Several papers which have appeared in the literature in the last few years implore those who are interested in the biological activity of mineral particles to be very cautious of the nomenclature used to describe mineral fragments. Their concern is that many minerals of considerable economic importance will be condemned and perhaps excluded from use because of their association with asbestos. The following quotation[16] appears to be typical.

> A definition of "asbestos" to include many amphiboles, chrysotile, and possibly other minerals that appear fibrous or acicular in the electron microscope coupled with a (proposed) fiber-concentration standard of 0.1 fibers/cm³ should serve to shut down a large number of our hard rock mines and quarries. Also, nothing has yet been said about the effect of such standards on construction workers building highways, tunnels, bridges, or dams on amphibole-bearing rock, nor of the agricultural workers who are exposed to fiber-containing dust while working the croplands. If the present concept of low or "zero threshold" health risk and broad use of "asbestos" definitions continue, much of the crust of the earth could be considered a health hazard.

It is quite obvious that the rocks which make up the major portion of the crust of the earth cannot be considered toxic under normal conditions. If that were the case, the human race would not have evolved in the form as we know it today. Hartung and Ohberg[17] highlight some of the problems which might be associated with a strictly asbestos-related definition of a biologically active fiber. They state that: "One pitfall is prohibition for use of valuable materials which in fact are reasonably safe. Still worse is lack of regulations for materials which must be judged as hazardous."

These authors proceed to list a series of questions which should be considered in drafting a new definition of a biologically active mineral fragment. These questions address themselves to the question of dimensions as well as to that of biological durability. Another layer of nomenclature will only serve to confuse the issue in the mind of the layman as well as the nonscientifically trained regulator. If agreement can be reached on the major factors responsible for the biological activity of mineral fragments, then it should be a simple matter to determine whether or not a particular mineral in a particular situation fulfills the requirements. If it is found that it does, then extra precautions will have to be taken. If, on the other hand, all of the requirements are not met, then one could presume that the operation could be permitted without any significant hazard to the workers or to those who are exposed only by virtue of their presence in the area.

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Quo Vadis Occupatium?

During recent surgery at a fine hospital in Santa Ana, Calif., I was intrigued by the name tags on the personnel attending me. Among them:

RN - Registered nurse
IP - Interim permit registered nurse
PA - Physician's assistant
NA - Nurse's assistant
LVN - Licensed vocational nurse
IT - Inhalation therapist
ITT - Inhalation therapist trainee
LVT - Licensed vocational therapist
LPT - Licensed physiotherapist
PT - Physiotherapist trainee
PT - Psychiatric therapist
PSW - Psychiatric social worker
MSW - Medical social worker
LR - Licensed radiologist
RT - Radiological technician
LLT - Licensed laboratory technician
LT - Laboratory technology trainee
AUD - Audiologist
ST - Speech therapist
MEA - Medical examiner's assistant
VA - Voluntary assistant

and of course the MD. With all the above, who needs him. (And this was just one ward.)

— Robert M DeuPree, M D, Los Angeles

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