ASSOCIATION OF ASBESTOS AND BRONCHOGENIC CARCINOMA IN A POPULATION WITH LOW ASBESTOS EXPOSURE

MARTHA L. WARNOCK, MD, AND ANDREW M. CHURG, MD, PHD

Quantitative counts of ferruginous bodies were performed on digests of lungs from 100 control and 30 lung cancer patients. It was found that the lung cancer group had significantly higher levels, although only 1 patient was known to be occupationally exposed to asbestos. It is suggested that even extremely low levels of asbestos exposure may have a carcinogenic effect.

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THE ASSOCIATION OF OCCUPATIONAL EXPOSURE to asbestos and subsequent development of bronchogenic carcinoma has been well established.[4,18] It is generally assumed that this process requires exposure for long periods and/or to high levels of the fiber;[18] however, almost no data are available on the effect of low asbestos levels. This question has assumed importance with the report of Smith and Naylor[16] that ferruginous bodies* could be found in the lungs of 100% of adult patients if suitable extraction and concentration techniques were employed. Recent investigations using electron microscopic and electron-diffraction techniques have established beyond doubt that at least a few asbestos fibers can be found in the lungs of almost everyone in an urban population.[10]

During the course of an attempt to confirm the findings of Smith and Naylor in our local autopsy population, it was noted that several patients with bronchogenic carcinoma had high ferruginous body counts. This group of patients was then separated from the controls; more cases were studied retrospectively. It was found that the counts were significantly higher in the carcinoma group, even though only one patient had a history of occupational exposure to asbestos.

From the Department of Pathology, The Pritzker School of Medicine, The University of Chicago, Chicago, IL.

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Address for reprints: Martha L. Warnock, MD, Dept. of Pathology, 950 E. 59th St., Chicago, IL 60637.

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* Ferruginous body as used here refers to the iron-protein coated fiber seen by the light microscope. Asbestos fiber is the term used to indicate definite asbestos seen in the electron microscope. It is likely that not all ferruginous bodies have an asbestos core[6] (see Discussion).

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MATERIALS AND METHODS

Patient Selection

Samples were collected prospectively from 100 unselected autopsies of patients over 20 years old without lung cancer. In addition, samples were taken from 30 patients with lung cancer. Nine of these were included in the prospective study, and 21 were collected retrospectively by obtaining wet formalin-fixed stock on cases with lung cancer retrieved from autopsy files. In these cases only single samples were available; these were not designated as upper or lower lobes.

Histologic Studies

Histologic sections and complete autopsy protocols of all cases with lung cancer were reviewed to confirm the diagnosis of primary lung cancer. All lung cancers were classified by one of us (M.L.W.) according to the WHO nomenclature. Two to 10 hematoxylin and eosin stained sections, 6 μm thick and about 3 cm^2, were scanned systematically for the presence of ferruginous bodies to correlate with the quantitative estimates obtained by digestion. These sections were taken from parenchyma generally free of tumor.

Preparation of Samples for Ferruginous Body Counts

Samples of lung weighing 1.5–6 g were taken from both the upper and the lower lobe of one

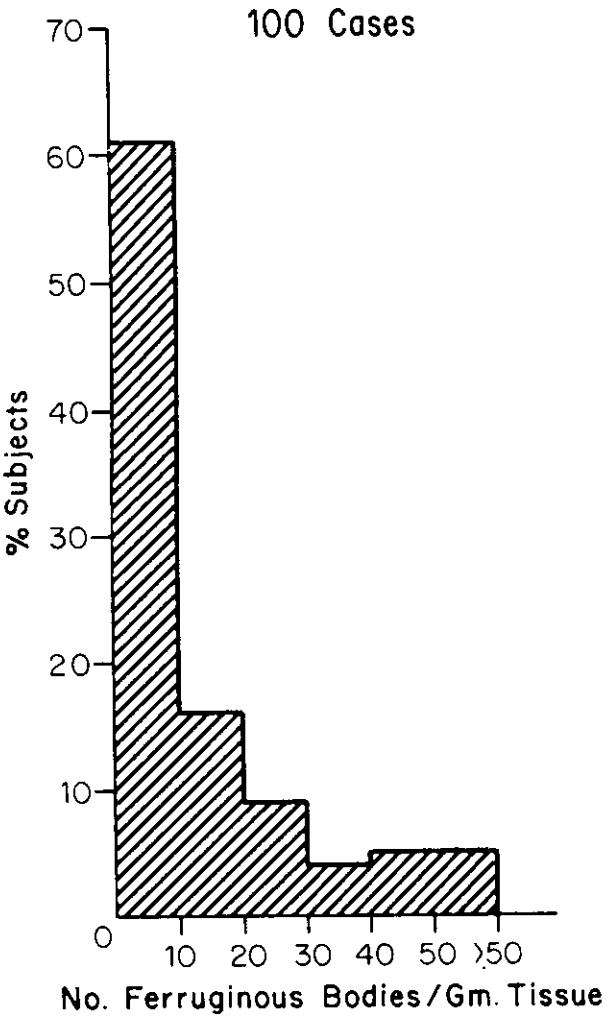

FIG. 1. Numbers of ferruginous bodies in lungs of control population (51 females, average age 56, range 21–88, and 49 males, average age 57, range 21–81).

and 8 or 27% (1 female and 7 males) had counts above 50/g. Comparison of this 27% and the 5% with counts greater than 50 in the control population gave a chi-square test (corrected for continuity, 1 degree of freedom) of 9.75, which is significant at the 0.005 level. (Because the comparison made was decided upon after examination of the data, the specific p value must be interpreted with caution.) Because the number of asbestos bodies may accumulate with age, we made another comparison of the data. The 64 control patients age 50 and over were compared with the 26 cancer patients age 50 and over. Four patients in the control group and 8 in the cancer group had counts greater than 50/g. A corrected chi-square of 7.61 is significant at the 0.01 level. Thus, when a control group similar to our cancer patients in age is used, the data still appear to differ significantly. Of the 8 patients with high counts, half were known smokers, one was a nonsmoker, and the history is unknown in 3. Since 50 bodies/g is an arbitrary dividing point based on inspection of the graphic data of Fig. 2, the role of the asbestos in lung cancer in the 4 intermediate cases is not clear. One had a history of occupational exposure to asbestos in shipyards during World War II. Three of the 4 in the intermediate group were smokers.

The average age of cancer patients with 0–10 asbestos bodies was 60, with a range of 33–80; the average age of patients with more than 50 bodies was 61, with a range of 53–68. If combined epidermoid and adenocarcinomas are counted both as adenocarcinomas and epidermoid cancers or if they are omitted from consideration, the frequency of epidermoid and adenocarcinomas is about 50% in both groups; no small cell undifferentiated cancers were found in the cases with high asbestos counts, although three occurred among the cases with low counts. Location of the tumor in the lung differed in the low and high groups: 17% of cases

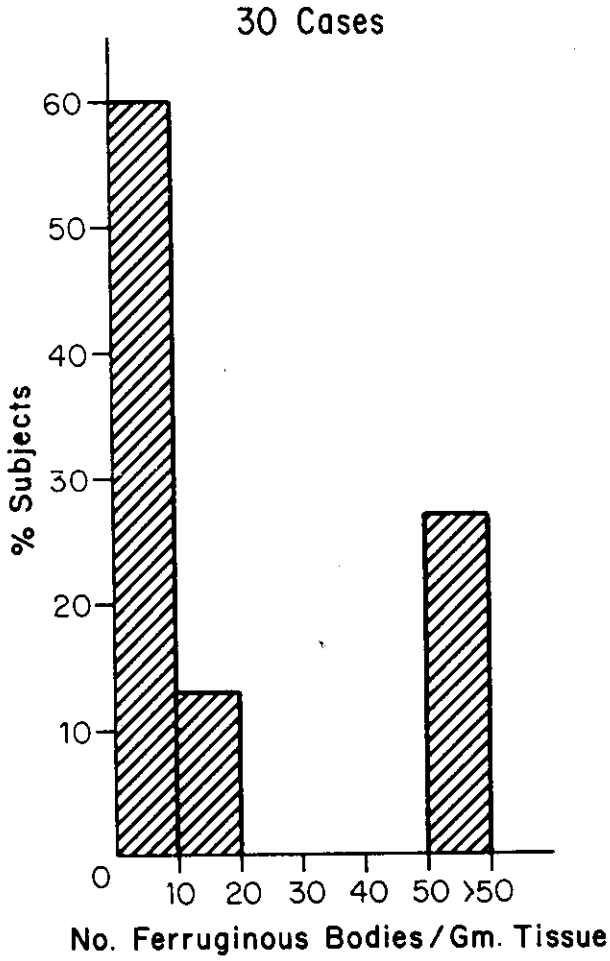

FIG. 2. Distribution of asbestos bodies in lungs of patients with carcinoma.

was found, however, that bodies on filters with very high counts were quite pleomorphic (Fig. 3A), and hence all types of ferruginous bodies were counted including those with a black central core. These are not counted by some investigators.[6,7]

Short asbestos fibers or fibrils with the typical morphological appearance of chrysotile (Figs. 3B and C) were identified in each of the cases of lung cancer with more than 50 bodies/g of tissue. Occasionally, long multifiber bundles, such as are shown in Figure 3C, were visible. No fibers were found in the preparations of plain Millipore filter or in digests of lung from five patients with 0–10 bodies/g. All of the fibers large enough to produce visible diffraction patterns with a 10-μm diffraction aperture showed the pattern typical of chrysotile (Fig. 3D).

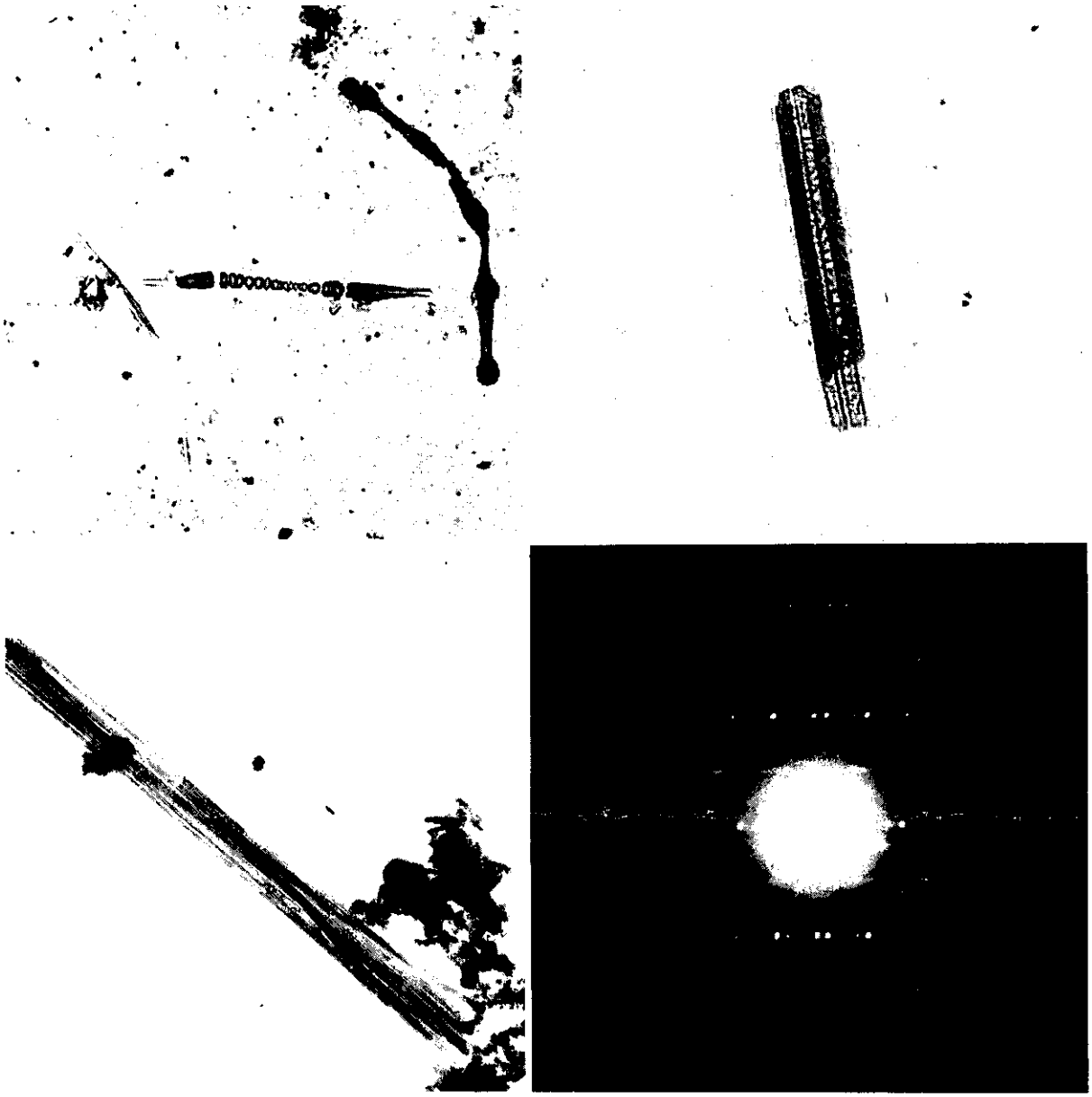

FIG. 3. A (*top left*). Light micrograph of ferruginous bodies collected on a Millipore filter, as described in the text. Note the great variety of morphological appearances (×200). B (*top right*). Appearance of short fragments of chrysotile in the electron microscope. Fibers of this type were seen in every case of carcinoma with greater than 50 bodies/g by light microscopy (×120,000). C (*bottom left*). Large fiber of chrysotile consisting of many filaments. This is the type of fiber described by Pooley[13] in occupationally exposed individuals; they were seen rarely in our material (×20,000). D (*bottom right*). Typical chrysotile electron diffraction pattern. Electron diffraction was used to confirm the presence of chrysotile in all the high count carcinoma cases.

cinoma; few of our sections showed more than five bodies, whereas theirs generally had many more.

The work of Pooley[13] also lends support to the idea that our high count patients did not have direct primary asbestos-handling exposure. In an electron microscopic study, he was able to demonstrate that primary asbestos workers (i.e. asbestos-processing factory workers, dockyard workers, etc.) generally had long single fibers, and also had a large proportion of multifilament strands in their lungs. His nonoccupationally exposed group generally had short single fibers, and few large aggregates. Our patients fit the latter classification. Other reports, too, indicate that fiber length and diameter may be important in determining carcinogenicity and may explain the low incidence of cancer found in Canadian chrysotile miners[11] and the high incidence in asbestos factory[3] and insulation workers.[14] In the future, measurements of fibers seen with the electron microscope may show a difference in preponderance of fiber sizes in asbestosis, bronchogenic cancer, mesothelioma, and exposed persons without disease.

It is interesting, however, that there is a large preponderance of males in our group of carcinoma patients with more than 50 bodies/g, which suggests occupational exposure, and that a high percentage of tumors was found in the lower lobe, as is the case with known asbestos-associated lesions.[8] Extremely detailed occupational histories in all lung cancer patients might clarify this problem.

Since it has been shown that asbestos and smoking have a multiplicative effect in causing lung cancer, even with fairly low exposures to asbestos,[3,5,14] it may be that even relatively small amounts of asbestos are important in carcinogenesis in patients who smoke. It has been suggested that the marked adsorptive capacity of asbestos may promote the persistence of carcinogenic hydrocarbons present in cigarette smoke.[2] Although we do not have smoking histories on all our patients, we assume that smoking is not the major factor influencing our results, since we do have smokers in both the high and low count lung cancer groups.

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