Pulmonary Ferruginous Bodies

Development in Response to Filamentous Dusts and a Method of Isolation and Concentration

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Formation of ferruginous bodies should not be confused with pathogenicity. Failure to understand this differentiation may result in the erroneous generalization that all fibrous dusts share the ability of abestos to produce lung damage. Such materials as fibrous aluminum silicate, silicon carbide whiskers, cosmetic talc, and glass fibers produce ferruginous bodies experimentally which are indistinguishable from those produced by asbestos fibers. A method of isolation and concentration of ferruginous bodies from lungs of animals and humans is described. Ferruginous bodies from asbestos fibers are much more pleomorphic than has generally been described, casting further doubt on morphological distinctions used in the past in separating so-called asbestos bodies from pseudoasbestos bodies.

WORLDWIDE attention was refocused on ferruginous bodies by the publication of Thomson,[1] who found this phenomenon in the lungs of more than 30% of unselected autopsied adult hospital patients in Capetown, South Africa. A similar percentage was noted in Miami,[2] 43% in Pittsburgh,[3] and 48% in Montreal.[4] The higher percentages reported in Pittsburgh and Montreal are possibly different in the more intensive searches carried out in these cities. These bodies are similar to asbestos bodies, though the natures of the central fibers have not been identified.

Asbestos bodies are golden-brown, ferro-coated formations found in the lungs of persons who have inhaled asbestos dust. They are generally described as symmetrical, segmented structures, usually with clubbed ends, 3μ to 5μ in diameter and 20μ to 50μ long. The core is composed of a transparent colorless asbestos fiber that is not always demonstrable.

Apparently the only difference between an asbestos body and a pseudoasbestos body is that in the former, the central fiber is composed of asbestos, and in the latter, of material other than asbestos.

Since asbestos-like bodies can form in response to respirable, transparent, colorless fibers deposited in the lungs and composed of materials other than asbestos; and since basing classification of these structures upon identification of the central fiber presents difficulties, a generic term, "ferruginous," has been proposed for all bodies formed in response to the presence (in body tissues) of a broad spectrum of fibers, including asbestos. Davis[5] and Collet (according to a letter in June 1966) demonstrated with the electron microscope that ferruginous bodies are formed within macrophages by granules of ferritin or a ferritin-like protein

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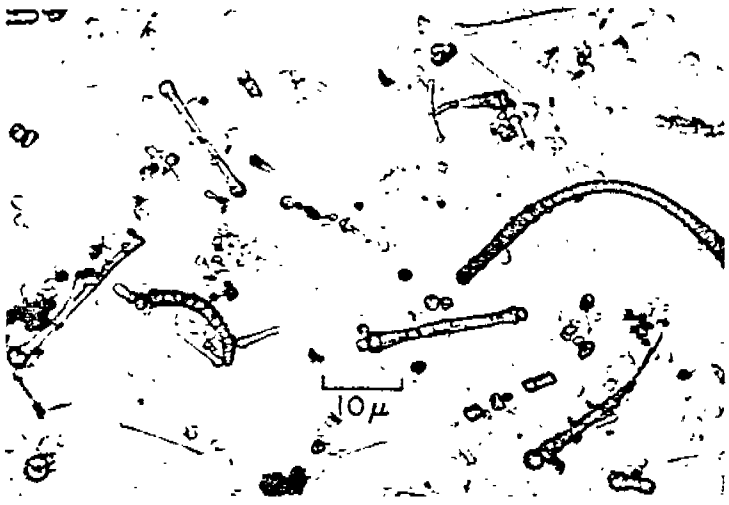

Fig 1.—Asbestos bodies from the lung of an asbestos worker to illustrate some of the more simple forms that may be found. In addition to some apparently naked fibers, there are pale, nonsegmented, rodlike bodies with bipolar clubbing. The dust was probably chrysotile (concentration method; smear: unstained; × 1,100).

that are precipitated upon and around some foreign materials.

An asbestos body, therefore, is only one kind of ferruginous body; one in which the central filament is an asbestos fiber. As will be seen later, the appearance and dimensions of these bodies are so varied as to defy the reasonably short description usually employed.

The problem now confronting investigators concerns the significance of the widespread finding of ferruginous bodies in the lungs of urban population groups. The solution of the problem is, of course, linked to the identity of the central fiber about which the ferruginous body forms and which is at present unknown. It is hoped that recent analytical advances, such as electron diffraction and microprobe will provide techniques for definitive identification of the central fiber.

Up to this point, the identification of ferruginous bodies in the lungs of unselected autopsied hospital patients as asbestos bodies [1] has been based on the hypothesis that transparent fibers of respirable size composed of materials other than asbestos either are not encountered in industrial and community environments, are not deposited in the lungs, or do not result in the formation of ferruginous bodies when inhaled.

Respirable fibers, however, are apparently ubiquitous.[6] They may be mineral, animal, or vegetable in nature and of either natural or synthetic origin. They are disseminated by industrial processing, community activities, personal habits, and the action of natural forces. Also, we have recently reported experimental production of ferruginous bodies with ceramic fibers of aluminum silicate. These bodies were indistinguishable by light microscope from many of those isolated from an asbestotic lung of a known asbestos worker [7] (Fig 1). Although nonsegmented, they were golden-yellow, symmetrical, clubbed bodies, staining deep blue with Perls' test and exhibiting a central transparent filament.

The present paper discusses our further findings as follows:

1.—Ferruginous bodies are developed in the lungs of hamsters in response to the presence of "biologically inert" filamentous aluminum silicate, glass, and silicon carbide particles.

2.—A simple method is given for isolating ferruginous bodies and bare fibers (including asbestos bodies) from lungs. The method is given in detail and the results obtained are described briefly.

The Production of Ferruginous Bodies

Groups of 12 hamsters each were injected intratracheally with 3.5 mg of fibers contained in 0.5 ml of aqueous suspensions. This was done under light ether anesthesia with the aid of an illuminated, self-retaining speculum that made the vocal chords visible and allowed the insertion of a long 18-gaug
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1. Ceramic aluminum silicate fibers. This is an uncoated ceramic fiber with a median diameter of 2μ. Fifty percent of the fibers were under 75μ in length, and many filaments were shorter than 15μ. No free silica was detected in the fibers.

2. Silicon carbide whiskers. These were 95—% SiC. Fiber diameter ranged from 5μ to 3μ, and fiber length that ranged from 100μ to 750μ.

3. Glass fibers, uncoated. The fibers had a mean diameter of 0.4μ and a mean length of 4.4μ.

4. Cosmetic talc. Fifty percent of the fibrous material in the talc was under 0.2μ in diameter and 1μ in length.

5. Attapulgite (fibrous clay mineral). Fifty percent of the fibers were under 0.2μ in diameter and 1μ in length.

6. Chrysotile (95% of the asbestos used in this continent is chrysotile). Most of the fibers were of ultramicroscopic dimensions.

Isolation and Concentration of Ferruginous Bodies

Samples of lung tissue cut into thin strips 3 to 4 mm thick, or fragments about 5 cc in volume, are placed in clean glass or plastic containers. To the tissue is added about 20 times the tissue volume of commercial 5% sodium hypochlorite solution. This is allowed to stand undisturbed at room temperature for several hours until all chemical action has ceased. More hypochlorite solution is then added at frequent intervals until the tissue has been digested.

For small lungs, such as those of rats and guinea pigs, the frequency and amount of addition of fresh hypochlorite solution should be such that all lung tissue is digested in approximately 24 hours. For human lungs, unless quantitative recovery of ferruginous bodies is desired, complete digestion is not necessary.

In the case of human lungs, the ferruginous bodies and bare fibers are often associated with a sticky lipidic film adherent to the bottom of the container. The stickiness allows one to pour off all the fluid and undigested lung tissue without loss of the bodies and fibers. Because of the presence of anthracotic pigment, the film is usually gray in color. The film is dissolved by vigorously washing with a mixture of one volume of chloroform and two volumes of approximately 50% ethyl alcohol; the total volume should be the minimal amount needed to remove all the film. The wash fluid is centrifuged at 2,000 rpm for about five minutes. Because of their high specific gravity, the ferruginous bodies and the insoluble mineral particles settle to the bottom of the tube. On the other hand, most of the carbonaceous material collects at the interphase between the chloroform and the aqueous alcohol. If too much alcohol is used, the carbonaceous material will lose some of the water that lowers its specific gravity. As a result, there will be no separation between the anthracotic material and the ferruginous bodies. In such cases, rehydration followed by the addition of chloroform will usually effect a good separation.

All of the fluid and the carbonaceous, more viscid material above the sediment at the bottom of the tube are discarded, and the walls of the tube are cleaned of the adherent anthracotic material. The sediment is washed several times with water to remove all hypochlorite and other water-soluble materials. It is then stored in an aqueous or alcoholic medium.

When smears are made of the suspensions, it may be advisable to dehydrate the smear and use a mounting medium to render much of the mineral dust associated with the ferruginous bodies less conspicuous. The naked fibers remain visible.

In the case of small animal lungs, chloroform and the supernatant fluid were poured into centrifuge tubes in a proportion of 1:2. After centrifuging, the supernatant fluid was carefully removed and discarded except for about 1 ml left un-

disturbed on the bottom. The film on the bottom of the original container in which the lung tissue was digested was then removed, as in the case of human lungs. This fluid was added to a pool of whatever sediment was obtained from the supernatant fluid. The subsequent procedure was the same as with human lungs.

We have worked with formalin-fixed tissue only, but there appears to be no reason why this method should not work equally well with fresh lung tissue.

Results

Paraffin Sections.—Initially the ferruginous bodies were sought only in paraffin sections that had been stained with hematoxylin and eosin or Perls' test for iron. Because of the paucity and small size of these bodies in the sections, the hematoxylin made the search more difficult. Subsequently, replicate sections that were given the Perls' test only, or also lightly counterstained with eosin and cleared, proved to be satisfactory.

The injected fibers generally were confined to the air spaces, where they were associated with free macrophages. Some of the filaments passed through the bodies of one to three, and even four, macrophages so that these cells appeared to be impaled as though upon a spit (Fig 3 *bottom left*). When the sections had been stained for iron, the dust-containing areas, under low magnification, were usually marked by a granular deep blue coloration.

In sections of lungs of hamsters killed one month after an intratracheal injection of aluminum silicate and glass fibers, occasional ferruginous bodies were found. These were non-segmented, light-yellow structures with bipolar clubbing and a transparent central filament (Fig 2 *top left*, and 3 *top left*). These, subsequent to the Perls' test, took on a deep blue color that often obscured the central filament. Very similar non-segmented bodies were seen in suspensions of isolated and concentrated human asbestos bodies derived from an asbestotic lung of a worker known to have been exposed to chrysotile asbestos dust for 30 years (Fig 1).

The ferruginous bodies that formed in response to chrysotile asbestos were smaller than those that formed in response to aluminum silicate and glass, and also different from the latter two in being segmented (Fig 4 *bottom left*). The ferruginous bodies were more readily found in the lung sections of hamsters injected with aluminum silicate filaments than in lung sections of animals injected with filamentous glass or chrysotile dust. No ferruginous bodies were found in the lung sections of hamsters injected with silicon carbide filaments at this time (one month after the injection).

Examination of lung sections of hamsters killed six months after the intratracheal injection of the filamentous dusts revealed no more ferruginous bodies than were encountered five months earlier. No segmented forms were found except in association with chrysotile dust. No ferruginous bodies were seen in lung sections of hamsters injected with silicon carbide. Dust-containing alveoli found in sections of lung from a hamster injected with talc were easily identified because of the blue coloration caused by the presence of iron; however, ferruginous bodies could not be identified. Similarly, no ferruginous bodies were found in lung sections from hamsters injected intratracheally with attapulgite.

Lung Digests.—The smears of the sediment derived from the digestion of the lungs from hamsters injected six months previously with aluminum silicate, glass, and chrysotile, respectively, consisted largely of naked filaments, but many ferruginous bodies were also seen. Although most of the ferruginous bodies that had formed in response to aluminum silicate and glass fibers were non-segmented, a number of segmented forms were also found (Fig 2 *top right, bottom left, bottom right*; and 3 *top right, bottom left, bottom right*). A more prolonged search of the

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sediment from lungs of hamsters injected with silicon carbide was necessary before several ferruginous bodies could be found. This search was facilitated by applying Perls' test for iron to the smear. The bodies were mostly nonsegmented, and except for the clubbed ends, the coating on the filaments was thin. One silicon carbide fiber was found with a club-shaped coating at one end, a fusiform coating near the other end, and a very slight thickening near the middle (Fig 4 *top left*). Two segmented ferruginous bodies that had formed around silicon carbide fibers were observed. Unfortunately, the diffusion of the blue pigment of the body rendered its outline indistinct (Fig 4 *top right*).

The sediment from a hamster lung injected with talc was composed largely of crystalline plates; but upon careful search, a number of non-segmented ferruginous bodies were also found. These too had a transparent central filament (Fig 2 *top left*, and 3 *top left*). The Prussian blue reaction for iron had also been used in this smear, and the outlines of these bodies were indistinct because of the diffusion of the pigment (Fig 4 *bottom left*).

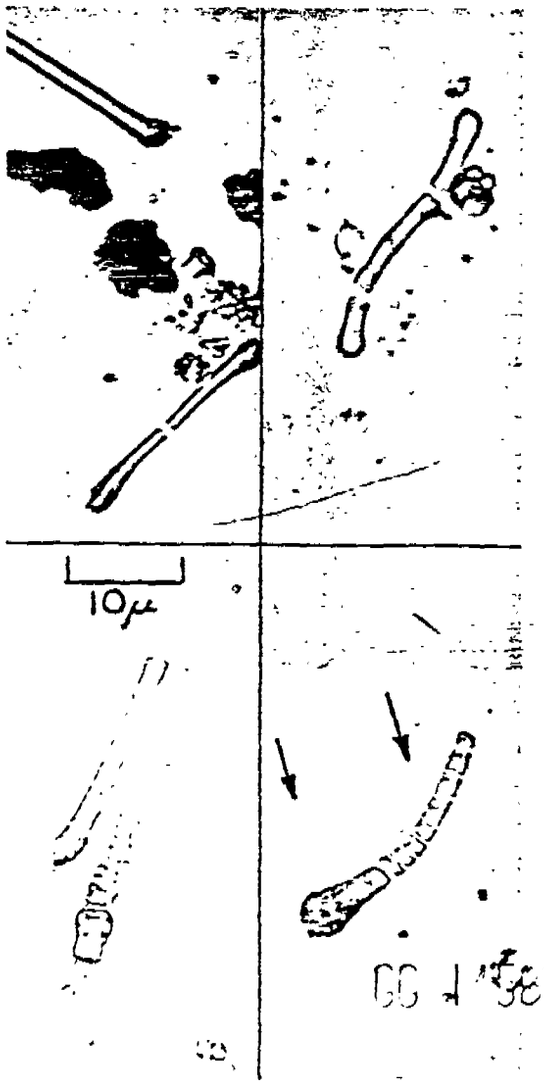
Unexpectedly, ferruginous bodies were more difficult to find in lung sections after chrysotile injections than after aluminum silicate injections. The same finding was observed with the concentration method. Although few in number, all asbestos bodies were segmented (Fig 4 *bottom right*).

One of the most interesting observations was that, when stained for iron, filaments that passed through the bodies of one or more macrophages showed a coating of ferritin or ferritin-like material only on the intracellular portions of the filament (Fig 3 *bottom left*).

The sediments from the lungs of hamsters injected with attapulgite revealed no ferruginous bodies. The failure to find ferruginous bodies in these sediments may be interpreted as a negative control to indicate that our positive findings were not attributable to the accidental inhalation of fibers in the ambient laboratory air.

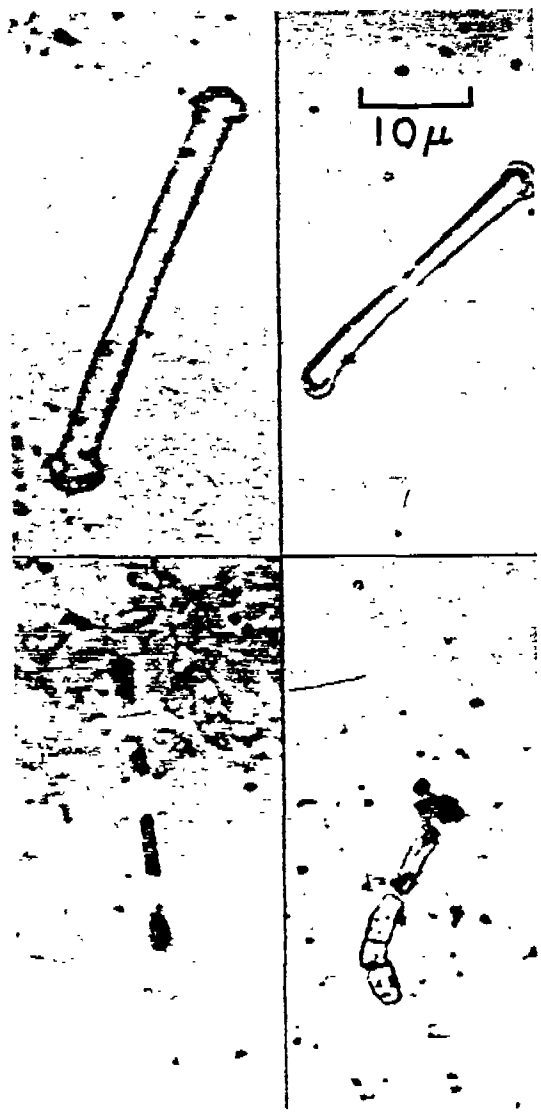
The sediment from the human asbestotic lung was a rusty, red-brown color. In the smear, a wide variety of asbestos bodies were seen in addition to innumerable naked fibers. As previously indicated, a large number of the asbestos bodies were pale, thin, and nonsegmented. Also of interest was the fact that many of the largest bodies did not have smooth surfaces, but were spiculated. The spicules

Fig 2.—Ferruginous bodies formed in response to aluminum silicate filaments in a hamster killed five months after an intratracheal injection of 3.5 mg of the dust. Bottom right, naked filament (concentration method; unstained smear; × 1,100).



were often coarse with squared ends. A few of the bodies lacked symmetry. Some pear-shaped bodies without a central filament were also seen. Although most of the bodies were more or less rectilinear, many curvilinear forms were also present. Some of the latter appeared to measure between 180° to 270°. In the larger spiculated forms, the central fiber was often obscured by the thick, dense, red-brown coating. Some of the very long thin fibers (50μ to 100μ) often had segments of ferroprotein at either end with relatively long stretches of naked fiber in between.

Fig 3.—Ferruginous bodies formed in response to filamentous glass dust. Bodies (top, left and right, and bottom right) are unstained. Four macrophages are faintly outlined. Only the intracellular portions of the filament are coated with iron (Perls' stain, × 1,100).



In an attempt to free asbestos bodies from adherent fine carbon particles in an otherwise "clean" suspension, it was subjected to ultrasonic vibrations for a few seconds. Unexpectedly, only naked fibers remained, and no asbestos bodies could be found in the suspending fluid.

The distinction heretofore made between asbestos bodies and pseudo-asbestos bodies may have been based in part on what the observer believed to be an appearance consistent or inconsistent with that of asbestos bodies. More often, however, this distinction was based on the observer's knowledge that the host had or had not been exposed to respirable asbestos fibers.

Regardless of the nature of the central fiber, the bodies that result in response to the presence of filamentous dust in the lung have as a common feature a coating of iron-containing protein (ferritin or ferritin-like). Furthermore, it appears, from a study of the pleomorphism of human asbestos bodies, which was so well illustrated by Gloyne and Merewether,[8] that differences in size, segmentation, or other morphologic features of the ferruginous coating probably would not serve to distinguish between ferruginous bodies of asbestotic origin and those of nonasbestotic origin.

Thomson has proposed to differentiate between asbestotic and nonasbestotic ferruginous bodies on the basis of the transparency or opacity of the central fiber.[2] This proposal seems inappropriate, inasmuch as we have demonstrated that a number of transparent fibers of respirable size other than asbestos are capable of producing ferruginous bodies that are indistinguishable from those produced by asbestos.

At any rate, it is obvious from the production of ferruginous bodies in hamsters in response to respirable, colorless, transparent filaments of aluminum silicate, glass, and silicon carbide, that such bodies

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represent a general reaction to filamentous particles and are *not* a specific reaction to asbestos fibers. To what extent our findings may have application to the ferruginous bodies that are being found with increasing prevalence in human lungs [1-4] remains to be determined. The applicability depends, of course, upon the identity of the central fiber in the ferruginous bodies. The method of isolation and concentration of uncoated fibers and ferruginous bodies from human lungs which is described in this paper may help in the study of the nature, identity, and prevalence of inhaled filamentous particles and associated pulmonary ferruginous bodies.

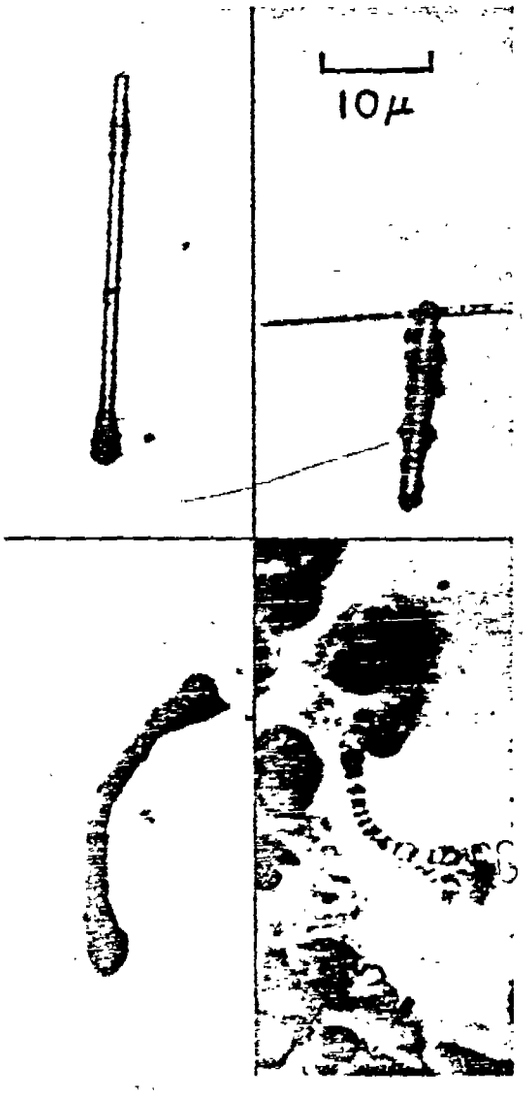
It is highly probable that the composition of the ferruginous body is altered by the method used for isolating it, since it is not likely that with the destruction of proteins leading to the liquefaction of all tissue elements in the lung, the protein in the ferruginous bodies should be spared. In all likelihood, the protein constituent of the bodies is destroyed, and only the iron and other inorganic components remain to retain and maintain the form of the bodies. The fragility of this chemically altered ferruginous coating is indicated by the ease with which it is removed when subjected to ultrasonic vibrations, thereby rendering the central fiber naked. This may further facilitate the identification of these fibers.

There appears an increasing tendency to consider all filamentous dusts in the same category as asbestos with regard to their pathogenic potential. This reasoning is probably based on a mechanistic concept of the pathogenicity of fibrous dust in general, and asbestos dust in particular. Such a mechanistic concept holds that the pulmonary fibrosis in asbestosis is the tissue response to mechanical trauma produced when pulmonary cells are perforated or impaled by the fine points of the asbestos fibers.

It need only be recalled that a similar mechanistic concept of the pathogenicity of crystalline silica was abandoned many years ago because of overwhelming evidence against its validity. Just as the proven biologic "inertness" of diamond dust was the coup de grace for the mechanistic pathogenetic concept of silicosis,[9] so should the proven biologic "inertness" of filamentous aluminum silicate [10] have discredited the mechanistic pathogenetic concept of asbestosis.

Extremely thin flakes of glass may also be considered to have sharp cutting edges; yet, glass has also been found biologically

Fig 4.—Ferruginous bodies formed in response to other filamentous dusts and stained for iron (Perls' test). The central fiber (top, left and right) is silicon carbide; and (bottom left) tremolite (talc) (×1,110).



"inert" when inhaled or injected into the lungs of animals. Silicon carbide is noted for its hardness, sharp edges, and points, which make it an ideal abrasive. When inhaled as a fine dust or injected intratracheally, it has caused a pulmonary response likewise classified as biologically "inert."[11,12]

Gaining increased attention is a newer concept that the potential of extraneous trace metals and other materials associated with fibrous minerals can cause the injury previously attributed to fibers. The respirable fibers may provide a transport mechanism for dosing tissues with injurious materials associated with the fibers. Cralley et al[13] have shown that asbestos textile workers in the past have been exposed to appreciable concentrations of nickel, chromium, and manganese associated with the fibrous mineral, and abraded from the alloy metal in asbestos processing equipment. They state further that there is evidence that this phenomenon exists in relation to a number of other fibrous minerals. There is also some indication that the biological response in the formation of ferruginous bodies may be related to the nature and extent of the layer of metal solute surrounding the fiber. Additional research needed in these areas is currently underway.

Unless the above facts are kept in mind, the finding that ferruginous bodies are formed in response to aluminum silicate, silicon carbide, and glass filaments in the lungs, may be used as still another reason for erroneously classifying these dusts with asbestos in their ability to produce lung damage.

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