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FATE OF INGESTED PARTICULATES

by

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ABSTRACT

People consume many solid particles everyday through food, water, and beverages. A review of the literature shows that while there is no mass penetration of particles through the walls of the gastrointestinal tract, there is considerable evidence that mineral fibers and other durable particulates do transmigrate from the G.I. tract to other parts of the body. Several mechanisms for particulate penetration have been postulated and the mechanism may well be different for different types of materials and for different sizes of particles. Penetration of asbestos fibers is a relatively rare occurrence and is estimated to be on the order of 1 fiber in 10,000. Once in the body, some fibers and other particulates may be accumulated in certain tissues but many are cleared and eliminated through the urinary tract.

Particulates form a general category which is not very well defined. In the drinking water industry we loosely classify the particulate component as pieces of material of varying composition ranging up to 100 micrometers in size. The finding of particles larger than 100 micrometers (0.1 millimeter) in publicly supplied drinking water usually brings vigorous complaints from the consumer. The question of the lower limit of the size of particulates has largely been ignored. In the present analytical techniques available for water, particles smaller than 0.1 micrometer are not considered. The question of what constitutes a particulate in food is far more difficult than when considering water. Analyzing food for particulates is an extremely difficult task.

If particulates swallowed with food, beverages, and water do not migrate across the gastrointestinal mucosa of the alimentary canal, the question of whether any ingested particle could be a cancer risk would be greatly simplified. It is clear that the food and liquids one consumes everyday contain a high number of solid particles and by far the bulk of the nondigested material moves through the digestive system as illustrated in Figure 1 and is discharged

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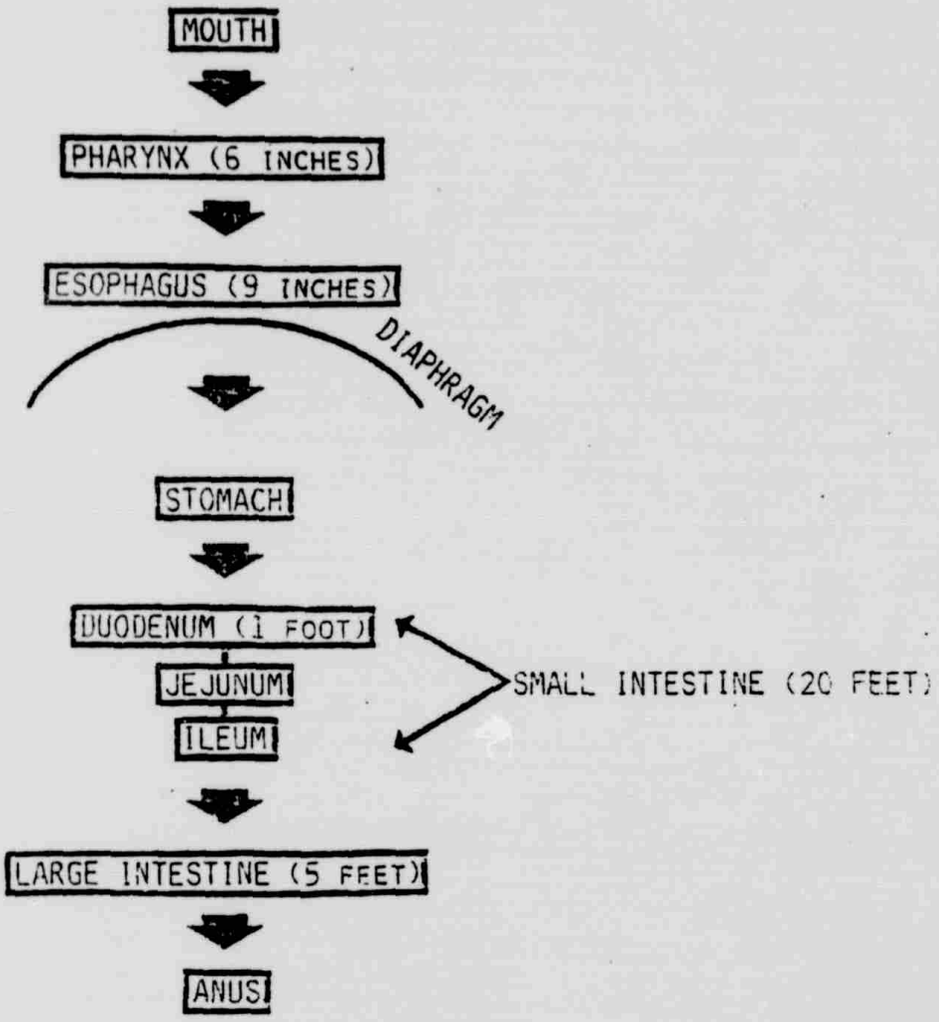


Figure 1. Pathway of ingested material not assimilated by the gastrointestinal tract.

in the feces. While enroute on a normal trip, which may take a number of hours, some particles are coated with secretions, subjected to gastric juices, digestive enzymes, and drastic pH changes from pH2 to pH8. Only particles with certain sustaining traits can be considered candidates for direct transport through the GI wall. A more complete discussion of the activities of the digestive tract can be found in the appendix of this article.

Since asbestos and other durable fibrous materials placed directly in the peritoneum of animals have resulted in malignant neoplasms, the questions of which materials and how much can pass through the walls of gastrointestinal tract are particularly important.

The results of three laboratories' investigations on asbestos fiber penetration were described in one publication in 1974.[1] The paper reported no evidence of penetration of the G.I. mucosa by mineral fibers. Although a review of the studies shows their results to be suggestive, the studies themselves were not adequately designed to answer the full question of penetration. In the first laboratory, three studies were performed. The first investigation consisted of ten rats fed laboratory chow containing 5 percent ball-milled chrysotile for 21 months. After nine years storage in formaldehyde, tissue of the G.I. tract was prepared for electron microscopy. The digests of the tissues of the G.I. tract contained chrysotile fibers but it was impossible to tell whether the fibers had been in the mucosa or were a result of contamination. Unfortunately at the time the tissues had been preserved, tissue from the G.I. tract was not isolated from other tissues and no attempt was made to keep the formaldehyde solution that had been contaminated with asbestos containing fecal material from contaminating the other tissues with asbestos fibers. Fibers were found in the digests of the mesenteric tissue from both test and control animals but because the experimental procedure used unfiltered water and contaminated reagents, the findings could not be interpreted. No fibers were found in sections of intestines examined with electron microscopy but the amount of tissue searched was not given in the experimental details.

In a second study, still in the first laboratory, 20 unanaesthetized rats were given 400 mg of amosite or taconite mine tailings in 1 ml of suspension by gavage. Fibers were found in the digest of G.I. tract tissues in some but not all of the rats given amosite. No data were given as to the amount of tissue analyzed.

A third study incorporated finely ground amosite or taconite tailings into oleomargarine to obtain 10 percent amosite content or 20 percent taconite content. Fibers were found in the mesentery, lung, or kidney digests of some of the animals exposed to amosite or taconite but not in the digests of the control rat tissues. No data were given as to the actual amount of tissue examined so it is impossible to estimate the significance of finding fibers.

In the second laboratory studies reported in the 1974 article, the gut and other tissues of rats fed 0.2-0.4 percent crocidolite asbestos in butter for varying periods of time were examined only with optical microscopy. No evidence of fiber penetration was found. No data on the magnification used or amount of tissue surveyed were given.

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Only partial data from the third laboratory was available for inclusion into the report. Chrysotile and crocidolite "properly ground" were mixed with butter to a 0.5 percent level by weight. Light microscopic examination of tissue sections showed no asbestos fibers that had penetrated. Electron microscopic examination of sections of small intestine and mesenteric lymph nodes also showed no signs of penetration. Again, no data were given as to the actual amount of tissue examined.

Together the results of the three laboratories suggest that there is no mass penetration of fibers through the gut wall, but because of the contamination of the first laboratory and lack of sensitivity in the second and third laboratories, the results in this 1974 article are not confirming evidence that durable fibers cannot transmigrate from the gastrointestinal tissues to the body.

A number of other investigators have addressed the question of digestive tract penetration by particulates. A number of their findings support the contention that particulate penetration is not a large scale event but does occur.

One of the first reports on the subject showed electron micrographs of asbestos fibers in many sites of the colonic epithelium and lamina propria of rats fed a 6 percent asbestos diet for 3 months.[2] Asbestos particles found in the tissue were up to 1 micrometer in length. No data were given on the size of the asbestos before feeding or the amount of tissue analyzed. The authors postulated that the particles had migrated through the mucous of the goblet cells into the cell itself and hence into the lamina propria.

In a human study, amphibole fibers were found in significant numbers in the lung, liver, and jejunum in 29 of 39 Duluth, Minnesota residents with oral exposure to mineral fibers in their drinking water lasting up to 15 years.[8] Among 21 control residents of St. Paul, MN and Houston, TX only two subjects were found to contain the amphibole type fiber, in each instance a single fiber from a single tissue site.

The methods of penetration of the digestive tract are postulated to be direct piercing of the cells by long fibers and pinocytosis of short fibers. According to Volkheimer,[9] particles in the nanometer size range can be channeled through the intestinal absorptive cell (enterocyte) by a pinocytosis-like process in minute bubbles with a diameter of up to 50 nm. Larger particles, whose diameter is well within the micrometer range, are suggested to be regularly incorporated by persorption. In this process particles are "kneaded" into the mucosa during their passage through the digestive tract. Volkheimer suggests that the particles pass between the epithelial cells into the subepithelial layer. It is easy to conclude that when durable fibrous materials are kneaded into the tissue some of the fibers would directly pierce the cells. Asbestos is known to be taken in by cultured cells.

Gross et. al.,[1] raised an important point in the question of penetration of the digestive tract by solid particles. If penetration of the GI mucosa by particulates did occur, the amount of stored material in the intestinal

submucosa and in mesenteric lymph nodes would increase with age. Recent data suggest that many of the particles which have penetrated may be cleared from the body via the urinary tract. Amphibole fibers were found in the urine of persons who had been drinking unfiltered water containing the mineral.[10] Asbestos fibers have also been found in the urine of a baboon forced to ingest the material.[11] In most individuals a balance between fibers taken in and those cleared may be reached over time. Fiber concentration in tissue may increase with age but at a slower rate than fiber penetration of the digestive tract.

Nonasbestos materials also penetrate the digestive tract. In their mini-review of intestinal absorption of particulate matter, Le Fevre and Joel list a number of materials which have been reported to pass the intestinal barrier.[12] These include colloidal metals, latex spheres, polyvinyl chloride pellets, and iron filings. Volkheimer[9] reports using starch granules, cellulose particles, powdered rabbit hairs, charcoal, pollen and silicate crystals in his persorption studies. Cook reported finding nonfibrous particles of silica, diatom fragments, fibers of iron, titanium and glass of probable man-made origin. Attapulgite clay fibers have been reported in the urine of a person ingesting large doses for medical purposes.[13]

Little data were available on the rate of transfer of various solid materials through the digestive tract. Estimates of the passage rate for asbestiform fibers range from 1 fiber in 1,000[10] to 1 fiber in 10,000.[14] From the data provided by Cook and Olson[10] for 4 subjects ingesting unfiltered Lake Superior water over a number of years, the average concentration of fibers in the urine was 0.66×10^6 per liter. Compared with the average fiber content of Lake Superior water of about 100 million fibers per liter, this fact suggests that as many as 1 in 200 fibers crosses the digestive tract. This estimate assumes that a steady state between the number of ingested fibers and the number of fibers eliminated in the urine could occur so that the number of fibers in urine would represent the minimum number of fibers passing through the intestinal mucosa. As indicated by Cook and Olson, even the ratio of 1 in 1000 fibers passing seems remarkably large and may be modified by further measure.

The value of 1 fiber penetrating in 100,000 was determined using a rat study in which an asbestos pellet weighing approximately 20 mg was introduced into the stomach of rats by catheter.[14] The value of 1 in 100,000 may be an underestimate of what happens when fibers are ingested in water since the number of individual fibers available for penetration was dependent on the rats' ability to break up the pellet internally. The same researchers have reported the passage of both chrysotile and crocidolite fibers across the gastrointestinal wall and that the larger chrysotile fibers appear to pass at a higher rate than short fibers.[15]

If there is a balance achieved between intake of fibers and excretion through the urine, a maximum accumulated level of fibers in some tissues may be attained. It is interesting to note that the highest accumulation of chrysotile fibers in tissues (other than lung) reported by three independent researchers were all on the order of 10 million fibers per gram of tissue. See Table 1.

TABLE 1. MAXIMUM TISSUE FIBER CONCENTRATIONS REPORTED FOR CHRYSOTILE

Tissue	Fibers per gram	Chrysotile Exposure
Rat omentum[4]	8.6×10^6*	1% in diet for 6 weeks
Human liver[8]	10.9×10^6**	Unknown exposure over lifetime
Baboon kidney cortex[7]	7.8×10^6*	3×10^{13} fibers/kg in 9 days

*Corrected for control tissue concentration.

**Corrected for blank filter concentration.

In another study, a single suspension of chrysotile asbestos was injected into the stomachs of 10 anaesthetized rats.[3] Asbestos fibers were found in animals sacrificed 2 to 4 days later in the omentum (which surrounds the small intestine), blood, spleen and brain. The authors postulated that long fibers may pierce the gut like a needle, whereas pinocytosis may account for the absorption of smaller fibers. Fibers in one tissue were as long as 15 um and one fiber in the blood was 23 um long. Some questions have been raised about the injection technique in that there might have been passage of fibers through the needle tract into the abdominal cavity.[1]

In a second experiment, the same researchers fed 10 rats a diet containing 1 percent chrysotile asbestos for 6 weeks.[4] Tissues were prepared using a procedure which included ashing, solubilization with dilute HCl, filtration, ashing the filter and dropping a 5 ul aliquot of tissue suspension on an electron microscope grid. Analysis of the tissues showed higher levels of asbestos in all tissues of test animals examined than in controls with the highest levels in the omentum (9.66×10^6 fibers per gram) followed by the brain, lung, liver, blood and kidney. Fiber lengths were up to 5 um. The authors concluded that ingested asbestos can penetrate the walls of the digestive tract but that when the amount of asbestos consumed by the rats in the 6-week period is considered, the amount found in tissues represent an extremely small portion.

One hour after amosite asbestos fibers suspended in saline were placed in an isolated segment of rat jejunum in vivo, the animal was sacrificed and fibers were found penetrating the epithelial surface.[5] Amosite fibers with diameters up to 1.4 um and visible lengths up to 30 um were seen in epithelial cells or in the lamina propria. All fibers seemed to enter the cell through its luminal surface. None penetrated the intercellular junctions. The authors concluded that penetration of the epithelial cells of the intestine directly through their cell bodies is at least one of the mechanisms by which asbestos fibers can gain access to the lamina propria of the intestine.

Fiber penetration of the digestive tract has also been documented in primates. Chrysotile asbestos fibers up to 35 um long were found in the kidney

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cortex of a newborn baboon fed asbestos containing milk formula for 9 days.[6,7] Statistically significant higher levels of fibers were found in the kidney (especially kidney cortex), lymph nodes, spleen, colon, and esophagus over control tissues. Five other tissues, stomach, liver, duodenum, cecum, and heart contained concentration of fibers not different from control tissues. The tissue was prepared using a procedure of low temperature ashing, solubilization with 1 percent acetic acid, filtration, ashing of the filter and placing 6 ul of tissue suspension on an electron microscope grid. There were fibers of various sizes found in the test animal tissues indicating, at least with the newborn, a range of sizes of asbestos fibers can penetrate.

This may indicate the upper level for chrysotile accumulation in tissue. Other particulates may accumulate to different levels and be regulated by different clearance mechanisms.

In summary, the research conducted on the penetration of the digestive tract by solid materials is sufficient to conclude that such penetration is not on a large scale but can and does occur. Research findings also suggest that while some fibers may be entrained in body tissue many are cleared through the urinary tract.

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APPENDIX

THE DIGESTIVE PROCESSES

Ingested material, whether it is considered food or foreign matter, must eventually either pass through the alimentary canal (gastrointestinal tract) or be assimilated by the body somewhat along the twenty seven or so feet of the canal.

Ingested material enters the GI tract through the mouth (and sometimes through the nasal cavity due to swallowing of material cleared from the respiratory tract). In the mouth, ingested material is acted upon by secretions from the Parotid, Submaxillary and Sublingual Salivary Glands. These secretions serve primarily to moisten the ingested material and mouth tissues, and to initiate the breakdown of ingested starches. Mastication serves to break up the material mechanically.

The ingested material then passes through the pharynx and into the esophagus, a short mucous-lined tube capable of producing wave like peristaltic motion that aids in moving material to the stomach. In the stomach lining, there are a number of specialized glandular cells whose function is to secrete digestive enzymes, buffers, hormones and hydrochloric acid. Ovoid parietal cells, in the lining, are stimulated by the vagus nerve, gastrin and histamine to secrete HCl into the lumen of the stomach. Mucous and alkaline fluids, secreted by the stomach lining, protect the stomach from being eaten away by the acid, which may range anywhere from pH 0.9-3.0 depending on the nature of the ingested material and the overall health of the individual. Some fluid absorption occurs in the stomach.

As the ingested material proceeds along its course into the duodenum of the small intestine, it is acted upon by alkaline pancreatic juices, $NaHCO_3$, insulin, glucagon, enzymes and proteins from the pancreas, bile from the liver and gall bladder; and secretin, duodenal juice, succus entericus and pancreozymin from the intestinal cells. The thick carpet of finger-like projections (villi) that line the small intestine allow for greater surface area and therefore more absorption. Most of the liquids, amino acids, sugars and other nutrients are taken up into the bloodstream via capillary beds among the villi and the hepatic portal vein (leading to the liver). This transport can occur by means of absorption, persorption or pinocytosis.

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The non-assimilated portion of the ingested material proceeds to the large intestine where water, salt and glucose are absorbed from the fecal material. The fecal material then passes through the rectum and out the anus.

In man, the time period for the complete passage of non-assimilated ingested material will vary with each member, but usually ranges between 20 and 25 hours.

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DISCUSSION ON THE ROUTES OF EXPOSURE: INHALATION, DEPOSITION AND CLEARANCE OF PARTICLES

REMARK (Dr. Gross): I am associated with the Industrial Health Foundation. I wish to comment on some of the statements that have just been made.

I have been a pathologist over the last 50 years. Half of that time was in hospitals where I spent a good deal of time studying the tissues of hospital patients who died as a result of their illness. One of the organs that was studied in great detail was the kidney.

I have always been impressed from a clinical point of view upon the exquisite ability of the circling unit of the kidney to hold back dissolved molecules of proteins that have a fairly high molecular weight and allow molecules of low molecular weight such as electrolytes to pass through.

When one considers the comparative size of a particulate, particularly a fiber, in relation to a micro-molecule such as albumin, which under normal conditions the circling membrane of the glomerulus (a unit in the kidney) holds back, there is an enormous difference and according to what Dr. Millette just said, quoting Dr. Cook's work, the passage of particulates through the renal circling membrane is not an unusual event. This is totally out of keeping with what we know of kidney function, the ability of the membrane of the glomerulus to hold back even dissolved molecules of appreciable size.

With regard to the passage of particles through the intestinal mucosa Dr. Millette quoted Volkheimer, who in his article claimed to find starch granules in the blood, in various tissues, and in the urine. These starch granules are 10 times the size of a red corpuscle and in order to pass, say through the intestinal wall into a blood vessel of any size it ultimately will have to pass through the capillary network that barely allows a single red corpuscle to pass through. Yet, we are supposed to believe that Volkheimer was able to demonstrate such huge particles in the urine.

As an example of the ability of the intestinal mucous membrane to hold back particles that happen to be in the intestinal ileum, I might mention that coal miners swallow a good deal of the dust that they inhale and in the swallowed coal dust are particles that are a fraction of a micron in diameter. If fibers, which are 1 micron in diameter, are capable of passing through the intestinal wall, then particles that are a small fraction of that size would have even a greater facility to pass through. Now, a coal miner may work in a coal mine for 30 years and every day he would swallow a fairly large amount of coal dust that he has inhaled and was brought up from his lungs, yet when one does autopsies, as I have done, on coal miners one does not see black discoloration of the lymph nodes. One rarely sees black spots in the liver and spleen, but that can be explained on the basis of lymphatic drainage from the lungs. But, one cannot see black lymph nodes in the mesentery, the lymph glands that drain the intestinal wall. One does not see that and one would see it if particles were capable of penetrating the intestinal wall.

You realize, of course, that I look with a very jaundiced eye on this presentation and I hope the audience will also be judicial in accepting this presentation.

REMARK (Dr. Kotin): I work for Johns-Manville Corporation. A couple of comments on the papers and then perhaps a few generalizations.

First, let me thank you, Dr. Rowe, for being sensitive enough to dedicate this session to Mearl Stanton. As a former associate of his at NCI there is no way we can overstate our debt to him and his associates. Also thanks for being good enough to stop me in the corridor to say I can talk for a few minutes if I want.

I am not sure that the case for penetration of the gut has been made by this presentation, but penetration of the gut does occur and I think that the criteria for penetration are probably not for this session.

I think that Dr. Millette might be well advised to know that both Doctors Cunningham and Pontefract were aware belatedly that the formaldehyde that they used for the fixation of tissues was loaded with asbestos fibers. Unfortunately it was filtered through asbestos and I think they are very candid in stating this, but in no way would I say that that necessarily throws out all of their data. I think quantitatively it might be challengable.

Again, I think the best thing that can be said about the Storeygard and Brown study is what Dr. Brown says himself. They were dealing with an exteriorized loop of intestine. He cannot be sure that he has got penetration or overlay on many of the sections, which I reviewed with him personally, so let us at least maintain the fact that maybe not these studies but others may very well substantiate the concept of penetration.

Dr. Lippmann, I think you might know that, and I am sure you are aware that Crystal and his associates at the Heart and Lung Institute are beginning to show, I think rather reliably and consistently, a role for the poly as well as for the macrophage in the fibrogenic capabilities. I think this has some relevance to the pathogenesis of a disease in people who are exposed to excessive amounts of asbestos.

Again, I have no new data to present because of the brevity of time, but let me restate a few verities that probably have been lost sight of and certainly I think have been given short shrift in the presentations.

Let me begin immediately by saying that the reality of asbestos-related disease has been amplified by the presentations at this meeting. I think at the very least you would have to have your sanity questioned to doubt the capability of excessive amounts of asbestos fibers to produce an array of asbestos related conditions. However,

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the disease-producing potential can not be divorced from accepted principles of pharmacology, toxicology, pathogenesis, pathology and clinical disease. Specifically, these principles include factors like dose response; multifactorial ætiology in both disease development and disease natural history; the demonstration by several, including a person attending this conference, of a no adverse effect level in a very competently studied population; and the necessity for biological availability for host effect, which, of course, relates to the two earlier presentations. This includes things that have been discussed before; localization, retention, translocation, the dimension of the particles, the solubility of the particles, and I think all these principles, and one could go on listing many more, find expression and are all applicable to the problem of asbestos exposure and one that is particularly relevant to EPA. I do not envy EPA's responsibility in trying to address the issue of asbestos outside the work place. OSHA has by far the easier of it.

The patterns of asbestos-related disease in occupational settings are well known. The patterns of asbestos response in para-occupational settings, neighborhood studies, and family studies have not been shown and this does not mean that the positive studies are useless. Not at all. What they do clearly demonstrate is that even outside the workplace dose response has its universal application.

Perhaps a fourth pattern of exposure to asbestos-related disease, and this does put the EPA right in the middle of the circle, is a category, for want of a better term, I call "living with asbestos." This includes the school buildings. This includes asbestos as part of the earth's crust where it is indeed part of the potable water supply or part of the airborne suspended material as a result of wind and soil erosion. For this group, really, and I can only repeat what Dr. Rowe said, the data are pitifully little and really do not permit conclusions nearly as much as they permit what Sir McFarland Burnett called in his Nobel speech, "responsible speculation." The data do permit responsible speculation that the "living with" group does not have any asbestos-related disease as yet. One gives added credence to the negative data because you do have two marker situations, mesothelioma and a rather characteristic type of fibrosis. But this is not to say that the answer is in by a long shot.

Then you have the fourth category and this is the casual exposure and I mean casual not in the cultural sense. I mean casual in a quantitative sense; not the people in this room; you either work with asbestos or are using it in your laboratory or so on, but the next crowd that goes to see the Redskins play would predominantly be people casually exposed. Here, again, I think despite ongoing studies that have been comprehensive, yet inadequate, there is absolutely no evidence of an effect.

I would make two major closing comments. First, the assumption that all four classes are interchangeable in terms of the generalizations I have made is not true of course. The dosage of exposure is different,

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the co-factors differ and so on. So, I think one has to be very, very jealous in terms of the discipline in which one approaches each of these categories and tries to conclude from one to the other.

The second point I would like to make is that the four categories, again, in no way contradict the occupational information that we have about asbestos but, again, I would emphasize the importance of dose. The assumption that doses, particularly in the para-occupational exposures, are low dose exposures, I do not think is a valid one on the basis of existing data, but the data are so pitifully small that one cannot either deny or assent; one can only say that much more information is necessary. Again, a short exposure is not necessarily a low dose exposure and a nonoccupational exposure may not be, either.

Let me close by saying one word on substitutes. Clearly the principles of biology that are applied to asbestos have to be applied to all substitutes, as I know in fact they are being applied, but it would be well to not repeat some of the omissions in our approach to the asbestos problem that have been taking place over the last half century in addressing these substitutes.

QUESTION (Mr. Kosner): I am from the NIEHS. We certainly owe a great debt to Dr. Kotin who is also the founding director of the National Institute of Environmental Health Sciences, the institute that I am with at the present time.

We do know that asbestos is associated with mesothelioma of the pleura and of the peritoneum. Unless we believe these substances act at a distance, we would have to believe that the particles must get to these sites in order to set up the conditions for the effect to occur.

I wonder if something also could be said about the stability of different types of fibers. For example, asbestos is quite different than fiberglass and some others in terms of its resilience and in terms of its strength and some other factors. It may be that some of these stay pretty much as they are, whereas other ones tend to break up and might be eliminated more rapidly. The way more sense is going to be made from this field in which so many different substances are being used is to find out these basic principles of uptake and release and integrity. We do know something about the importance of the length to the diameter.

Does Dr. Millette know something about the integrity of different types of fibers; rock wool versus fiberglass versus asbestos, et cetera?

ANSWER (Dr. Millette): In terms of ingestion there certainly is very little data on any material other than asbestos that has even been attempted. So, all you would have would be the casual findings of certain other types of fibers in other tissues, such as, gastrointestinal tissues, or finding, say, attapulgite fibers in the urine of a person receiving it in a high medical dose. So, very little really has been done with that.

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REMARK (Dr. Rowe): That was a very good comment and question. I think that is an area that will have to be avidly pursued in the future.

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