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Inorganic Particles in Human Tissues and Their Association with Neoplastic Disease

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An increased gastrointestinal cancer risk is associated with occupational exposure to asbestos fiber. Examination of tissues obtained from extrapulmonary organs of exposed workmen demonstrates the presence of asbestos fibers and bodies. The amount of fiber present in these tissues is many magnitudes less than encountered in the lung tissues from the same individuals. Ingestion of asbestos fiber in some environmental instances may approach in magnitude the amount resulting from occupational exposure. Disease factors are discussed.

Inorganic Particles in the Environment and Their Possible Health Effects

Recently, there has been concern about the possible long-term biological effects in humans of ingestion of large numbers of extremely small-sized, yet small-mass amounts, of some specific inorganic particles. These are primarily silicates, either not normally encountered in the ambient environment or those which generally occur at levels not greater than a detectable trace. They find their way into humans, some at significantly elevated concentrations, as contaminants. These substances have been shown to produce fatal malignant tumors in animals and are implicated as whole or cocarcinogens in epidemiological studies involving humans. These latter studies have largely been of workmen occupationally exposed to high concentrations of these materials. Some have been associated with increased occurrence of gastrointestinal cancers.

These particles may originate from specific sources, such as solid waste discharge of crushed silicate rock in mining or milling operations, which may contaminate potable water and air supplies *(1)*, or disintegration of man-made products, e.g., pharmaceutical or beverage filters *(2)*. In such instances, silicate particles are inadvertently added to some substance which is directly ingested by humans. This has apparently become more common as the result of modern technology. Silicate particles have even been observed as contaminants in polar ice caps. Mineralogical analyses of ice samples from polar areas have shown an increased occurrence of talc particles with progression in time, to the present. This has been attributed to the increased usage of talc as an excipient in pesticides. These small particles have entered the air streams and have precipitated with rain and snow *(3)*. This may be true for a number of other industrial minerals which have become increasingly more important and useful with widening applications. For example, our laboratory has examined ice samples from the Greenland polar ice cap and has found chrysotile asbestos fibers to be present in all samples examined thus far.

Concern has been derived from a number of observations: (a) the incidence of cancer of the gastrointestinal tract is rising in the United States; (b) there are some epidemiological studies which have established an association between exposure to specific inorganic particles

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and increased gastrointestinal cancer risk; (c) particles accumulate in tissues for the lifetime of the individual; (d) particles may, in some way, interact with other substances in the environment to produce a synergistic, multiplicative effect; (e) there may exist a zero threshold for particle tolerance in humans, insofar as cancer is concerned,

Gastrointestinal Cancer in the United States

It has been estimated that upwards of 335,000 men, women, and children died of cancer, of all sites, in the United States in 1971 *(4)*. Cancer is the second leading cause of death in this country, second only to heart diseases. The leading cause of neoplastic death in men is lung cancer; in females, it is cancer of the breast. Although the second leading cause of neoplastic death in women was uterine cancer in 1971, colon and rectum cancers were almost equal in number. In both men and women, over 46,000 deaths from cancer of the rectum and colon were recorded in 1971 (Table 1). The rate of rectum–colon cancer is increasing, so that it has been estimated that before the end of the decade this disease may be the second most common cause of cancer deaths in the United States for both men and women.

Table 1. Deaths from Cancer in the United States: 1971.

	No. of deaths
By sex	
Males	183,000
Females	152,000
Total	335,000 (best estimate)
By site	
Males, lung	53,100
Males, colon-rectum	22,400
Females, breast	30,500
Females, uterus (genital)	25,929
Females, colon-rectum	23,600

[a] 70–80% of malignant tumors of the large bowel occur in the cecum, sigmoid and rectal regions.

Hyperplastic and neoplastic lesions have been found, on scrutiny by light microscopy of random autopsy material, to be far more numerous and widely disseminated in the bowel, colon and rectum that has been previously reported *(5)*. However, considering the physical extent and mass of this organ, most malignant lesions tend to be confined to the lower bowel (sigmoid) and the rectum. A question is then whether increased gastrointestinal cancer in the United States is in any way related to the observed increased silicate contamination of foods, beverages, water supplies, pharmaceuticals, or any other substance which is directly ingested by humans.

Association between Mineral Particles and Neoplastic Diseases

A number of studies over the last 25 years has established an association between occupational exposure to some specific species of inorganic particles and increased risk of neoplastic disease in workers. Workmen exposed to asbestos dust (at least five separate mineral species and their chemical ranges) *(6–12)*, hematite miners (hematite dust in the presence of free silica and other gangue silicates, including perhaps asbestos) *(13)*, talc miners and millers *(9)*, miners and millers of uranium ores *(14)*, workmen who process chromium ores *(15)*, and heavy metal processors who are exposed to lead, zinc or copper fumes *(16)* all have substantially increased risk of developing malignant neoplasms. Most of the reported tumor excess tend to be in the thoracic organs. However, in asbestos exposure, there are other tumors as well (Table 2). Exposure to

Table 2. Epidemiological studies demonstrating an association between exposure to mineral particles and increased risk of gastrointestinal cancer. [a]

Study	No. men	Material used
Keal *(6)*	42	Amosite; chrysotile; crocidolite
Selikoff et al. *(7)*	632	Chrysotile and insulation
Kleinfeld et al. *(9)*	91	Talc; tremolite; anthophyllite
Enterline and Kendrick *(8)*	1,843	Chrysotile (textiles)
Elmes and Simpson *(10)*	170	Mixed fiber; insulation
Newhouse et al. *(11)*	928	Crocidolite
Selikoff et al. *(12)*	230	Amosite

[a] Most of the studies deal with one or more forms of asbestos mineral fiber. At least five of the major fiber types are implicated as being biologically active.

asbestos fiber leads to increased risk of developing neoplastic tumors of the gastrointestinal tract. Difference in fiber type appears to have little affect on relative excess mortality (Table 3).

Table 3. Asbestos fiber type and increased risk of gastrointestinal cancer.

Fiber	No. cases	Expected	Observed
Amosite [b]	230	1.6	5.0
Chrysotile [c]	632	9.4	29.0

[a] Two occupational settings utilizing different fiber types. Approximately three times as much gastrointestinal cancer occurs in both groups.

[b] Data of Selikoff et al. *(12)*.

[c] Data of Selikoff et al. *(7)*.

Fiber Amounts in Tissues and Disease; Important Questions, No Answers

Observations concerning fiber amounts in tissues and the occurrence of disease in occupationally exposed workmen, raises some important questions. One can ask whether asbestos is such a potent carcinogen, in and of itself, that it may be associated with a threefold increase of gastrointestinal cancer in occupationally exposed workmen when the amount of fiber in the affected tissues is many magnitudes less than observed in their lungs. This may suggest that tissues, other than pulmonary, are more sensitive to the insult of the dust. Perhaps the gastrointestinal tract is such a more sensitive tissue, thereby, making it one more "target" organ. It may also suggest that there are factors other than the fibers themselves which may be responsible for increased tissue response. The question arises as to the effects of "organic additives", such as nitroso compounds, and the role they may play in the etiology of gastrointestinal disease. Synergism, for neoplastic development between particle exposure and cigarette smoking was suggested several decades ago *(16)*, but established epidemiologically for asbestos and smoke only recently *(25)*. Multiple interaction of fiber and organic compound increases neoplastic disease risk in a multiplicative manner. What are the effects of such combinations as particle to particle, particle to gas, and particle to organic phase in asbestos disease etiology? And, most important, does direct ingestion of small amounts of asbestos fiber, in food and water likely less than one observes for the working environment, pose a serious threat of neoplastic disease for individuals not occupationally exposed to the fiber? Does environmental direct ingestion of small amounts of asbestos fiber approach in magnitude the amounts of fiber inadvertently ingested, or migrated, following occupational exposure?

Is asbestos a unique substance with respect to disease? If so, what are the special properties which render it so unique? Is a narrow chemical or physical entity of asbestos within a broader range, the only biologically active member of that series? Although amosite is a narrowly defined mineral entity within the cummingtonite–grunerite series, it has been implied that all other members of this series are biologically inactive. This appears unlikely because the magnesium member of this series, which alters crystal form slightly, is another amphibole mineral called anthophyllite. Anthophyllite has been shown to be biologically active.

Considerations and Future Work

Future work in the area concerning the biological effects of inorganic particles will have to take into consideration a number of parameters. For example, there is a natural background, and a wide variety of inorganic particles which are normally ingested. Foods contain inorganic components, as well as adventitious minerals within the substance itself; some of which have formerly been considered inert. Opal phytoliths have long been known to occur as siliceous parts of plants *(22)*. Their long-term biological activity is known only in animals *(23)*. Potable water may carry large quantities of dissolved and suspended materials which are ingested. Their effects are unknown. The "natural" background of particles in ambient air is only partially known and is continually fluctuating qualitatively and quantitatively. The identity of many of the particulate components still have to be determined. In addition to these natural airborne materials, particle contaminants and additives in food, water, and beverages add to the body's burden.

In addition to characterizing of these particles, one must systematically examine the affected tissues. To this date, this has not been done. We observe in lung tissues of workmen that each portion of the lung contains a slightly different particle size fraction assemblage. This has not been studied for any of the extrapulmonary organs. Judging from the prevalence of neoplastic lesions in bowel, colon, and rectum, one may expect that the accumulation of particles in the digestive tract is site related. The development of proper tissue preparation techniques and instrumental methods of analysis has been achieved to a large degree *(24)*. The expansion of this research into possible etiologic agents responsible, in part, for the development of malignant lesions in the human gastrointestinal tract, is only at the beginning stage.

Asbestos Exposure and Neoplastic Disease

Asbestos fibers may be easily detected in lung tissues of asbestos workmen *(17)*. These men are generally exposed to highly concentrated dust aerosols so that the inhalation and entrapment of fibers in their lung tissues is certain. Many fibers are eliminated from the lungs by the body's normal defense mechanism. However, elimination never equals the quantity of material which is inhaled. The fate of these fibers which are removed from the lung may be twofold: they are eliminated from the body or they are removed from the lung, but migrate to other body sites *(18–20)*. Migration may include hematogenous and/or lymphatic mechanisms *(19)*. The size distribution of even the larger amphibole fibers is such that this transport may be accomplished without size obstacle. A statistical study of the size distribution of amosite fibers in the lung of a workman exposed to dust occupationally, has demonstrated that 95% of the fibers in his lung was shorter than 5 μm in length and the width distribution for these fibers was modally centered at 0.15 μm size range *(21)*. Even in these cases, the vast majority of fibers may easily migrate within the body. Therefore, asbestos fibers found in the extrapulmonary tissues of workmen may have come to rest in these organs through migration and/or direct ingestion.

We have studied extrapulmonary organs of asbestos workmen by both light and electron microscopy in order to determine the presence or absence of fibrous particles. The results of one such light microscopy study is shown in Table 4. On the basis of this very limited study by optical microscopy, we report that large fibers, those detectable by light microscopic techniques, exist in all extrapulmonary organs examined. However, their amounts are substantially less than light visible objects normally encountered in lung tissue from the same individual. Also, uncoated fibers exceed coated fibers (asbestos bodies) by substantial amounts. Using light visible objects as markers, fibers are observed in extrapulmonary organs, but they are magnitudes less in number than in the lung.

We also have examined a number of such extrapulmonary tissues by electron microscopy. Here also, on the sublight microscopic level, we

Table 4. Presence of asbestos bodies and uncoated fibers in lung and extrapulmonary tissues of workmen occupationally exposed to asbestos dust (light microscopy).[a]

	Lung		Liver		Pancreas		Kidney		Adrenal		Spleen	
Case	Body	Fiber	Body	Fiber	Body	Fiber	Body	Fiber	Body	Fiber	Body	Fiber
1	>99	>99	1	5	2	16	0	47	—[b]	—	—	—
2	>99	>99	—	—	—	—	—	—	—	—	15	30
3	>99	>99	3	4	7	48	1	>99	—	—	—	—
4	>99	>99	0	1	—	—	0	69	0	5	—	—
5	>99	>99	0	2	2	10	0	60	—	—	—	—

[a] Analyses were made on 175 μm stacks of seven 25 μm thick tissue sections. These are ashed in a low-temperature asher, immersed in an appropriate oil, covered and scanned under phase-contrast at 440 × magnification. Area scanned about 10 × 10 mm. Counts stopped at 99.

[b] Denotes no tissue available.

observed uncoated fibers. Again, as with light microscopy, their concentration is significantly less than encountered in lung tissues. The observation that asbestos fiber may be present in organs which have limited direct contact with the outside environment, by direct ingestion and blood or lymph routes, emphatically demonstrates the ability of asbestos to infect the entire human body. It has been noted experimentally that asbestos fibers are found in liver, spleen, and kidney of experimental animals after asbestos instillation into the lung *(19)*. Inhalation of asbestos fiber invariably means dissemination of fiber throughout the body, although the number of fibers which may come to rest in extrapulmonary organs may be magnitudes less than one observes entrapped in lung tissues.

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