JMEA #5190

PATHOPHYSIOLOGY IN RELATION TO THE CHEMICAL AND PHYSICAL PROPERTIES OF FIBERS

PAUL KOTIN, M.D.
JOHNS-MANVILLE CORPORATION
DENVER, COLORADO 80217

Any postulated role for exogenous agents in the etiology (cause) and pathogenesis (development) of tissue change or clinical disease is critically dependent on the biological availability of the agent. Biological availability is defined here as, "possessing chemical, physical, and steric properties that allow reaction with receptor sites in the living system at the host, organ, tissue, cell, and macromolecule levels." In consequence, the environmental presence of a potentially toxic agent need not inevitably assume an adverse biological effect. For example, fly ash, no less than soot, contains carcinogenic hydrocarbons; yet the latter may be carcinogenic to man whereas the former is harmless since it cannot be respired. A low dose of a chemical may be metabolized to a harmless metabolite while by an alternative biochemical pathway a higher dose may yield a proximate carcinogen, as, for example, with vinyl chloride. Perhaps nowhere does biological availability play a greater role in the pathogenesis of disease than in relation to fibers.

Clinical and epidemiological studies describing the asbestos-related diseases have already been presented, and later in this workshop, Dr. Mearl Stanton will report on his elegant experimental studies on fibers. My presentation will attempt to describe in an omnibus and therefore relatively superficial fashion the continuum of environmental and host factors that result in pathology and disease due to exposure to excessive concentrations of asbestos.

Presented at the Workshop on Asbestos: Definition and Measurement Methods, sponsored by the National Bureau of Standards, July 18-20, 1977.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/1

To accomplish this, I will formulate a series of questions and let the answers provide the desired overview. Before doing this, however, let me emphasize now, and elaborate throughout my remarks, that the adverse effects of asbestos, like those of all environmental agents, occur in accordance with recognized toxicological principles. The chronic effects of asbestos exposure--asbestosis, mesothelioma, lung cancer, and possibly gastrointestinal cancer, if it indeed is truly related to asbestos exposure--are characterized by four relatively common aspects of environmental response:

1. A long latent period ensues following onset of exposure for either stigmata of exposure or clinical disease to appear. For the latter, time is measured in decades or segments of the total life span.

2. Exposure is in accord with recognized principles of dose-response in relation to disease development and appearance. Dose, the product of concentration or intensity of exposure multiplied by duration of exposure (time), is clearly the indispensable element in any current hazard analysis and in future projection. Dose-response considerations apply at all levels of response from the single cell to the intact host.

3. A no-effect level of exposure or threshold (if that particular word does not create argument) exists for asbestos-related disease.

4. Multifactorial etiology plays a role for some of the asbestos-related diseases. The issue of the determinant and the modifier in a multicausation situation is a critical one. It appears to be that cigarette smoking is the determinant for lung cancer. The data on the role of cigarette smoking in the development of asbestosis, though a factor, are too recent to permit any conclusions even though a modifier role appears reasonable.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/2

Now, the questions that can be used to provide an overview of our subject are:

1. Inasmuch as asbestos is a generic term for a group of fibrous crystalline hydrated silicates, which of the spectrum of characteristics of this group are of relevance to the initiation of asbestos-related disease?

The mineralogy and chemistry of asbestos have been reviewed in detail in this morning's session. Of the two major sets of characteristics, chemical and physical, fiber chemistry appears at this time to play only a minor role, if in fact any role at all, in relation to asbestos-associated disease. Physical characteristics, specifically fiber size, surface character, internal architecture and substructure, are all related in varying degrees to biological effect.

Prior to addressing the second question, a brief description of the gross and microscopic anatomy and the physiology of the respiratory tract is necessary. As can be seen in figure 1, fibrous particles enter the lungs via the trachea following inhalation through the nose or mouth and are distributed throughout the tracheobronchial tree, ultimately reaching the alveoli or air sacs. These air sacs are like the spaces in sponges are are lined by thin membranes in which the capillaries and venules flow.

The entry and penetration of fibers into the lung is governed by physical laws. For those particles which get into the tracheobronchial tree, some will settle on the lining and they will move upward (on the muco-

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/3

ciliary escalator) where they will be unconsciously swallowed or spit out. Particles small enough to reach the alveoli will settle out on the lining of the air spaces where they may be engulfed by phagocyte cells (macrophages) which may neutralize them or carry them up to the mucociliary escalator so they can be removed. The mechanism whereby uningested fibers penetrate the lining of the tracheobronchial tree or the air spaces so that they may reach the pleura is largely unknown. Thus it is the mucociliary escalator and the macrophages that are the primary defense mechanisms of the lung. Of particular interest is the fact that cigarette smoke is the most potent and ubiquitous of all inhalants in its capability to neutralize or destroy the effectiveness of the lung defense mechanisms.

The second question in relation to fiber effect is:

2. Following host entry, which of the anatomic and physiologic characteristics of the respiratory tract that I have just described affects the anatomic fate of the inhaled fiber? What is the algebraic summation of deposition, retention, parenchymal localization and mobilization as factors governing lung clearance?

With respect to the chemical characteristics of fiber, there appears to be no consistent identifiable effect of chemical composition after host entry of fibers by inhalation. With respect to physical characteristics the following effects are noted:

Size. Fibers greater than 5 microns in diameter are

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/4

virtually entirely lodged in the nose and do not penetrate the respiratory tract. Fibers greater than 3 microns and less than 5 microns in diameter enter the trachea but do not reach the conducting airways deeply enough to be retained in the lung. Fibers less than 3 microns and more than one micron can penetrate to the smaller bronchi. Fibers in the millimicron range in diameter are deposited in the peripheral airways and air spaces through Brownian movement. All these dimensions are very close approximations.

Length is probably less critical than diameter in relation to anatomic localization but it is of great importance in relation to biological effect. One possible measure of localization is the length of fibers found in the lungs in both experimental animals and man following environmental exposure. There are few fibers longer than 100 microns. There are virtually none longer than 200 microns. The majority are less than 50 microns in length.

We can conclude that only fibers thinner than 3 microns and shorter than 200 microns are of significance in eliciting a biological response in intact animals.

Shape. Chrysotile asbestos is curly and spiral whereas amphibole is harsh and rigid. It is imperative to emphasize that in relation to interception and deposition on the wall of air-conducting passages a curly or a spiral fiber behaves like a straight fiber having the diameter of the spiral fiber's maximum dimensional curl. Timbrell [1] concludes from his studies that chrysotile fibers (curly, pliable) do not penetrate into the deeper and more peripheral portions of the lung to the extent that the more rigid fibers of crocidolite and amosite do. More recently, using isotopically labeled fibers, Morgan [2] has obtained data that tend to question this generalization.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/5

It seems, then, that as a major determinant of biological localization and effect, shape is still an open question.

Surface character and internal architecture. Surface charge and leaching characteristics have not been identified to date as being of major importance in relation to question two. Time may change this.

In contrast, internal architecture has been shown to be relevant. In fact, chrysotile stands in sharp contrast to the amphiboles. The long, pliable fibers are readily split longitudinally into progressively finer fibrils and this feature may be critically related to biological effect. An unanswered yet crucial question is the one of durability of fibers in living systems. Quantitative data on the splitting of fibers and their solubility in relation to persistence of fibers are an urgent need.

In summary, size and shape are the major determinants of anatomical localization and retention.

Now let's move on to question three and see what can or may follow when fibers set up residence in the lung:

3. During and subsequent to anatomic localization, what characteristics affect the biological fate of asbestos fibers at physiological, pharmacological, and biochemical levels, and what is the sequence of the morphogenetic events and altered morphology resulting from asbestos exposure at cell,

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/6

tissue, and organ level sites?

It is clear that as desirable as data from man might be in assessing the importance of the chemical and physical variables of asbestos in relation to asbestos-associated disease, reality forces the conclusion that observations on humans, alive or dead, are incapable of providing all the information necessary for this purpose. Most of our current knowledge is derived from laboratory experimentation, and it is to this resource that we must turn for our needs.

Experimental data have been derived from research in which animal models have been exposed (a) in chambers to clouds of asbestos fibers (the most physiological method and the most analogous to human environmental exposure experience); (b) by intratracheal installation of the test material (less physiologic but highly useful and informative); or (c) by intracavitary installation (the least physiologic and the most artifactitious inasmuch as this method "forces" biological availability where, in fact, in the human situation none may exist; this method is useful as a tool for studying in-site cellular responses and mechanisms).

Chemical composition of the several forms of asbestos can be dismissed as a major factor in the pathophysiooogy of asbestos, not because fiber chemistry may not indeed play a role, but because at our current level of ignorance we have no proven concept of what such a role might be. In support of eliminating chemical composition as a factor is the consistent observation that in experimental

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/7

models all forms of asbestos can produce asbestosis, lung cancer, and mesothelioma depending on the mode of exposure. The report on the Federally supported asbestos feeding study, to be presented later during this workshop, may shed more light on this mode of exposure.

The size of the fiber, in sharp contrast to chemical composition, is the most clearly documented physical characteristic that determines biological effect. Data on the fiber size and cause-and-effect relationship are virtually entirely derived from the laboratory, since, in human experience, exposure has been in a mixed length and diameter milieu, thereby rendering epidemiological data worthless for assessing single size fiber effect.

If only one axiom were permissible in my remarks it would be that on the basis of the dynamics and kinetics of the behavior of airborne fibers, and in accordance with our knowledge of biological availability both anatomically and pathophysiologically, fibers thicker than 3.5 microns and longer than 200 microns or thicker than 3.5 microns and shorter than 5 microns are devoid of biological effect. Inhalation experiments have confirmed this anatomically, and intrapleural studies support the conclusion pathophysiologically.

Three studies can be cited to challenge this statement:

1. Holt [3] reported the production of pulmonary fibrosis in animals exposed in chambers to a cloud of predominantly short fibers. However, his own data record the contamination of his sample with long fibers (greater than 10 microns).

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/8

2. King [4] is silent on the percent of longer fibers contaminating his short fiber sample when he reports fibrosis produced in animals. He says the sample was almost all short fibers, but he used a technique for sample preparation that in the hands of others (experienced fiber researchers) consistently fails to yield a "pure" short sample.

3. Pott and Friedrichs [5] recently reported the production of peritoneal mesothelioma with samples made up of fibers shorter than 2 microns. This is a serious challenge to the long-thin concept. I can suggest possible factors confounding their experiment and conclusions, but at present suffice it to say that we are reviewing their findings in great detail.

This controversy would be rhetorical were it not that except for the above, all physiological studies and research reports on biological mechanisms are compatible with experimental bioassay in relation to the role of fiber size. Briefly, the sequence of events is as follows:

Respired particles can settle at levels of the tracheobronchial tree which are covered by a mucous blanket that is constantly being propelled cephalad toward the pharynx by the ciliated cells. Clearance of the particles from the lung by this mechanism is brisk, rapid (minutes to hours), and effective. Particles can also penetrate to the distal bronchioli and air sacs (the nonciliated regions). They can be cleared here also, provided they do not penetrate but remain on the surface. This clearance is slow (days to years), moderately effective, and the particles may need help via

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/9

phagocytosis to decrease penetration and to migrate up to the mucous escalator.

The importance of size can be demonstrated at this stage. Allison [6] and others have shown that short fibers (those less than 5 microns) appear to be readily and completely phagocytosed, whereas long fibers are not, even when simultaneously attacked by more than a single macrophage. This process may lead to cell fusion and the formation of giant cells which are usually found in abundance at the site. Estimates as to the efficiency of the combined clearance mechanisms range up to 95 to 98 percent. It is especially noteworthy, though, that mucociliary clearance is minimally affected during exposure to fibers, even in patients with asbestosis, while it is maximally affected by cigarette smoke.

The swallowing of fibers subsequent to their escalation to the throat is postulated as the mechanism for the reported low-level increased risk to gastrointestinal cancer in asbestos workers. When the term "ingestion" is used in relation to occupational risk to gastrointestinal cancer, it is this passive form of ingestion that is meant. I will say nothing about penetration of asbestos through the wall of the gastrointestinal tract because the data are meager and are truly conflicting.

The next step in the sequence of events depends on what happens to the retained fiber. One of two things may occur:

1. The short fibers, and to a certain degree the long fibers, are engulfed by pulmonary phagocytes or macrophages,

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/10

the latter often fusing to engulf large fibers. These fibers then become coated with an iron/protein complex. On the basis of animal studies, coating is now believed to be an intracellular process and follows the engulfing of particles by macrophages to which they adhere. These coated fibers are what have traditionally been called "asbestos bodies"; now they are called "ferruginous bodies" because they are not necessarily limited to asbestos exposure and they take a positive iron stain due to the iron/protein complex coating the fiber. There is evidence to suggest that the coating of a fiber renders it nonfibrogenic.

2. A majority of the fibers, approximately 75 percent, will remain uncoated, which can facilitate effective penetration and retention of thin fibers, or the breakdown of thicker fibers into thinner fibrils. These fibers tend to accumulate in the peripheral regions of the lower lobes, the site of early fibrosis (asbestosis). The fibers remain in situ (static) for long periods of time. Some may migrate nakedly through the lymphatic channels, while others may follow the migration paths of the cells they have entered.

There is no entirely satisfactory or universally accepted explanation for fibrogenesis. Suggested mechanisms have included (a) simple irritation, (b) leaching out of metal ions or silicic acid, and now (c) the immune mechanism.

There are, however, cellular data that suggest a reasonable mechanism, and this mechanism assumes that fibrogenesis is evoked

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/11

through the macrophage response. Such an explanation is attractive since:

1. It is compatible with the observation that long-thin fibers are the hazardous ones.

2. Macrophages tend to aggregate in the peribronchial area, site of the earliest fibrosis.

3. The cumulative effect of exposure is nicely explained by the repetitive and constant response of macrophages to asbestos exposure.

The sequence of fibrosis and its relation to other asbestos-associated diseases is unknown except for the mechanical impairment of cardiopulmonary function by the scarring. Fibrosis produces interference with lung function through replacement of the air spaces (alveolar septa) with scar tissue and by restricting the normal excursion of the lining during breathing.

Asbestos may affect anatomical sites in the following ways:

1. First and foremost, the gas exchange area or distal segments of the tracheobronchial-alveolar tree of the lung may be partially replaced by scar tissue, with resulting decreased lung function, x-ray changes, changes in physical findings, blood gas changes.

2. The pleura (visceral and parietal) may thicken with the formation of plaques; pleural effusion may fill the chest cavity with fluid; or mesothelioma may spread and infiltrate all layers of the lung and chest wall. The peritoneum may also be affected, although how the fibers

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/12

reach this site is unknown.

3. Lung cancer or bronchogenic cancer may result. The role of cigarette smoking and its impact on the mucociliary apparatus is a critical factor in the development of lung cancer.

4. Gastrointestinal cancer may occur through entry of fibers into the gastrointestinal tract by pharyngeal transpassage from the trachea.

The development of cancer, or carcinogenesis, is a multistage process in which the chemical interaction between the carcinogenic agent and the DNA is a necessary but certainly an insufficient step in itself for the development of clinical cancer. The issue of dose-response and no-effect level cannot be pursued in appropriate depth here, but suffice it to say that a synthesis of experimental and epidemiological data clearly supports a no-effect level.

The experience with asbestos has, very appropriately, given rise to concern that other fibers to which man is exposed may also represent a potential hazard to health. Organic fibers and manmade mineral fibers are in common use. I will limit my comments to manmade mineral fibers:

1. The dynamics of fiber entry, clearance, retention, and localization apply to manmade mineral fibers as they do to asbestos.

2. The concept of long-thin fibers as the source of

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/13

potential hazard, as given for asbestos, also appears to be applicable to the chronic biological effect of manmade mineral fibers.

3. In relation to chemistry, however, manmade mineral fibers differ from asbestos. While chemistry may be dismissed in relation to asbestos, solubility, fiber integrity, fiber fracture, and fiber persistence in manmade mineral fibers are most logically related to the chemistry of manmade mineral fibers. For example, glass does not seem to split vertically; rather it fractures horizontally. It is soluble, and in some exposure studies it seems to have disappeared from predicted sites of localization. A natural fibrous material like gypsum disappears so rapidly that it cannot be detected even at the site of administration after a very short interval. These facts are well recognized.

Lest one become overly sanguine as to the ease or speed with which critically necessary information about manmade mineral fibers can be obtained, it is sobering to reflect that despite our extensive knowledge of asbestos and asbestos-related disease, the following issues are still unresolved and subject to controversy:

1. Relation of fiber type to asbestos-associated disease.

2. The role of host factors (immunological state; peculiarities of respiratory tract architecture; concurrent or antecedent disease) in susceptibility to asbestos-related disease.

3. Progression of asbestos-related disease subsequent to cessation of exposure to asbestos and the specific etiologic influence on cancer of the lung or gastrointestinal tract in the absence of asbestosis or other anatomic evidence of exposure to asbestos.

I can best conclude by reiterating that there are special characteristics of asbestos that, though specific and not unique, to the best of our knowledge, invoke no mystique. The principles of asbestos-related disease are those of environmental biology, specifically toxicology and carcinogenesis.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/15

REFERENCES

/1/ Timbrell, V., Aerodynamic Considerations and Other Aspects of Glass Fiber, in Occupational Exposure to Fibrous Glass--Proceedings of a Symposium , pp. 33-50 (HEW publication NO. (NIOSH) 76-151, Washington, 1976).

/2/ Morgan, A., Progress report to IOEH/QAMA, Montreal, Canada (1976).

/3/ Holt, P.F., Mills, J., and Young, D.K., Experimental asbestosis with four types of fibers: Importance of small particles, N.Y. Acad. Sci. 132, 87 (1965).

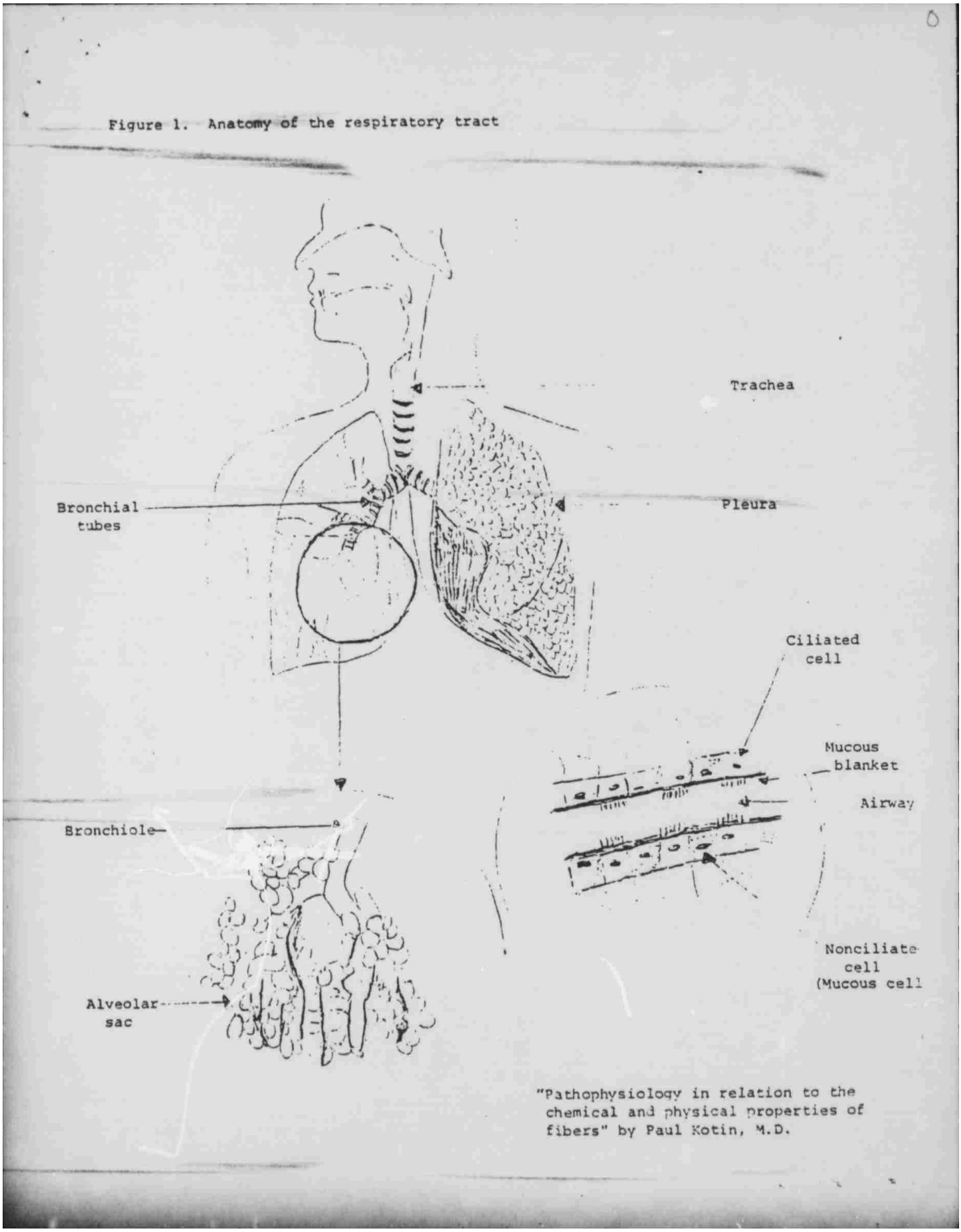
/4/ King, E. J., Clegg, J. W., and Rae, V.M., The effect of asbestos, and of asbestos and aluminum, on the lungs of rabbits, Thorax 1, 188 (1946).

/5/ Pott, F., Friedrichs, K.-H., and Huth, F., Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans, Zbl. Bakt. Hyg., I. Abt. Orig. B 162, 467-505 (1976).

/6/ Allison, A. C., Lysosomes and the toxicity of particulate pollutants, Arch. Internal Med. 128, 131-139 (1971).

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/16

Figure 1. Anatomy of the respiratory tract



"Pathophysiology in relation to the chemical and physical properties of fibers" by Paul Kotin, M.D.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/17

PATHOPHYSIOLOGY IN RELATION TO THE CHEMICAL AND PHYSICAL PROPERTIES OF FIBERS

J MEA 5190

PAUL KOTIN, M.D.
JOHNS-MANVILLE CORPORATION
DENVER, COLORADO 80217

Any postulated role for exogenous agents in the etiology (cause) and pathogenesis (development) of tissue change or clinical disease is critically dependent on the biological availability of the agent. Biological availability is defined here as, "possessing chemical, physical, and steric properties that allow reaction with receptor sites in the living system at the host, organ, tissue, cell, and macromolecule levels." In consequence, the environmental presence of a potentially toxic agent need not inevitably assume an adverse biological effect. For example, fly ash, no less than soot, contains carcinogenic hydrocarbons; yet the latter may be carcinogenic to man whereas the former is harmless since it cannot be respired. A low dose of a chemical may be metabolized to a harmless metabolite while by an alternative biochemical pathway a higher dose may yield a proximate carcinogen, as, for example, with vinyl chloride. Perhaps nowhere does biological availability play a greater role in the pathogenesis of disease than in relation to fibers.

MARGINALIA REDACTED

Clinical and epidemiological studies describing the asbestos-related diseases have already been presented, and later in this workshop, Dr. Mearl Stanton will report on his elegant experimental studies on fibers. My presentation will attempt to describe in an omnibus and therefore relatively superficial fashion the continuum of environmental and host factors that result in pathology and disease due to exposure to excessive concentrations of asbestos.

Presented at the Workshop on Asbestos: Definition and Measurement Methods, sponsored by the National Bureau of Standards, July 18-20, 1977.

To accomplish this, I will formulate a series of questions and let the answers provide the desired overview. Before doing this, however, let me emphasize now, and elaborate throughout my remarks, that the adverse effects of asbestos, like those of all environmental agents, occur in accordance with recognized toxicological principles. The chronic effects of asbestos exposure--asbestosis, mesothelioma, lung cancer, and possibly gastrointestinal cancer, if it indeed is truly related to asbestos exposure--are characterized by four relatively common aspects of environmental response:

1. A long latent period ensues following onset of exposure for either stigmata of exposure or clinical disease to appear. For the latter, time is measured in decades or segments of the total life span.

2. Exposure is in accord with recognized principles of dose-response in relation to disease development and appearance. Dose, the product of concentration or intensity of exposure multiplied by duration of exposure (time), is clearly the indispensable element in any current hazard analysis and in future projection. Dose-response considerations apply at all levels of response from the single cell to the intact host.

3. A no-effect level of exposure or threshold (if that particular word does not create argument) exists for asbestos-related disease.

4. Multifactorial etiology plays a role for some of the asbestos-related diseases. The issue of the determinant and the modifier in a multicausation situation is a critical one. It appears to be that cigarette smoking is the determinant for lung cancer. The data on the role of cigarette smoking in the development of asbestosis, though a factor, are too recent to permit any conclusions even though a modifier role appears reasonable.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/19

ciliary escalator) where they will be unconsciously swallowed or spit out. Particles small enough to reach the alveoli will settle out on the lining of the air spaces where they may be engulfed by phagocyte cells (macrophages) which may neutralize them or carry them up to the mucociliary escalator so they can be removed. The mechanism whereby uningested fibers penetrate the lining of the tracheobronchial tree or the air spaces so that they may reach the pleura is largely unknown. Thus it is the mucociliary escalator and the macrophages that are the primary defense mechanisms of the lung. Of particular interest is the fact that cigarette smoke is the most potent and ubiquitous of all inhalants in its capability to neutralize or destroy the effectiveness of the lung defense mechanisms.

The second question in relation to fiber effect is:

2. Following host entry, which of the anatomic and physiologic characteristics of the respiratory tract that I have just described affects the anatomic fate of the inhaled fiber? What is the algebraic summation of deposition, retention, parenchymal localization and mobilization as factors governing lung clearance?

With respect to the chemical characteristics of fiber, there appears to be no consistent identifiable effect of chemical composition after host entry of fibers by inhalation. With respect to physical characteristics the following effects are noted:

Size. Fibers greater than 5 microns in diameter are

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/20

It seems, then, that as a major determinant of biological localization and effect, shape is still an open question.

Surface character and internal architecture. Surface charge and leaching characteristics have not been identified to date as being of major importance in relation to question two. Time may change this.

In contrast, internal architecture has been shown to be relevant. In fact, chrysotile stands in sharp contrast to the amphiboles. The long, pliable fibers are readily split longitudinally into progressively finer fibrils and this feature may be critically related to biological effect. An unanswered yet crucial question is the one of durability of fibers in living systems. Quantitative data on the splitting of fibers and their solubility in relation to persistence of fibers are an urgent need.

In summary, size and shape are the major determinants of anatomical localization and retention.

Now let's move on to question three and see what can or may follow when fibers set up residence in the lung:

3. During and subsequent to anatomic localization, what characteristics affect the biological fate of asbestos fibers at physiological, pharmacological, and biochemical levels, and what is the sequence of the morphogenetic events and altered morphology resulting from asbestos exposure at cell,

virtually entirely lodged in the nose and do not penetrate the respiratory tract. Fibers greater than 3 microns and less than 5 microns in diameter enter the trachea but do not reach the conducting airways deeply enough to be retained in the lung. Fibers less than 3 microns and more than one micron can penetrate to the smaller bronchi. Fibers in the millimicron range in diameter are deposited in the peripheral airways and air spaces through Brownian movement. All these dimensions are very close approximations.

Length is probably less critical than diameter in relation to anatomic localization but it is of great importance in relation to biological effect. One possible measure of localization is the length of fibers found in the lungs in both experimental animals and man following environmental exposure. There are few fibers longer than 100 microns. There are virtually none longer than 200 microns. The majority are less than 50 microns in length.

We can conclude that only fibers thinner than 3 microns and shorter than 200 microns are of significance in eliciting a biological response in intact animals.

Shape. Chrysotile asbestos is curly and spiral whereas amphibole is harsh and rigid. It is imperative to emphasize that in relation to interception and deposition on the wall of air-conducting passages a curly or a spiral fiber behaves like a straight fiber having the diameter of the spiral fiber's maximum dimensional curl. Timbrell [1] concludes from his studies that chrysotile fibers (curly, pliable) do not penetrate into the deeper and more peripheral portions of the lung to the extent that the more rigid fibers of crocidolite and amosite do. More recently, using isotopically labeled fibers, Morgan [2] has obtained data that tend to question this generalization.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/22

tissue, and organ level sites?

It is clear that as desirable as data from man might be in assessing the importance of the chemical and physical variables of asbestos in relation to asbestos-associated disease, reality forces the conclusion that observations on humans, alive or dead, are incapable of providing all the information necessary for this purpose. Most of our current knowledge is derived from laboratory experimentation, and it is to this resource that we must turn for our needs.

Experimental data have been derived from research in which animal models have been exposed (a) in chambers to clouds of asbestos fibers (the most physiological method and the most analogous to human environmental exposure experience); (b) by intratracheal installation of the test material (less physiologic but highly useful and informative); or (c) by intracavitary installation (the least physiologic and the most artifactitious inasmuch as this method "forces" biological availability where, in fact, in the human situation none may exist; this method is useful as a tool for studying in-site cellular responses and mechanisms).

Chemical composition of the several forms of asbestos can be dismissed as a major factor in the pathophysiooogy of asbestos, not because fiber chemistry may not indeed play a role, but because at our current level of ignorance we have no proven concept of what such a role might be. In support of eliminating chemical composition as a factor is the consistent observation that in experimental

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/23

models all forms of asbestos can produce asbestosis, lung cancer, and mesothelioma depending on the mode of exposure. The report on the Federally supported asbestos feeding study, to be presented later during this workshop, may shed more light on this mode of exposure.

The size of the fiber, in sharp contrast to chemical composition, is the most clearly documented physical characteristic that determines biological effect. Data on the fiber size and cause-and-effect relationship are virtually entirely derived from the laboratory, since, in human experience, exposure has been in a mixed length and diameter milieu, thereby rendering epidemiological data worthless for assessing single size fiber effect.

If only one axiom were permissible in my remarks it would be that on the basis of the dynamics and kinetics of the behavior of airborne fibers, and in accordance with our knowledge of biological availability both anatomically and pathophysiologically, fibers thicker than 3.5 microns and longer than 200 microns or thicker than 3.5 microns and shorter than 5 microns are devoid of biological effect. Inhalation experiments have confirmed this anatomically, and intrapleural studies support the conclusion pathophysiologically.

Three studies can be cited to challenge this statement:

1. Holt [3] reported the production of pulmonary fibrosis in animals exposed in chambers to a cloud of predominantly short fibers. However, his own data record the contamination of his sample with long fibers (greater than 10 microns).

2. King [4] is silent on the percent of longer fibers contaminating his short fiber sample when he reports fibrosis produced in animals. He says the sample was almost all short fibers, but he used a technique for sample preparation that in the hands of others (experienced fiber researchers) consistently fails to yield a "pure" short sample.

3. Pott and Friedrichs [5] recently reported the production of peritoneal mesothelioma with samples made up of fibers shorter than 2 microns. This is a serious challenge to the long-thin concept. I can suggest possible factors confounding their experiment and conclusions, but at present suffice it to say that we are reviewing their findings in great detail.

This controversy would be rhetorical were it not that except for the above, all physiological studies and research reports on biological mechanisms are compatible with experimental bioassay in relation to the role of fiber size. Briefly, the sequence of events is as follows:

Respired particles can settle at levels of the tracheobronchial tree which are covered by a mucous blanket that is constantly being propelled cephalad toward the pharynx by the ciliated cells. Clearance of the particles from the lung by this mechanism is brisk, rapid (minutes to hours), and effective. Particles can also penetrate to the distal bronchioli and air sacs (the nonciliated regions). They can be cleared here also, provided they do not penetrate but remain on the surface. This clearance is slow (days to years), moderately effective, and the particles may need help via

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/25

phagocytosis to decrease penetration and to migrate up to the mucous escalator.

The importance of size can be demonstrated at this stage. Allison [6] and others have shown that short fibers (those less than 5 microns) appear to be readily and completely phagocytosed, whereas long fibers are not, even when simultaneously attacked by more than a single macrophage. This process may lead to cell fusion and the formation of giant cells which are usually found in abundance at the site. Estimates as to the efficiency of the combined clearance mechanisms range up to 95 to 98 percent. It is especially noteworthy, though, that mucociliary clearance is minimally affected during exposure to fibers, even in patients with asbestosis, while it is maximally affected by cigarette smoke.

The swallowing of fibers subsequent to their escalation to the throat is postulated as the mechanism for the reported low-level increased risk to gastrointestinal cancer in asbestos workers. When the term "ingestion" is used in relation to occupational risk to gastrointestinal cancer, it is this passive form of ingestion that is meant. I will say nothing about penetration of asbestos through the wall of the gastrointestinal tract because the data are meager and are truly conflicting.

The next step in the sequence of events depends on what happens to the retained fiber. One of two things may occur:

1. The short fibers, and to a certain degree the long fibers, are engulfed by pulmonary phagocytes or macrophages,

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/26

the latter often fusing to engulf large fibers. These fibers then become coated with an iron/protein complex. On the basis of animal studies, coating is now believed to be an intracellular process and follows the engulfing of particles by macrophages to which they adhere. These coated fibers are what have traditionally been called "asbestos bodies"; now they are called "ferruginous bodies" because they are not necessarily limited to asbestos exposure and they take a positive iron stain due to the iron/protein complex coating the fiber. There is evidence to suggest that the coating of a fiber renders it nonfibrogenic.

2. A majority of the fibers, approximately 75 percent, will remain uncoated, which can facilitate effective penetration and retention of thin fibers, or the breakdown of thicker fibers into thinner fibrils. These fibers tend to accumulate in the peripheral regions of the lower lobes, the site of early fibrosis (asbestosis). The fibers remain in situ (static) for long periods of time. Some may migrate nakedly through the lymphatic channels, while others may follow the migration paths of the cells they have entered.

There is no entirely satisfactory or universally accepted explanation for fibrogenesis. Suggested mechanisms have included (a) simple irritation, (b) leaching out of metal ions or silicic acid, and now (c) the immune mechanism.

There are, however, cellular data that suggest a reasonable mechanism, and this mechanism assumes that fibrogenesis is evoked

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/27

through the macrophage response. Such an explanation is attractive since:

1. It is compatible with the observation that long-thin fibers are the hazardous ones.

2. Macrophages tend to aggregate in the peribronchial area, site of the earliest fibrosis.

3. The cumulative effect of exposure is nicely explained by the repetitive and constant response of macrophages to asbestos exposure.

The sequence of fibrosis and its relation to other asbestos-associated diseases is unknown except for the mechanical impairment of cardiopulmonary function by the scarring. Fibrosis produces interference with lung function through replacement of the air spaces (alveolar septa) with scar tissue and by restricting the normal excursion of the lining during breathing.

Asbestos may affect anatomical sites in the following ways:

1. First and foremost, the gas exchange area or distal segments of the tracheobronchial-alveolar tree of the lung may be partially replaced by scar tissue, with resulting decreased lung function, x-ray changes, changes in physical findings, blood gas changes.

2. The pleura (visceral and parietal) may thicken with the formation of plaques; pleural effusion may fill the chest cavity with fluid; or mesothelioma may spread and infiltrate all layers of the lung and chest wall. The peritoneum may also be affected, although how the fibers

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/28

reach this site is unknown.

3. Lung cancer or bronchogenic cancer may result. The role of cigarette smoking and its impact on the mucociliary apparatus is a critical factor in the development of lung cancer.

4. Gastrointestinal cancer may occur through entry of fibers into the gastrointestinal tract by pharyngeal transpassage from the trachea.

The development of cancer, or carcinogenesis, is a multistage process in which the chemical interaction between the carcinogenic agent and the DNA is a necessary but certainly an insufficient step in itself for the development of clinical cancer. The issue of dose-response and no-effect level cannot be pursued in appropriate depth here, but suffice it to say that a synthesis of experimental and epidemiological data clearly supports a no-effect level.

The experience with asbestos has, very appropriately, given rise to concern that other fibers to which man is exposed may also represent a potential hazard to health. Organic fibers and manmade mineral fibers are in common use. I will limit my comments to manmade mineral fibers:

1. The dynamics of fiber entry, clearance, retention, and localization apply to manmade mineral fibers as they do to asbestos.

2. The concept of long-thin fibers as the source of

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/29

potential hazard, as given for asbestos, also appears to be applicable to the chronic biological effect of manmade mineral fibers.

3. In relation to chemistry, however, manmade mineral fibers differ from asbestos. While chemistry may be dismissed in relation to asbestos, solubility, fiber integrity, fiber fracture, and fiber persistence in manmade mineral fibers are most logically related to the chemistry of manmade mineral fibers. For example, glass does not seem to split vertically; rather it fractures horizontally. It is soluble, and in some exposure studies it seems to have disappeared from predicted sites of localization. A natural fibrous material like gypsum disappears so rapidly that it cannot be detected even at the site of administration after a very short interval. These facts are well recognized.

Lest one become overly sanguine as to the ease or speed with which critically necessary information about manmade mineral fibers can be obtained, it is sobering to reflect that despite our extensive knowledge of asbestos and asbestos-related disease, the following issues are still unresolved and subject to controversy:

1. Relation of fiber type to asbestos-associated disease.

2. The role of host factors (immunological state; peculiarities of respiratory tract architecture; concurrent or antecedent disease) in susceptibility to asbestos-related disease.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/30

3. Progression of asbestos-related disease subsequent to cessation of exposure to asbestos and the specific etiologic influence on cancer of the lung or gastrointestinal tract in the absence of asbestosis or other anatomic evidence of exposure to asbestos.

I can best conclude by reiterating that there are special characteristics of asbestos that, though specific and not unique, to the best of our knowledge, invoke no mystique. The principles of asbestos-related disease are those of environmental biology, specifically toxicology and carcinogenesis.

Published by AsbestosClaims.Law
asbestosclaims.law/library/25428/31

REFERENCES

[1] Timbrell, V., Aerodynamic Considerations and Other Aspects of Glass Fiber, in Occupational Exposure to Fibrous Glass--Proceedings of a Symposium , pp. 33-50 (HEW publication NO. (NIOSH) 76-151, Washington, 1976).

[2] Morgan, A., Progress report to IOEH/QAMA, Montreal, Canada (1976).

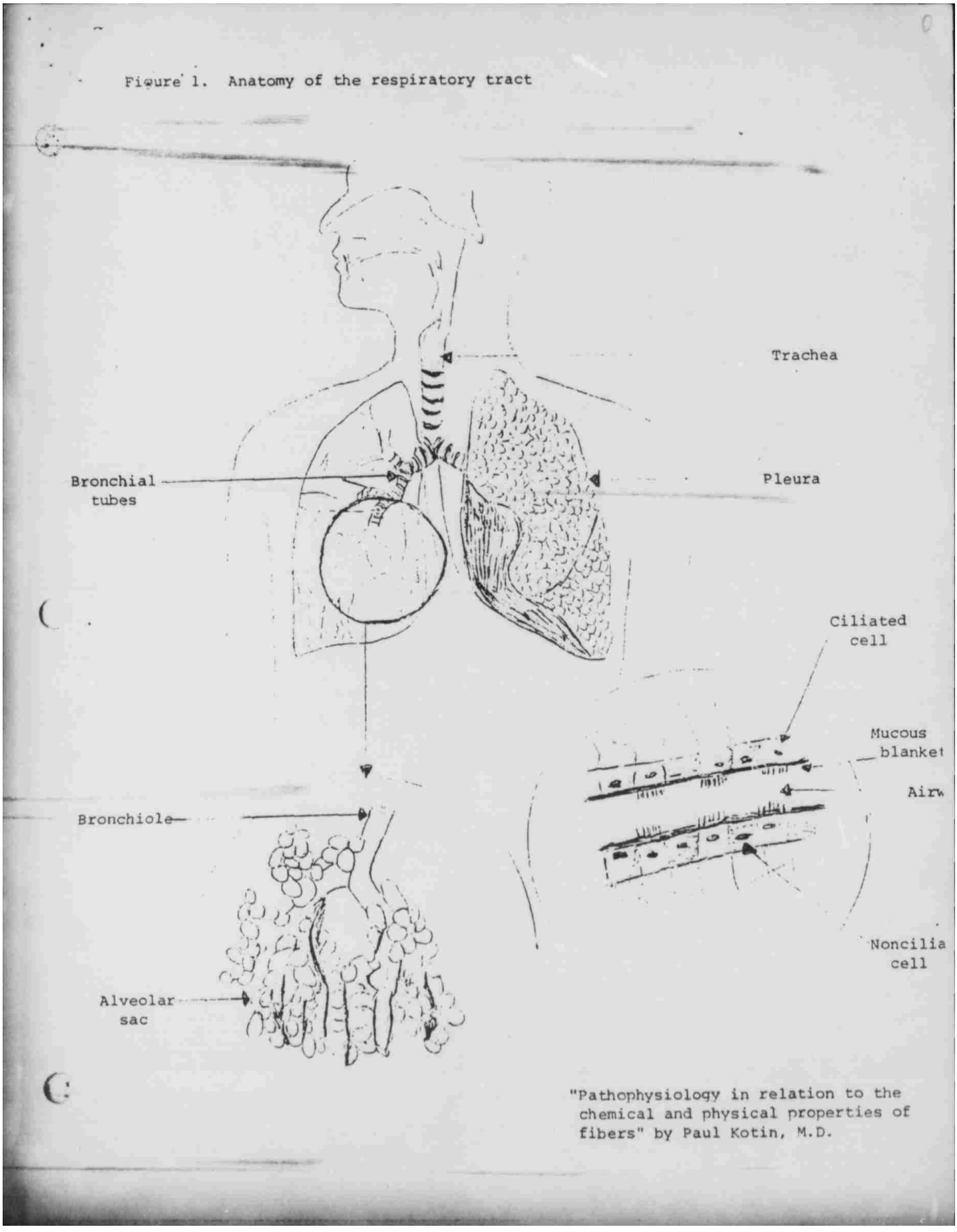
[3] Holt, P.F., Mills, J., and Young, D.K., Experimental asbestosis with four types of fibers: Importance of small particles, N.Y. Acad. Sci. 132, 87 (1965).

[4] King, E. J., Clegg, J. W., and Rae, V.M., The effect of asbestos, and of asbestos and aluminum, on the lungs of rabbits, Thorax 1, 188 (1946).

[5] Pott, F., Friedrichs, K.-H., and Huth, F., Results of animal experiments concerning the carcinogenic effect of fibrous dusts and their interpretation with regard to the carcinogenesis in humans, Zbl. Bakt. Hyg., I. Abt. Orig. B 162, 467-505 (1976).

[6] Allison, A. C., Lysosomes and the toxicity of particulate pollutants, Arch. Internal Med. 128, 131-139 (1971).

Figure 1. Anatomy of the respiratory tract



"Pathophysiology in relation to the chemical and physical properties of fibers" by Paul Kotin, M.D.