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Global Problems from Exposure to Asbestos

by Arthur L. Frank

Considerable human-derived data about the health consequences of asbestos exposure are available. Usually, less information is available from laboratory models of asbestos-related health effects. Animal data mirror the experience in man, and cellular studies help in to understand the mechanistic changes related to asbestos. Although it is clearly carcinogenic, asbestos has shown much variability when examined for its mutagenic activity. Asbestos, a commercial term referring to a family of six naturally occurring mineral fibers, has been widely used around the world. Disease has been recognized into the last century, and at this time every *occupational group that has been examined for possible asbestos-related disease has demonstrated it.* Disease associated with asbestos makes no distinction based on race or geography, and wherever asbestos is handled it produces disease. With shifting global commercial patterns, disease patterns can be expected to shift also.

Introduction

Major industrial use of asbestos goes back to the 19th century, and the fibrotic lung disease caused by exposure was noted in the 19th century (*1*).Within the first three decades of the 20th century, the disease had been more widely recognized, insurance policies for some asbestos-exposed workers were no longer written, and the disease asbestosis was given its scientific name. Asbestosis was added to the growing list of pneumoconioses as first described by Zenker in 1867 (*2*). The original description of the process by which dusts damaged the lungs and surrounding tissue took note of both the parenchymal and pleural changes induced by exogenous materials. Asbestos exposure was soon seen to fit the model as put forth by its first proponent.

In the mid-1930s, the first suggestion was made that asbestos exposure could lead to the development of lung cancer (*3*), and in the early 1940s Hueper (*4*) believed that asbestos could be properly addressed as an occupational lung carcinogen. It was in this era that efforts were undertaken for the first time, as documented by subsequent reviewers, to mislead scientific and regulatory interests regarding the potential health effects of asbestos (*5*). The uses of asbestos became numerous, and at one time asbestos had several thousand uses. There is at present, however, a series of efforts in the long-time industrialized nations of the world to reduce or entirely eliminate the use of asbestos in modern society. Contrasting with this is a shift in use patterns in the world (*6*).

Department of Preventive Medicine and Environmental Health, University of Kentucky, College of Medicine, Lexington, KY 40536-0084.

Human Disease Patterns

It is now clear that asbestos-related disease in humans is well understood and in many ways incontrovertable, although there are still some areas of controversy, and important questions of mechanism and related issues are still unsettled (*7*). However, sufficient information is understood to deal with asbestos as the public health problem that it represents. There is something rather curious about the state of knowledge of human disease and asbestos exposure; more is appreciated about human exposure and disease than is generally known about the effects of asbestos in animal or cell culture systems. While not unique, given the experience with tobacco, this knowledge base is unusual.

Asbestos has been described mineralogically as a group of six related minerals divided into two groups, the serpentine group represented by chrysotile, and the amphibole group represented by croccidolite, amosite, anthophyllite, actinolite, and tremolite. All commercially produced fiber types have been shown to produce disease in man. The disease patterns can be classified as nonmalignant diseases and malignant diseases.

The nonmalignant problems related to asbestos include the relatively inconsequential problem of asbestos warts; the earliest of the serious asbestos problems in terms of its appearance after first exposure, benign asbestotic pleural effusion; and asbestosis, representing the nonmalignant medical conditions associated with exposure. For asbestosis, it appears that the disease in all of its manifestations is one that is dose related. Smoking, although not causing the disease, appears to have some role in altering the biologic response of an individual, mostly related to the profusion of changes on chest radiographs

and complicating pulmonary function testing. Traditional understanding of pulmonary function changes, which do not appear to be at all well correlated with radiographic appearance, would lead one to think that restrictive changes are associated with asbestosis, although there have been suggestions of obstructive change as well. Even pleural change by itself has been suggested as being capable of producing some diminution as measured by pulmonary function test results. The traditional clinical correlates of dry rales or clubbed fingers are not useful clinical signs in that they occur in a small percentage of cases. Although consistent with the disease process when present, the absence of these symptoms does not negate the diagnosis of asbestosis, which can be made on the basis of a history of exposure and an appropriately altered X-ray. Obviously, tissue confirmation is rarely available.

Malignancy and asbestos exposure have been linked for some 50 years. The most important malignancy associated with asbestos in terms of being a cause of excess mortality is of lung cancer. The classic interaction and synergistic effect of smoking with asbestos exposure is now well appreciated (*8*). All commercial fiber types are associated with human lung cancer.

Asbestos exposure is well recognized as the current, major identifiable cause of mesothelioma, a usually rare tumor that was little appreciated before the 20th century. Members of both fiber groups, the serpentine and amphibole groups, can cause this rare and difficult-to-treat disease. There is controversy with regard to chrysotile and mesothelioma, but the controversy is not well supported by the preponderance of scientific evidence from human and animal studies.

Also controversial is the role of asbestos in a variety of gastrointestinal tract cancers. However, if one approaches this problem by asking what is the best available evidence to address this issue, it seems incontrovertible that asbestos exposure, as illustrated by the experience of a cohort of 17,800 asbestos insulation workers who have been followed to this date from the early 1960s, clearly demonstrates an excess of a variety of gastrointestinal cancers (*9*). Other cancers that have also been suggested as being associated with asbestos exposure include kidney cancer and pharyngeal cancers, and the evidence regarding laryngeal cancer is also quite strong. Laryngeal cancer has been recognized in several U.S. government documents as being related to asbestos exposure (*10*).

There are currently many scientific issues related to asbestos exposure and the development of human disease. From a public health perspective, it should be noted that in every population investigated that has had documentable evidence of asbestos exposure there appears to be disease, that diseases of all types appear to be dose related, and that there appears to be no geographic or racial alteration in the basic disease process. Studies in the United States looking at ethnic differences in terms of the development of disease have proven negative. Women as well as men can develop asbestos-related disease, and the difference in disease patterns reflects differences in exposure histories.

Animal and *in Vitro* Studies

The study of disease in nonhuman experimental models is an invaluable modality for some aspects of understanding the natural history of disease. Various manipulations that can be accomplished in animal populations or by using *in vitro* studies allow questions to be asked, and sometimes answered, that are not readily amenable to the study of human populations. It is clear from a scientific point of view, referring to such issues as mechanism, matters of fiber size, rates of deposition, dissolution, and other intriguing questions of basic biology, that there is much that is yet to be learned. This does not, however, in any way diminish what is already understood in terms of human disease patterns, and it should not in any way complicate what is really a rather simple issue of controlling or eliminating exposure to asbestos. Animal studies can take place in both intact systems and in *in vitro* models, and the use of *in vitro* models will even allow for the examination of interaction with human tissues.

There are excellent animal data that demonstrate the inhalation of both chrysotile and amphibole fibers produce lung cancer and mesothelioma in animals (*11*). There is even information available as to the length of time that such exposure must take place, although this is not always well correlated with true amounts of exposure. In animals, as little as 1 day of exposure appears to be capable of producing disease, and exposure on the order of weeks or months can do so in man as well; there are even anecdotal cases of as little as 1 day of heavy exposure in humans leading to disease many years later. Given the large amount of human data that has accumulated, there is little that whole animal studies can contribute to the basic understanding of the disease process.

In some ways the possibilities of various cell and tissue culture models in the study of the effects of asbestos are more intriguing. Unfortunately, there appears to be wide variability in responses depending on the system being studied (*12*). For some cellular systems, such as hemolysis testing, there is little variability, but the ultimate usefulness of this form of toxicity appears to be limited (*13*). Studies of chromosomal aberrations have given widely different results in the hands of different investigators, but in some assay systems the irregularity of chromosome number, as is seen with other carcinogens, has been documented. Cellular toxicity or lethality as measured by trypan blue exclusion or radioactive chromium release is perhaps more stable, but again, of somewhat limited usefulness. Another often-noted finding, that of nuclear size alteration and DNA content after exposure to asbestos, could ultimately be more useful in the development of screening tests to study asbestos analogs (i.e., other fibers) and perhaps, ultimately, possible asbestos substitutes.

The use of organ cultures in understanding asbestos-related mechanistic change has been used by several investigators, but such work only tends to corroborate *in vitro* what has been well documented *in vivo*, or again must be looked at as a possible testing mechanism for the screening of potential carcinogenic agents (*14,15*).

Taken together, the irregularity with which asbestos can cause any specific change in certain cell systems and the lack of the "expected" response in tests such as the bacterial mutagenesis assay system removes many of these modalities as being potentially useful, either for mechanistic studies or even for studying human populations that are exposed to asbestos. Whereas other techniques such as the ^{32}P postlabeling technique may have some usefulness (*16*), the use of such laboratory assays after asbestos exposure is much more problematic. One may be able to use such tests and indirectly evaluate the potential effect of asbestos by seeing if a combination of asbestos and a more "usual" mutagen or carcinogen has its activity altered by the concomitant administration or exposure to asbestos.

Patterns of Use and Disease

As noted above, in all groups studied in all countries where there has been significant past use of asbestos, in all races, and in both occupational and nonoccupational settings, asbestos has produced disease in man. In those countries with a strong history of asbestos use during the 20th century, there is now a clear pattern of diminishing use or even outright banning. Given the long latency of asbestos-related disease, this will have little effect in the short-term, but perhaps in a generation or two one will be able to measure the effect of such administrative control of exposure.

What can be noted at the present time, however, is the changing pattern of asbestos use in the world. Chrysotile, the fiber that has been used more than all others combined, is being used increasingly in countries where there had been little asbestos use or manufacture. There is a long history in occupational medicine of disease being "imported" with the beginning of industrial processes or operations (e.g., dye stuffs, uranium mining, etc.), and it appears that this pattern is now under way on a global scale with asbestos.

If the global community were to move, as some countries have, to reduce or eliminate the use of asbestos, it is expected that substitute materials will be suggested for use. This is in keeping with proper industrial hygiene principles, and the use of substitution is well recognized as a method of reducing potential risk. There may well be an important role for mutagenic and carcinogenic studies for such asbestos substitutes before their introduction into the human environment. The work of Stanton (*17*) has demonstrated the importance of fiber size, regardless of chemical structure, in the production of malignant disease, and there may well be a role for laboratory models in helping to make assessments about the potential risk of substitute materials.

Just as there is a spreading of the possibility of asbestos exposure, one should also note that as some countries, among them the United States, are experiencing a reduction in the use of tobacco products, multinational companies are working diligently to export their tobacco products into a global market. As increasingly affluent industrial workers are able to afford tobacco products, one can easily predict that for those workers occupationally exposed to asbestos, as well as others, the spread of asbestos exposure and the concomitant spread of tobacco use will result in a disease development pattern over the next decades and probably beyond. Asbestos and exposure to tobacco smoke are two sources of exogenous exposure that individually and synergistically can cause disease in man, and these disease processes are entirely preventable. Although it will be necessary to conduct experiments for many years to understand some of the nuances of biological interactions with exogenous agents such as asbestos, a fascination with science should not inhibit the scientific community from intervening to prevent the predictable disease patterns after exposure to materials such as asbestos.

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