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MALIGNANT PERITONEAL MESOTHELIOMA IN A 17-YEAR-OLD BOY WITH EVIDENCE OF PREVIOUS EXPOSURE TO CHRYSOTILE AND TREMOLITE ASBESTOS

ALBERTO ANDRION, MD, SILVANO BOSIA, MD, LUIGI PAOLETTI, MD, ELDA FEYLES, MD, CLAUDIO LANFRANCO, MD, DONATA BELLIS, MD, AND FRANCO MOLLO, MD

We describe a case of malignant peritoneal mesothelioma arising in a 17-year-old boy. The diagnosis was based on a comprehensive study including light microscopy, histochemistry, immunohistochemistry, evaluation of the clinical course, and autopsy examination. Analytical transmission electron microscopy showed a concentration of 510,000 asbestos fibers/g dry lung tissue. The fibers were represented by chrysotile (62%) and tremolite (38%) asbestos. About 40% of the total fibers were longer than 5 μ m. The presence of tremolite fibers was probably due to environmental exposure to contaminated cosmetic talc. This is the first reported case of pathologically proven exposure to asbestos dust in malignant mesothelioma of childhood and adolescence. HUM PATHOL. 25:617-622. Copyright © 1994 by W.B. Saunders Company

Most malignant mesotheliomas (MMs) occur in adults, and many patients have a history of asbestos exposure with a

documented latency period of two to five decades.¹ In the rare MMs that do occur in childhood and adolescence asbestos has not been identified as an important risk factor. Indeed, possible exposure is mentioned in only two instances, and the mineral was not pathologically shown in any of the studied subjects.^{2,3} In the present case we established the presence of chrysotile and tremolite asbestos fibers in the lung tissue of a 17-year-old boy with malignant mesothelioma of the peritoneum.

CASE REPORT

Clinical History

A previously healthy 17-year-old boy, a nonsmoker, was referred to the City Hospital, Asti, Italy, in May 1991 with a 1-month history of abdominal discomfort. On physical examination the abdomen was distended and tender, suggesting the presence of ascitic effusion. All laboratory investigations were within normal limits except for a slightly elevated white blood cell count with an increase in the number of eosinophils (25%). A computed tomography scan confirmed ascites, whereas all abdominal organs were normal. After paracentesis endoscopic examination showed a peritoneal cavity studded with myriads of small nodules identical to those of carcinomatous peritonei. Microscopic examination of the ascitic fluid and biopsy samples was consistent with MM. Subsequent chemotherapy with vincristine, carboplatin, and epidoxorubicin was unsuccessful. The patient experienced recurrent ascites, pancytopenia, and dramatic weight loss. He died of progressive disease 8 months after the onset of symptoms. Autopsy examination confirmed the original diagnosis of MM.

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Key words: mesothelioma, peritoneum, childhood tumors, asbestos, ultrastructure, immunohistochemistry, environmental pathology, cosmetic talc.

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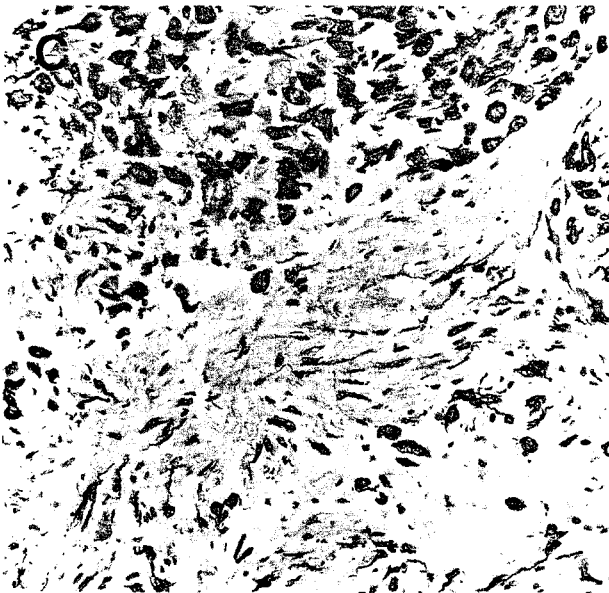
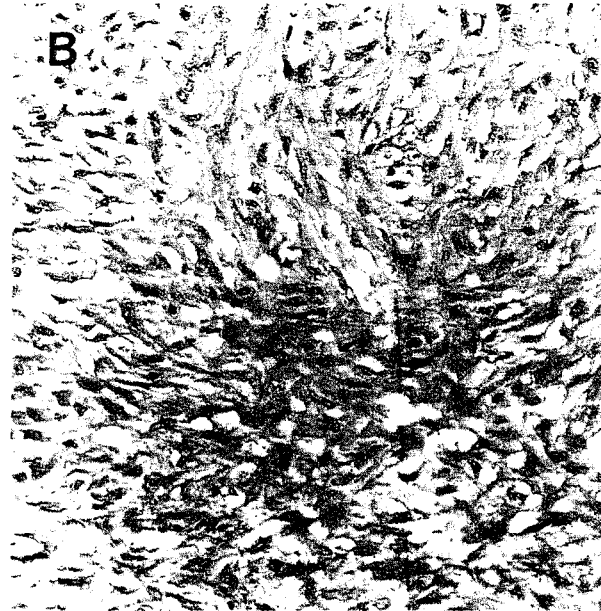
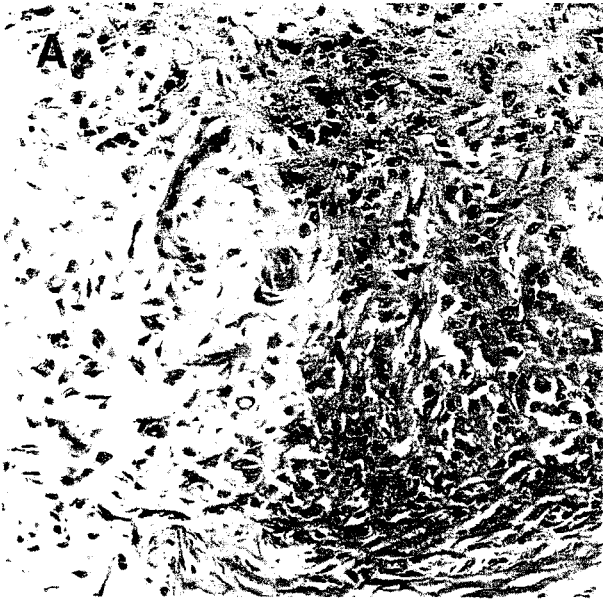


FIGURE 1. (A) Irregular spaces lined by cuboidal tumor cells are intimately associated with myxoid areas. (Hematoxylin-eosin stain; original magnification $\times 170$.) (B) Fibrosarcomatous pattern. (Hematoxylin-eosin stain; original magnification $\times 170$.) (C) Epithelial-like and spindle tumor cells showing keratin reactivity. (Anti-keratin/35-Beta-H11/ABC immunostain; original magnification $\times 200$.)

Pathological Findings

Endoscopic biopsies taken from the peritoneal nodules yielded small fragments of soft, tan to yellow-gray tissue. Microscopically, the tumoral specimens were composed of round to polygonal epithelial cells lining irregularly branching spaces, grouped in solid sheets, or dispersed in a prominent myxoid stroma (Fig 1, upper left). Not infrequently, fibrosarcomatous areas were seen (Fig 1, upper right). The bulk of the extracellular matrix and the cytoplasm of many epithelial cells stained with PAS and alcian blue. The reactivity was almost entirely abolished by predigestion with diastase or hyaluronidase, respectively. Sections from paraffin-embedded material were used for immunohistochemical studies. They were treated according to the avidin-biotinylated peroxidase complex procedure.⁴ The following series of reactions was performed: low molecular weight keratin-AE1 (Biogenex, San Ramon, CA, 1:150), CEA monoclonal (Dako, Glostrup, Denmark, 1:160), Leu-M1 (Becton-Dickinson, Mountain View, CA,



FIGURE 2. Diffuse neoplastic nodularity and massive induration of the omentum.

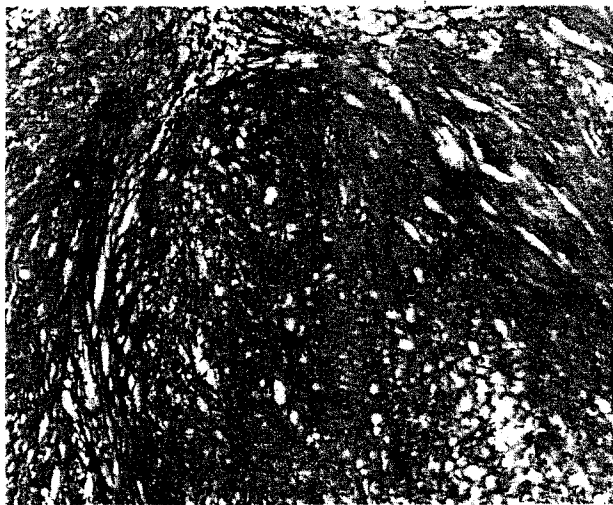


FIGURE 3. A poorly cellular dense fibrous "desmoplastic" area of tumor. (Hematoxylin-eosin stain; original magnification $\times 125$.)

1:4), B72.3 (Biogenex, 1:160), Ber-EP4 (Dako, 1:100), HMFG-2 (Serotec, Kidlington, UK, 1:300), smooth-muscle actin (Dako, 1:300), and vimentin (Dako, 1:150). Appropriate positive and negative tissue controls as well as internal controls were used. The epithelial tumoral cells together with many fibrosarcomatous elements were intensely labeled by keratin monoclonal antibody (Fig 1, bottom). Vimentin and smooth-muscle actin immunostains were positive and had the same topographic distribution within the tumor as that observed for keratin. Immunoreaction with anti-HMFG-2 antibody showed membrane staining in some epithelial and sarcomatous cells. Immunostains against CEA, Leu-M1, B72.3, and Ber-EP4 were negative.

Autopsy Findings

The abdominal cavity contained 6 L of bloody stained fluid and showed multiple confluent nodules of the peritoneal surface with massive induration of the omentum (Fig 2). Extensive visceral adhesions with encasement of transverse, descending, and sigmoid colon were seen. There was bilateral pleural effusion with diffuse neoplastic thickening of the parietal pleura on the left side. No solid organ primary site was found. The neoplastic component was microscopically identical to the original abdominal tumor except for the presence of fibrosarcomatous areas showing prominent desmoplasia (Fig 3). Microscopic examination of both histological sections of pulmonary tissue and sediment from digested lung failed to show asbestos bodies.

Occupational and Environmental History

The patient was born and lived in a rural area (vineyard cultivation). He attended school until the age of 14. At the

age of 15 he worked for 2 months in a plant that manufactured plastic tools. From the age of 16 until hospitalization he was employed as construction worker. The patient said that during this period he had only once sawed a sheet of asbestos cement using a protective mask. Among the next of kin, none had occupational exposure to asbestos. A large asbestos cement tank filled with water was present in the rural home where the boy lived. The patient's father stated that the tank water had never been used for drinking. There was no history of radiation or drug assumption. Finally, the boy's mother remembered that her son, from the age of 9 until about the age of 12, had a curious habit, ie, he used large quantities of cosmetic talc daily.

Mineral Analysis of Lung Tissue

The study of the mineral particulate extracted from lung tissue samples, according to a previously described procedure,⁵ was carried out with a Philips 430 analytical transmission electron microscope (ATEM) equipped with an EDAX x-ray energy dispersion spectrometer. Fragments of lung tissue were dehydrated, weighed, and oxidized in 1 mb of atomic oxygen plasma until completely incinerated. The remaining mineral particulate matter was collected by suspension in pre-filtered, particle-free deionized water. The suspension was then filtered through 0.45- μ m pore-size cellulose membrane filters. The particles remaining on the filter surface were then transferred onto carbon-coated copper grids for ATEM analysis. The fiber concentration in the lung parenchyma was calculated by the dry tissue weight, the total number of observed fibers, and the percentage of the analyzed membrane filter.

Asbestos mineral was found at a concentration of 510,000 fibers/g of dry lung tissue. Table 1 illustrates the main characteristics of the fiber burden in the pulmonary tissue. Sixty-two percent of fibers were identified as chrysotile asbestos (Fig 4, upper left); the nature of these fibers was confirmed by comparing their diffraction patterns and x-ray spectrographs (Fig 4, upper right) with appropriate controls (chrysotile samples, National Institute for Occupational Safety and Health, USA) (Fig 5A). The other fibers (38%) showed a different morphology consistent with amphibole asbestos on the basis of their selected-area electron diffraction patterns (Fig 6). The analysis of the x-ray spectrographs of these fibers, when compared with standard spectrographs from NIOSH tremolite samples (Fig 5B), made it possible to identify the bulk of these structures as tremolite fibers (Fig 4, bottom). In addition to asbestos fibers, many talc particles were seen with a concentration of about 720,000/g of dry lung tissue.

DISCUSSION

Although the occurrence of MMs in people under 20 years of age is extremely rare and subject to high diagnostic unreliability,^{2,3} evidence suggests that the lesion described in this report is consistent with MM. The tumor diffusely involved the peritoneum with encasement of abdominal organs, accompanied by recurrent ascites and spreading to pleural cavity. The histological features showed a combination of epithelial and fibrosarcomatous elements that strongly suggested the

TABLE 1. Asbestos Fibers in Lung Tissue

Type of Fibers	Counted	Total Fibers (%)	Concentration in Dry Lung Tissue	Length		Diameter		Fibers < 5 μ m	Fibers > 5 μ m
				Mean	Range	Mean	Range		
Chrysotile	26	62	316,000 fibers/g	12 μ m	1.5-20 μ m	0.3 μ m	1-0.05 μ m	55%	45%
Tremolite	16	38	194,000 fibers/g	5 μ m	0.5-15 μ m	0.1 μ m	1-0.01 μ m	70%	30%

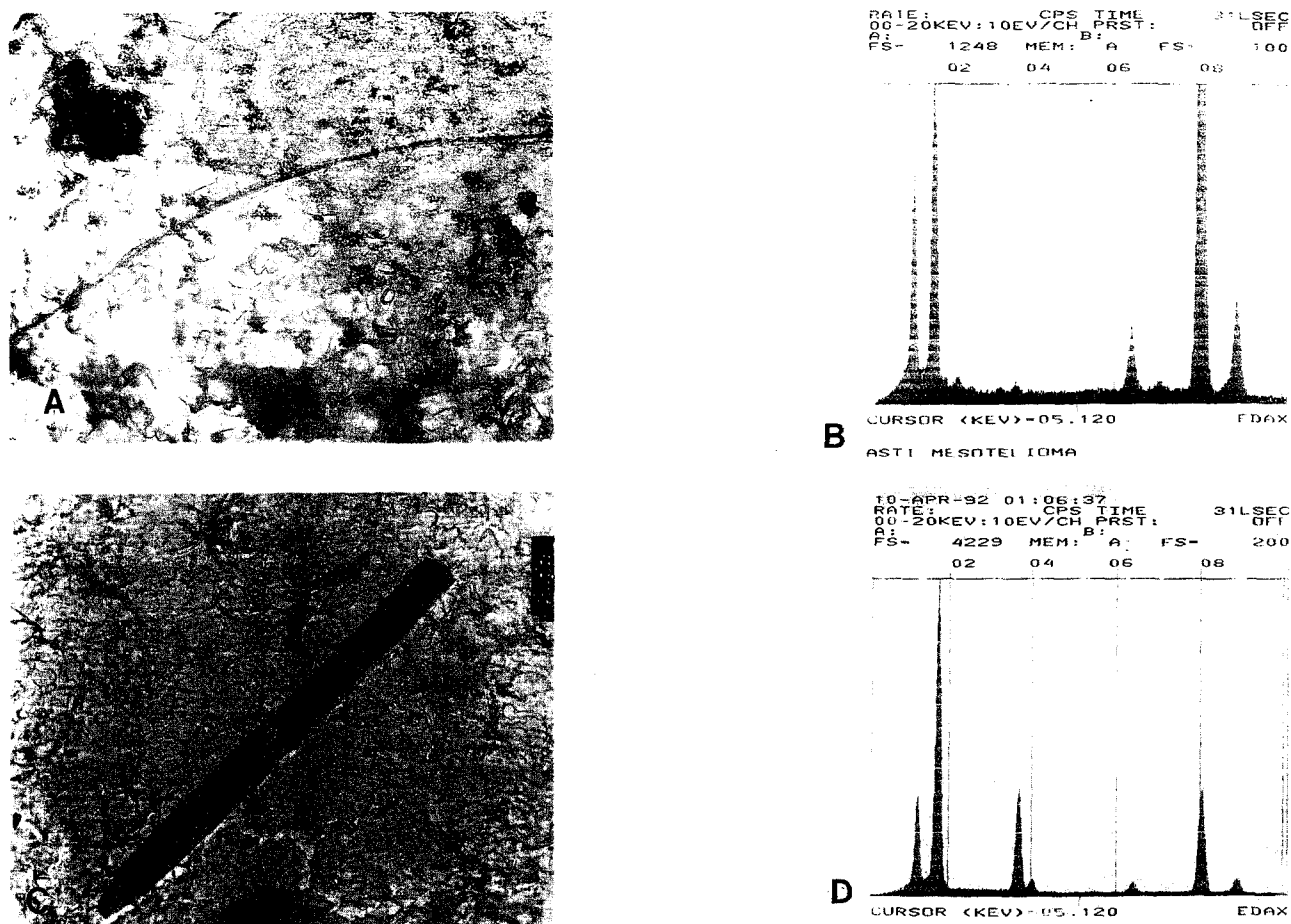


FIGURE 4. Asbestos fibers extracted from lung tissue samples. (A) Transmission electron microscopic appearance of chrysotile fiber (original magnification $\times 16,000$) and (B) the related x-ray energy-dispersive plot. (C) Transmission electron microscopic appearance of tremolite fiber (original magnification $\times 8,500$) and (D) the related x-ray energy-dispersive plot.

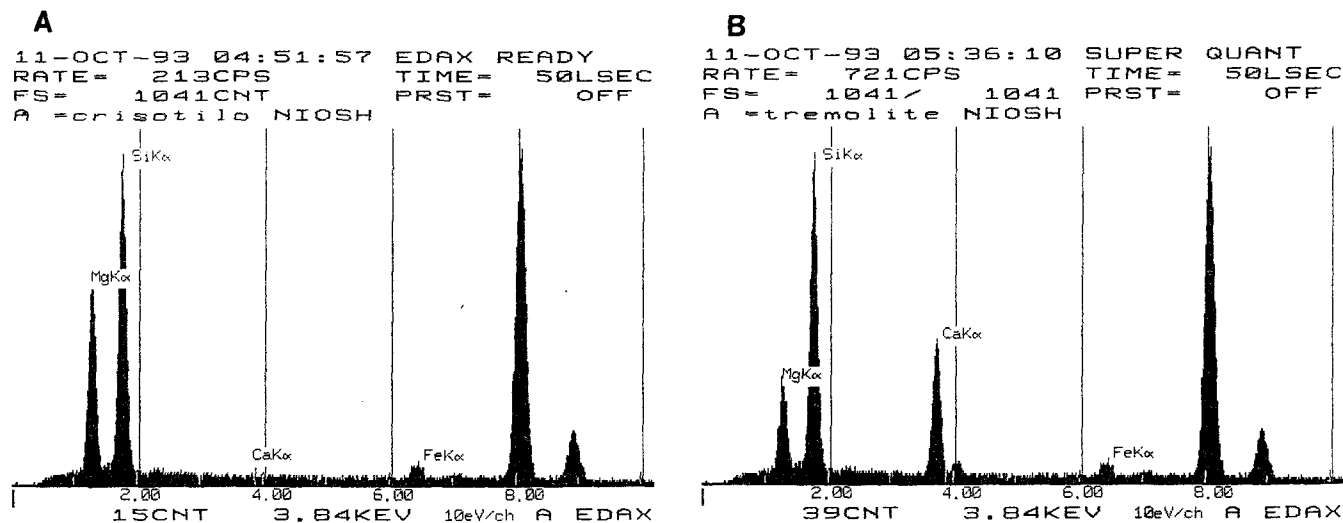


FIGURE 5. X-ray energy-dispersive plots of control assays (asbestos samples provided by National Institute for Occupational Safety and Health, USA). (A) Chrysotile asbestos and (B) tremolite asbestos.



FIGURE 6. Selected-area electron diffraction pattern obtained from a single fibril of presumptive tremolite asbestos fibers detected in the lung.

biphasic form of MM.⁶ The results of the histochemical stains, characterized by the presence of PAS-positive diastase-sensible and alcian-positive hyaluronidase-sensible intracellular and extracellular material, were typical of MM.⁶ Immunohistochemical reactivity of both epithelial and fibrosarcomatous components for low molecular weight keratin, vimentin, and smooth-muscle actin; the faint reaction for HMFG-2; and lack of positivity for CEA, Leu-M1, B72.3, and Ber-EP4 confirmed the diagnosis of MM.⁷⁻⁹ Finally, the length of survival from the time of the first symptoms was consistent with that reported for the biphasic type of MM.¹⁰

Childhood MM has been considered in the past to be a curiosity.¹¹ To the best of our knowledge world literature has reported, to date, no more than 80 proven cases of this tumor.^{2,3,12-14} In only two instances has a history of possible exposure to asbestos been mentioned.² On the basis of the reported figures, it has been suggested that asbestos is insignificant as an etiologic agent of these neoplasms, and indeed factors other than asbestos, such as radiation, prenatal medications (isoniazid), and genetic susceptibility, may be implicated in the development of childhood MM.³ Accordingly, the reported cases of childhood MM also have been cited as evidence suggesting the existence of nonasbestos-related MM in adults.^{15,16} Nevertheless, on examining most of the original papers cited by a review article² it was seen that post-mortem examination was performed in only a few cases, the light microscopic search for pulmonary asbestos bodies was sporadic, and in no case was the mineral analysis of the particulate extracted from lung tissue samples performed. Moreover, investigations of the patients' previous exposure to asbestos minerals were often superficial or even absent.

In this study both the patient's history and the mineral analysis of the pulmonary tissue showed an environmental

and/or paraoccupational exposure to asbestos dust. However, because asbestos fibers may be found in the lungs of the vast majority of individuals living in industrialized countries one must be exceedingly cautious in establishing a cause and effect relationship between the mineral and the disease. Although no threshold below which an individual is not at risk has, as yet, been clearly identified,^{1,17} concepts such as the "one fiber theory," which maintains that one fiber of inhaled asbestos will cause cancer, are not supported by any reasonable evidence.¹⁸

The first question that arises relates to the evaluation of the fiber burden in the lung tissue. Appreciable variations in the analysis performance occur in different laboratories.¹⁹ It has therefore been suggested that the obtained values must be compared with the internal experience rather than with some generic standard or results from other laboratories.^{19,20} In the experience of our referring laboratory 84% of 85 forensic autopsies of subjects living in a highly polluted urban area and not affected by neoplastic diseases showed lung asbestos-fiber concentrations lower than 200,000/g dry tissue, and 16% had an asbestos burden ranging between 200,000 and 3,000,000 fibers/g.²¹ The overall figures were consistently higher than those found by the same laboratory in people from remote rural areas.²² Thus, it may be argued that the lung asbestos content of our patient (510,000 fibers/g) was unusual in a rural dweller and was similar to the lung asbestos concentrations found in urban residents belonging to the subgroup with the highest fiber burden.²¹

The second relevant question relates to the biological effects of different types of fibers. Accumulating evidence indicates that chrysotile probably is not associated with the occurrence of MM at low levels of exposure,¹⁸ whereas amphiboles, including fibrous tremolite, seem to be the major causative agents of this disease.^{1,18,19,23-25} Moreover, most investigators believe that fibers longer than 5 μ m are the key fibers in the pathogenesis of MM.^{19,25} In the present case chrysotile and fibrous tremolite represented 62% and 38% of the total fibers. Structures longer than 5 μ m were found in 45% of chrysotile and 30% of tremolite fibers. This means that, on the whole, about 40% of the total burden was represented by fibers having a critical length for carcinogenic potential. It is interesting to note that in the above-cited urban population²¹ the fiber length had a mean value of only 3 μ m and no case presented a burden of long fibers similar to that observed in our patient. The morphology of tremolite we found deserves attention because only x-ray spectrography was able to confirm its true nature. On the other hand, manufacturing processes, the biological environment, and the laboratory procedures are all factors that may at times lead to degeneration of the "normal" fiber structure.²⁶

Although chrysotile is used in a wide range of products present in the environment and may be considered as ubiquitous, fibrous tremolite is a noncommercial amphibole and relatively rare from a geological point of view. Moreover, there is wide demonstration that some types of talc may be contaminated by tremolite asbestos.^{27,28} Because many pulmonary talc particles were detected at the ultrastructural level the presence of tremolite was probably caused by inhaled cosmetic talc.

As far as the latency time is concerned, we may consider the induction period plausible. The interval between the onset of exposure and the onset of symptoms was 8 years. Little information is available regarding the biological effects of asbestos in young people.²⁹ Nevertheless, MM in adults can have a latency period shorter than 10 years.³⁰⁻³²

Although definite proof of the asbestos-related nature of this MM cannot be established with certainty in the absence of any other documented etiologic factors, it is difficult not to

draw the conclusion that the relationship between asbestos exposure and development of MM remains the most coherent explanation of the pathological event we observed. When MMs of childhood and adolescence are diagnosed an interdisciplinary approach in which pathologist interacts with primary-care physicians and other specialists would be of value for a better understanding of the disease.^{3,33}

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CORRESPONDENCE

Guidelines for Letters

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Helicobacter Pylori Infection and Follicular Gastritis in Childhood

To the Editor:—With reference to the article by Genta et al¹ published in *HUMAN PATHOLOGY* in June 1993, we have seen 122 gastric endoscopic biopsy specimens of infants and children (mean age, 3.5 + 1 years; male to female ratio, 3:1) in which gastritis was present.

In 62 of the 122 cases (50.9%) it was present as a chronic superficial gastritis, in 30 cases (24.5%) as a slight chronic superficial gastritis, and in 30 cases as a slight chronic atrophic

gastritis with slight activity. In these 92 cases (75.4%) *Helicobacter pylori* infection was not present. Only in 30 cases (24.6%) have we seen the *Helicobacter* infection. In seven of these 30 cases (23.3%) it was present as a follicular gastritis; the same pattern of follicular gastritis was present in 14 cases of gastritis without *Helicobacter* infection (15.2%; *P* was not significant by the Student's *t*-test). In 20 of 30 cases with *Helicobacter* infection it was seen as an active inflammatory component, but this activity was slight (neutrophils and eosinophils only in the lamina propria) without erosions or ulcerations in those cases with follicular gastritis. In the cases without a follicular component but with *Helicobacter* infection, in 15 cases (50%) it was noted as a slight activity and in five cases (16.6%) as an erosive gastritis with moderate atrophy, whereas in three cases (10%) it was noted as a superficial gastritis. All the biopsy specimens were obtained in the antrum.

In our experience the linkage between *H pylori* infection and follicular gastritis has been less frequent than that described by Genta et al¹ in their report. There is probably less chance of chronic antigenic stimulation exerted by the microorganism during childhood. Indeed, the presence of superficial gastritis or slight chronic atrophic gastritis with slight activity without follicular reaction shows that the *H pylori* in the early phases causes an acute inflammation with little epithelial damage and without a meaningful increment of the lympho-

