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Transmigration of Ingested Asbestos

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There has been speculation that the ingestion of asbestos in food and drinking water may play some role in the etiology of cancer of the gastrointestinal (GI) tract. An important question in the evaluation of the possible human cancer risk associated with asbestos ingestion is whether fibers can penetrate into and through the GI tract in sufficient numbers to cause adverse systemic or local effects.

Factors that complicate interpretation of the available data on the transmigration of ingested asbestos are discussed, and the preliminary results of our ongoing investigation of the penetration of amosite fibers into the normal and abnormal intestinal mucosa of the Wistar rat are reported.

Introduction

An important question in the evaluation of the possible human cancer risk associated with the ingestion of asbestos is whether fibers can migrate from the lumen into and through the walls of the gastrointestinal tract in sufficient numbers to cause adverse systemic or local effects. There is considerable disagreement concerning this subject.

There has been evidence of transmigration in studies involving electron microscopic examination of tissue residues or urine of humans in which exposure was assumed to be via the gastrointestinal route (*1,2*) or in animals following introduction of asbestos into the lumen of the GI tract (*3–8*). On the other hand, there has been no evidence of penetration in one study involving electron microscopic examination of the fiber content of human urine (*9*) and in several studies in which tissue residues were examined by electron microscopy following oral administration of asbestos to various species of animals for various periods of time (*10–13*).

Moreover, in those studies with positive results, there has been conflicting evidence concerning the dimensions of fibers which transmigrate, with Sebastien et al. (*8*) reporting preferential passage for long fibers and Cook and Olson (*2*) reporting greater transmigration of shorter fibers. The available data are inconclusive due to several factors which complicate the interpretation and comparison of the results of the studies involving electron microscopic examination of the fiber content of tissue residues or biological fluids. In several of the studies in which there was no evidence of widespread transmigration, the sensitivity of the analytical technique was not well characterized and it is possible that the method was not sufficiently sensitive (*10,11*). Alternatively, fibers may have been lost during sample preparation.

It is also extremely difficult to avoid contaminating samples from external sources. In some cases, there may be contamination that is not monitored in blank sample preparation and analysis. For example, in a study conducted by Carter and Taylor (*1*) amphibole fibers were identified in ashed tissue samples of residents of Duluth (where concentrations of up to 100×10^6 fibers/L have been measured in the drinking water supply). However, it is possible that the tissue samples of the Duluth residents may have been contaminated since it has been previously reported that the formalin used to fix autopsy specimens in some Duluth hospitals was diluted with city tap water containing amphibole asbestos fibers (*14*). There is also the possibility of cross contamination from the gut lumen in the animal studies designed to examine fiber content of tissue residues following oral administration of asbestos, particularly since asbestos fibers adhere firmly to the gut surface; scanning electron microscopy has revealed the presence of fibers on the surface of the gastrointestinal tract, even after vigorous

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washing of the mucosa at autopsy (*11*). In some of the studies, there was insufficient time between feeding of the asbestos and killing of the animals to allow clearance of fibers from the gastrointestinal tract (*7*). In addition, at autopsy, it is difficult to avoid contamination of tissues by fibers which may have adhered to the fur of the animal during feeding. As a result, the fiber content of tissues in the asbestos-fed animals may be higher than that in the control animals, due to contamination. In several of the studies reporting positive results, no attempt was made to replicate fiber counts, and there were relatively few control subjects or animals (*2,8*).

There have also been several studies in which thin samples of the gastrointestinal mucosa, rather than bulk tissue residues, have been examined for fiber content by electron microscopy following introduction of asbestos into the lumen of the GI tract of animals (*10,15–17*). The results of these studies have also been contradictory; fibers have been identified in epithelial cells and the lamina propria in some but not all of these investigations. However, only small areas of tissue can be examined in this manner and it has been suggested that fibers may be forced into (*11,16*) or dragged from the cells during thin section preparation. Similarly, the results of studies concerning the effects of ingested asbestos on proliferation and other biochemical parameters in epithelial cells of the gastrointestinal tract have also been contradictory (*11,18–21*).

Although fibers have been identified in tissue residues or biological fluids of animals and humans ingesting asbestos, there has been no conclusive confirmatory evidence of a tissue response associated with penetration of the gastrointestinal epithelium. Jacobs et al. (*17*) observed light and electron microscopic evidence of cellular damage in the intestinal mucosa of rats fed 0.5 or 50 mg of chrysotile per day for 1 week or 14 months. However, most of the changes were nonspecific and are commonly observed in the mucosae of control animals. Such changes may have occurred in the absence of actual fiber penetration; in fact, no fibers were detected in the mucosa of the treated animals upon examination by electron microscopy. The presence of "iron-containing" macrophages in the duodenal and ileal mucosae of baboons fed asbestos for up to 5 years has been reported; however, few data were presented concerning the study protocol (*22*). Confirmation of such a pathological response would help to verify that fibers in the gastrointestinal wall or other tissues in previous studies were not present due to contamination from the gut lumen or from exogenous sources which may have occurred during tissue processing.

Experimental Investigation and Results

We have, therefore, been conducting animal studies to investigate the tissue response associated with the presence of asbestos fibers in the wall of the intact gastrointestinal tract. In our first experiment, histopathological sections of duodenal tissues of two 200 g Wistar rats were examined by light microscopy 4 days following the injection of 0.1 mL suspensions of UICC amosite fibers in physiological saline into the wall of the duodenum during laparotomy. A 10 mL volume of the upper layer of a solution of 3.9 μg of UICC amosite in 20 mL of physiological saline was used as the stock solution for the injections. This is an nonphysiological route of administration and does not simulate the exposure of man to ingested asbestos. However, this experiment was conducted solely to investigate and characterize the short-term tissue response associated with the presence of amosite in the wall of the gastrointestinal tract.

Granulomas which were characterized by dense masses of macrophages were present at the sites of injection of amosite; intracellular crystals with the polarizing characteristics of amosite were clearly visible. A smaller and more localized tissue reaction was evident at the sites of injection of physiological saline in two control animals. These granulomas were characterized by few capillaries and fibroblasts and relatively scanty macrophages.

Having characterized the tissue response associated with the presence of amosite in the wall of the gastrointestinal tract, intestinal tissues of Wistar rats were examined by light microscopy for pathological changes following the ingestion of asbestos. Although there may be gastrointestinal-induced changes in ingested fibers, it seems likely that penetration of amosite into the gut wall would provoke a macrophage response which would result in infiltration of macrophages, since asbestos fibers induce a well-marked granulomatous condition in the lungs and since a similar response was evident in the wall of the gastrointestinal tract several days after the injection of amosite in this study. However, there was no evidence of a macrophage response or other pathological changes in the small intestine of animals 5 days following administration of 100 mg UICC amosite by gavage daily for 5 days.

Therefore, there was no pathological evidence of penetration of amosite asbestos into the gastrointestinal mucosa of Wistar rats, based on examination by light microscopy. Although the method employed in this investigation does not preclude entirely the possibility of limited penetration of small fibers, these results are consistent with the lack of widespread transmigration reported in several studies involving electron microscopic examination of tissue residues following oral administration of asbestos to various species of animals for various periods of time (*10–12*).

We have also examined in a preliminary fashion, the extent of transmigration in regions of ulceration. This is an area of considerable interest, particularly in light of the fact that it is estimated that up to 10% of all males between the ages of 20 and 50 have areas of intestinal mucosal damage (*23*). A 100 mg portion of UICC amosite suspended in corn oil was administered by gavage to six female Wistar rats daily for 2 days; six control rats received a similar volume of corn oil at the same time. On the third day, 10 mg/kg indomethacin was administered by gavage to both asbestos-treated and control animals to induce ulcers. The asbestos-treated animals received a further 25 mg UICC amosite on the same day and daily thereafter until they were killed sequentially at intervals of approximately 24, 48, 54, 72, 96 and 120 hr following indomethacin administration. The indomethacin-control group received similar volumes of corn oil and were killed on the same schedule. At postmortem, areas of the gastrointestinal tract with visible signs of ulceration were removed and processed for histological examination by light microscopy. No intracellular fibers were observed upon polarizing light microscopic examination of the areas of ulceration.

Conclusions

These preliminary results indicate that the gut wall of rats may present an effective barrier to the penetration of asbestos even under conditions of loss of the epithelium. However, there are several limitations inherent in this investigation and additional studies are underway. For example, the administration period may not have been sufficiently long or further study involving electron microscopic examination of macrophages in the vicinity of gastrointestinal ulcers might reveal the presence of fibers of sizes which are below the limit of resolution of the light microscope. In our further studies, mucosal cells of the intact GI tract will be examined by electron microscopy for pathological evidence of fiber penetration following prolonged oral administration of asbestos in combination with a low-fiber diet. Similarly, macrophages in the vicinity of gastrointestinal ulcers in both acute and chronic stages will be examined for the presence of fibers by electron microscopy. This will be combined with an experiment to determine the likelihood of extraction of fibers during preparation of thin tissue sections.

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REFERENCES

1. Carter, R. E., and Taylor, W. F. Identification of a particular amphibole asbestos fiber in tissues of persons exposed to a high oral intake of the mineral. Environ. Res. 21: 85–93 (1980).
2. Cook, P. M., and Olson, G. F. Ingested mineral fibers: elimination in human urine. Science 204: 195–198 (1979).
3. Hallenback, W. H., and Patel-Mandlik, K. J. Presence of fibers in the urine of a baboon gavaged with chrysotile asbestos. Environ. Res. 20: 335-340 (1979).
4. Patel-Mandlik, K. J., Hallenback, W. H., and Millette, J. R. Asbestos: A modified preparation of tissue samples for analysis by electron microscopy; 2. Presence of fibers in tissues of a baboon fed chrysotile asbestos. J. Environ. Pathol. Toxicol. 2: 1385–1395 (1979).
5. Patel-Mandlik, K.J., and Millette, J. R. Evidence of migration of ingested asbestos into various baboon organs. Scanning Electron Microscopy 1: 342–354 (1980).
6. Cunningham, H. M., and Pontefract, R. D. Asbestos fibers in beverages and drinking water and tissues: their passage through the intestinal wall and movement through the body. J. Assoc. Offc. Anal. Chem. 56: 976–981 (1973).
7. Cunningham, H. M., Moodie, C. A., Lawrence, G. A., and Pontefract, R. D. Chronic effects of ingested asbestos in rats. Arch. Environ. Contam. Toxicol. 6: 507–513 (1977).
8. Sebastien, P., Masse, R., and Bignon, J. Recovery of ingested asbestos fibers from the gastrointestinal lymph in rats. Environ. Res. 22: 201–216 (1980).
9. Boatman, E. Analyses of urines from residents drinking water containing asbestos in the Pacific Northwest. Paper presented at the U.S. Summary Workshop on Ingested Asbestos, Cincinnati, October 13-14, 1982.
10. Gross, P., Harley, R. A., Swinburne, L. M., Davis, J. M. G., and Greene, W. B. Ingested mineral fibers. Do they penetrate tissue or cause cancer? Arch. Environ. Health 29: 341–347 (1974).
11. Bolton, R. E., Davis, J. M. G., and Lamb, D. The pathological effects of prolonged asbestos ingestion in rats. Environ. Res. 29: 134–150 (1982).
12. Hallenback, W. H., Markey, D. R., and Dolan, D. G. Analyses of tissue, blood, and urine samples from a baboon gavaged with chrysotile and crocidolite asbestos. Environ. Res. 25: 349–360 (1981).
13. Bolton, R. E., and Davis, J. M. G. The short-term effect of chronic asbestos ingestion in rats. Ann. Occup. Hyg. 19: 121–128 (1976).
14. Auerbach, O., Hammond, E. C., Selikoff, I. J., Parks, V. R., Koslow, H. O., and Garfinkel, L. Asbestos bodies in lung

parenchyma in relation to ingestion and inhalation of mineral fibers. Environ. Res. 14: 286–304 (1977).
15. Storeygard, A. R., and Brown, A. L. Penetration of the small intestinal mucosa by asbestos fibers. Mayo Clin. Proc. 52: 809–812 (1977).
16. Westlake, G. E., Spjut, H. J., and Smith, M. N. Penetration of colonic mucosa by asbestos particles. Lab. Invest. 14: 2029–2033 (1965).
17. Jacobs, R., Humphrys, J., Dodgson, K. S., and Richards, R. J. Light and electron microscope studies of the rat digestive tract following prolonged and short-term ingestion of chrysotile asbestos. Brit. J. Exptl. Pathol. 59: 443–543 (1978).
18. Epstein, S. S., and Varnes, M. The short-term effects of ingested chrysotile asbestos on DNA synthesis in the pancreas and other organs of a primate. Experentia 32: 602–604 (1976).
19. Jacobs, R., Dodgson, K. S., and Richards, R. J. A preliminary study of biochemical changes in the rat small intestine following long-term ingestion of chrysotile asbestos. Brit. J. Exptl. Pathol. 58: 541–548 (1977).
20. Amacher, D. E., Alarif, A., and Epstein, S. S Effects of ingested chrysotile on DNA synthesis in the gastrointestinal tract and liver of the rat. Environ. Health Perspect. 9: 319–324 (1974).
21. Amacher, D. E., Alarif, A., and Epstein, S. S. The dose-dependent effects of ingested chrysotile on DNA synthesis in the gastrointestinal tract, liver and pancreas of the rat. Environ. Res. 10: 208–216 (1975).
22. Webster, I. The ingestion of asbestos fibers. Environ. Health Perspect. 9: 199–200 (1974).
23. Best, C. H., and Taylor, N. B. The Physiological Basis of Medical Practice, 8th ed. Williams and Wilkins, Baltimore-Toronto, 1967.