

Metsovo Lung: Pleural Calcification and Restrictive Lung Function in Northwestern Greece. Environmental Exposure to Mineral Fiber as Etiology¹

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Pleural calcifications are described in 122 of 268 (45.5%) inhabitants of four villages (Metsovo, Anilio, Milea, and Votonosi) in a small area of northwestern Greece (total population about 5000). All affected individuals are of one ethnic group, Vlachi. Calcifications were not noted in any of the 103 persons in the control group made up of 73 non-Vlachi inhabitants from the same and neighboring villages and 30 Vlachi from distant villages. The calcifications were seen in both sexes, equally, and their frequency increased with age, from 28.6% between 30 and 39 years to 81.0% in individuals over 70 years of age. When plaque development was extensive, a small restrictive pulmonary function defect was noted. Because of its prevalence in the Metsovo area we call this clinical pattern Metsovo lung. The identification of tremolite, related amphibole fibers, and traces of chrysotile fiber in settled dusts and soil specimens and of identical fibers in tissue specimens obtained at lung biopsy from 8 people with plaques supports the hypothesis that abestiform minerals are the agents responsible for these disease processes. Further, reports of the occurrence of mesothelioma and benign pleural effusions in inhabitants in the Metsovo area, along with the striking similarities to disease patterns observed in the Karain area of Turkey, add further weight to the hypothesis that mineral fiber(s) in the environment of the four villages are agent(s) in the etiology of Metsovo lung. © 1985 Academic Press, Inc.

INTRODUCTION

Diffuse bilateral pleural calcification frequently occurs in individuals exposed to asbestos (Selikoff, 1965). Although such exposures are most often occupational in nature, there have been reports of endemic pleural calcifications from Finland (Kiviluoto, 1960), Bulgaria (Burilkov and Michailova, 1970), Czechoslovakia (Navratil and Trippe, 1972), and southwest Turkey (Yazicioglu, 1976) in clearly nonoccupational settings. These scattered foci of pleural disease appear to be unrelated to the direct mining, milling, fabrication, or commercial use of asbestos. In all of the forementioned occurrences, plaques have been attributed to environmental exposure to chrysotile in Czechoslovakia, to anthophyllite + tremolite + sepiolite in Bulgaria, to anthophyllite in Finland, and to tremolite and chrysotile in Turkey.

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In South Africa and central Turkey, pleural changes (thickening in South Africa, thickening and plaque development in Turkey) have been associated with malignant mesothelioma as well (Wagner *et al.*, 1960; Artvinli and Baris, 1979). These changes occur in individuals without history of employment involving asbestos but rather are linked to environmental exposure to crocidolite in South Africa and erionite in Turkey. A recent report suggests that asbestos fiber may also play some role in the etiology of the diseases observed in central Turkey (Rohl *et al.*, 1982).

In 1969, during the antituberculosis campaign in Greece, it was found that the inhabitants of three neighboring villages of northwestern Greece, Metsovo, Anilio, and Milea, where there are no known asbestos outcroppings, mining, or any heavy industry, showed a high incidence of pleural calcification. This was re-evaluated in 1980. Bazas *et al.* (1981) reported that 28% of a selected subset of this population had signs of pleural calcification. This latter report, while highlighting these findings, offered no explanation for these occurrences although direct asbestos exposure (especially occupational) was ruled out as a factor in the etiology.

We now report clinical, roentgenological, and functional profiles of the disease we call "Metsovo lung." On the basis of analytical electron microscopic analysis of eight biopsies obtained at bronchoscopy, mineral fibers, some consistent with asbestiform tremolite, were present in the pulmonary tissues of these individuals. It is likely that this exposure is attributable to environmental exposure, with the fibers originating from local soils and rock outcroppings. This report may now be added to those which underscore the importance of mineral fiber exposure in a nonoccupational setting in the development of pleural disease.

BACKGROUND

Geological Setting

The villages of Metsovo, Anilio, and Milea are located within the Pindos ophiolite complex of Eocene age (~60 million years ago), in northwest Greece (Fig. 1). The region is mountainous, rugged in terrain, extensively faulted and folded, and represents the southern extremity of the European Alps. Metsovo and Anilio are situated approximately 2 km to the east of a regional fault trace that represents the remnants of a tectonic plate along which suboceanic lithosphere and upper mantle-derived peridotites, dunites, pyroxenites, and other mafic rock types have been thrust into contact with crustal schists and igneous rocks. The mafics and ultramafics have been extensively serpentinized (Institute for Geology and Subsurface Research, 1959; Montigny *et al.*, 1973).

Local drainage flows from the mountainous serpentinized highland (on the north-east), southward toward Metsovo and Anilio which lie on schists and granulites west of the serpentine body. Milea, some 15 km to the north of Metsovo, is located within the peridotite-serpentine complex. Many other ultramafic units occur within the area as well, e.g., olivine-gabbros. These are also extensively serpentinized and often occur intercalated within the ophiolitic melange (Montigny *et al.*, 1973).



FIG. 1. Location of study area. Shaded zone represents the study area. Details of the boxed area are shown. Major villages are indicated. Circles with centers represent "distant" villages.

The area has underfiles reflect unsorted mineral components crushed and pulverized particles. These are a

Although serpentine asbestos mining or krbestos mine is located, outcroppings of asbestos exploited commercially show pleural calcification scribed in the present

Regional Rock Types

Serpentine rock is fibrous in form, chrysotile, and is a commercial product. Serpentine is composed of a number of amphibole minerals, some of which are naturally asbestiform and some of which are not. The amphiboles described in the present study are aluminum-rich (high-pi

ing in South Africa. associated with malignancy (Rohrbaugh, 1979). These involving asbestos in South Africa fiber may also play a role (Rohrbaugh *et al.*,

as found that the Greece, Metsovo. mining, or extraction. This was re-selected subset of report, while high-exposures although not as a factor in

cles of the disease microscopic analysis is consistent with these individuals. exposure, with the report may now fiber exposure in

within the Pindos northwest Greece. heavily faulted and in the Alps. Metsovo regional fault trace suboceanic lithonites, and other igneous units (Institute of Geology, 1973).

and (on the north-south) and granulites of Metsovo, is ultramafic units also extensively melange (Mon-

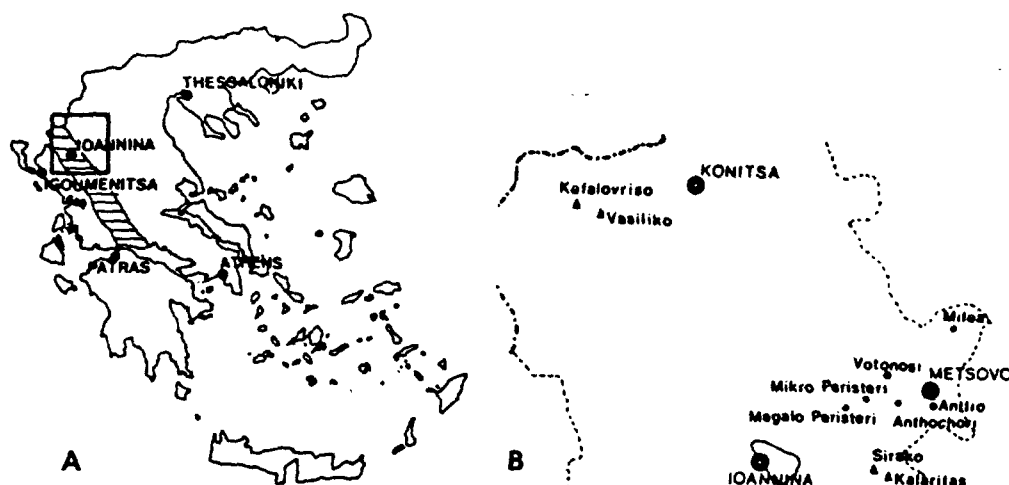


FIG. 1. Location of study area in Greece. (A) The Metsovo area shown on a map of Greece. The shaded zone represents the Pindos serpentine belt. For reference, the city of Ioannina is marked. Details of the boxed area are shown in (B). Villages in study are shown in relation to each other. Major villages are indicated by circle size. Solid circles represent villages where calcifications were noted; circles with centers represent villages where calcifications have not been found; solid triangles represent "distant" villages where no calcifications were found in Vlachi inhabitants.

The area has undergone Pleistocene alpine-type glaciation so that the soil profiles reflect unsorted and unconsolidated debris. The soils in the area also reflect mineral components from the underlying rock types. The forces of glaciation crushed and pulverized bedrock in places producing submicrometer-size mineral particles. These are also components within the soil profile.

Although serpentine bodies are hosts for chrysotile concentration, there is no asbestos mining or known outcroppings in the immediate area. The nearest asbestos mine is located some 80 km northeast (near Kozani). There are known outcroppings of asbestos some 30–40 km north of this area, yet they are not exploited commercially. The inhabitants of villages near these deposits do not show pleural calcification in the manner or extent exhibited by the villagers described in the present study.

Regional Rock Types as Sources of Mineral Fiber

Serpentine rock is composed of a number of minerals, including chrysotile. Fibrous in form, chrysotile represents the most common asbestos fiber in world commerce. Serpentine rock, and the associated ultramafics, may also contain a number of amphibole minerals, many of which may also be fibrous in form (either naturally asbestiform or "fibrous" by processes of comminution (able to reduce into acicular cleavage fragments).

The amphiboles described from this area include tremolite, anthophyllite, and aluminum-rich (high-pressure) phases, as well as common hornblende. Both ser-

pentinized and unserpentinized rock types may act as a source of mineral fiber for the environment (Rohl *et al.*, 1977; Puffer *et al.*, 1983).

The Populations Affected

Of the villages included in this study, Metsovo is the principal one with a population of some 3500 people. Anilio, Milea, and Votonosi are smaller in size with populations of between 1000 and 1500. The principal occupations among the men are shepherding, woodcutting, and carpentry. The women are occupied with housekeeping chores as well as handcrafting, e.g., wool knitting. Although Greek, these inhabitants belong to a different ethnic subgroup (Vlachi) from their closest neighbors.

MATERIALS AND METHODS

Mineral dust analyses. Soil and settled dust specimens were examined by polarized light microscopy in the standard manner utilizing immersion oils of known indices of refraction. The specimens were further examined by continuous scan X-ray diffraction following the standard protocol for our laboratory (Environmental Sciences Laboratory, Mount Sinai School of Medicine). Thirty-seven major reflections were characterized in the scan range and those with intensities $3\times$ greater than background were assigned a d -spacing value. Analysis of these specimens was also carried out with a JEOL 100 CX analytical electron microscope (AEM) interfaced with a Tracor Northern TN 2000 Energy Dispersive X-Ray Spectrometry System (EDX). Water-fractionated specimen splits were pipetted onto carbon-coated, Formvar-covered, TEM nickel locator grids. These were allowed to evaporate to dryness, recoated with carbon, and examined by AEM. Morphological, structural, and chemical information was obtained as photographic records and selected area electron diffraction patterns and by chemical probing of single particles.

Tissue analyses. We studied nine specimens of lung tissue biopsies, obtained at fiberoptic bronchoscopy, from inhabitants of Metsovo who suffered with "Metsovo lung." These specimens, averaging approximately 4 mm^3 in volume, were withdrawn from their Formalin containers and placed in a 5% KOH solution, set in a hot water bath maintained at 80°C , and allowed to digest. Several cycles of water washing were required for complete cleaning of digestates. Residues were dispersed by sonication for approximately 3 sec and micropipetted onto appropriate TEM substrates for examination by AEM. The analytical technique has been previously described (Langer and McCaughey, 1982). Of the nine, only eight specimens were analyzed, as no residues were recovered from one specimen. The inorganic residues recovered were scant.

Clinical data. We have examined chest roentgenograms of 246 inhabitants of Metsovo, Anilio, and Milea (Table 1) and 125 inhabitants from two "control" areas. The first consisted of 95 individuals from the neighboring villages of Votonosi, Anthochori, Megalo Peristeri, and Micro Peristeri; the second group was made up of 30 Vlachi persons from other, more distant villages. Twenty-two inhabitants of Votonosi, who were also Vlachi, were eventually grouped together

with Metsovo, Anilio (Table 1).

The chest X rays of the General Hospital (27) voluntarily took part in the clinical data are of 98 persons from Metsovo, a complete clinical examination by the British MRC questionnaire on the Aetiology of Chronic Tuberculosis; a complete spirometry data which included the standards of 98. Additionally, we have the location and extent of the disease.

The spirometric data were obtained in 1 sec, FEV₁ (1971).

Mineral Studies

Representative specimens from Metsovo village were examined by continuous scan X-ray diffraction of the material.

GEOGRAPHICAL DISTRIBUTION

Village	Number
Milea	125
Anilio	125
Metsovo	246
Votonosi	125
Total	621
Total excluding Votonosi	496

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The chest X rays either were obtained from the medical records of the Ionannia General Hospital (273 persons) or were taken during examination of those who voluntarily took part in the survey (98 persons). For the first group of 273 persons, the clinical data are limited to the X-ray films. However, from the second group of 98 persons from Metsovo, Milea, Anilio, and Votonosi, we have the following: a complete clinical evaluation, including a respiratory questionnaire (similar to the British MRC questionnaire (Medical Research Council Committee on the Aetiology of Chronic Bronchitis, 1960)), with additional questions relating to tuberculosis; a complete physical examination: chest X ray; and pulmonary function data which includes spirometry with a 5-liter Stead-Wells spirometer following the standards of the American Thoracic Society (Ferris, 1978) in 55 of the 98. Additionally, we have graded the pleural calcifications according to their location and extent (Fig. 2). These grades include 0, I, II, III, IV.

The spirometric indices (forced vital capacity, FVC, and forced expiratory volume in 1 sec, FEV₁) are expressed as percentages of normal (Morris *et al.*, 1971).

RESULTS

Mineral Studies

Representative specimens of soil and settled dust obtained in houses within the Metsovo village were analyzed by polarized light microscopy (PLM) and continuous scan X-ray diffraction (XRD). Fine splits were examined by AEM. Examination of the materials by PLM showed the presence of quartz, carbonate min-

TABLE 1
GEOGRAPHICAL DISTRIBUTION OF POPULATIONS STUDIED AND OCCURRENCE OF PLEURAL PLAQUES

Village	Number of X rays read	Cases		Group A (- Plaque)	Group B (+ Plaque)	Plaque (%)
		Sex	n			
Milea	23	M	12	5	7	56.5
		F	11	5	6	
Anilio	29	M	17	9	8	44.8
		F	12	7	5	
Metsovo	194	M	108	57	51	46.4
		F	86	47	39	
Votonosi	22	M	12	7	5	27.3
		F	10	9	1	
Total	268	M	149			45.4
		F	119	146	122	
Total excluding Votonosi	246	M	137	130	116	47.2
		F	109			

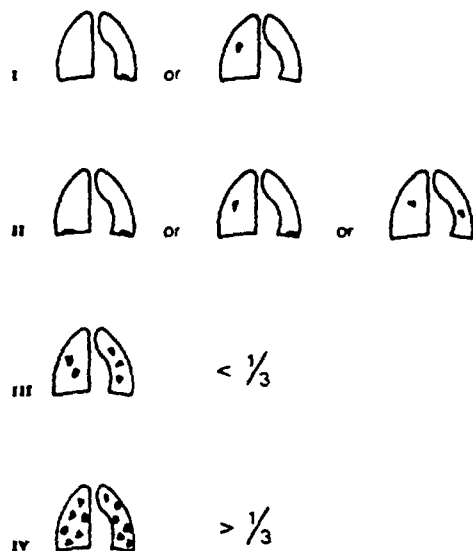


FIG. 2. Grading of pleural plaques according to location and extent. No plaques = 0; small meniscus on diaphragm or single irregular node = I; bilateral meniscus or two irregular nodes, in one or both lungs = II; multiple lesions, not exceeding one third of lung fields = III; multiple lesions, exceeding one third of lung fields, tending to coalesce = IV.

erals, and feldspars. Plagioclase predominated in the feldspar population. Micas were also observed, as were limonite minerals and clays (with some possible talc). No mineral fibers of any kind were observed, although one fibrous opaline phytolith was noted. The soil from Metsovo, analyzed by XRD, was composed of quartz, feldspar (labradorite, andesine, and oligoclase), calcite, and dolomite as the major minerals, and mica (both biotite and phlogopite), chlorite-vermiculite (possibly some serpentine minerals, as evidence by a split in the 7° reflection region), montmorillonite clay, and, possibly, talc. Occasional chrysotile fibrils were observed by transmission electron microscopy. Trace amounts of amphibole, which appeared to be acicular cleavage fragments, and other silicates were observed as well. Some rare fibers (only two) appeared to display closely spaced polysynthetic twins coplanar with (100). These fibers displayed selected area electron diffraction patterns consistent with an amphibole structure in that orientation. Additionally, these fibers displayed the general chemistry of iron-poor tremolite (with measurable concentrations of aluminum).

Tissue Burden Studies

Although materials obtained at transbronchial biopsy represented only some 1/250 of the mass of tissue usually prepared for similar dust burden studies, fibers were found in five of the eight preparations. Because of the nature of the tissue specimens, e.g., variation in mass and size of tissue and different tissue biopsied, quantitation was not attempted.

The fibers³ observed in the pulmonary tissues of patients with "Metsovo lung"

³ The term *fiber* is used in the morphological sense.

have been identified morphological appearance (3) chemistry, as determined (et al., 1973). Complete Fibers recovered ratios (length-to-width (Fig. 4). These features instance, these characteristic augite. The fib (length), another feature parallel, with an average banding is occasionally (100) and Wadsley d confined to the amphiboles. The presence but no identification was

Where the fibers were beam through the crystal SAED pattern was recorded set of conditions occurred

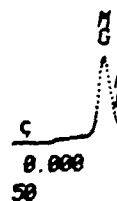


FIG. 3. Diagnostic criteria for fiber diameter (fiber is ~0.25 μm). The pattern (pattern obtained on senting values for an amphibole composition. Potassium is a

have been identified according to the three essential diagnostic criteria: (1) morphological appearance; (2) structure, by selected area electron diffraction; and (3) chemistry, as determined by energy dispersive X-ray spectrometry (Langer *et al.*, 1973). Complete analysis of a single fiber is shown in Fig. 3.

Fibers recovered from these biopsy materials are elongate, some with aspect ratios (length-to-width) exceeding 48:1. Fiber lengths up to 10 μm were observed (Fig. 4). These features are characteristic of asbestiform materials; in the present instance, these characteristics rule out fragments of calcic pyroxenes, e.g., diopside, augite. The fibers tend to display curvilinear form parallel to their *c* axes (length), another feature common to asbestiform minerals; their edges tend to be parallel, with an average diameter of about 0.20 μm (Figs. 3 and 4). Contour banding is occasionally observed across the fiber axis, displaced along both twin (100) and Wadsley defect (010) boundary planes. These features, although not confined to the amphibole asbestos minerals, are common to the asbestiform amphiboles. The presence of mineral fragments as well as irregular fibers was noted but no identification was attempted.

Where the fibers were thin enough to permit the transmission of the diffracted beam through the crystal, and coating material was not present on the fiber, the SAED pattern was recorded on a photographic plate (Fig. 4). Unfortunately, this set of conditions occurred infrequently. When present, these patterns were re-

ques = 0; small meniscus
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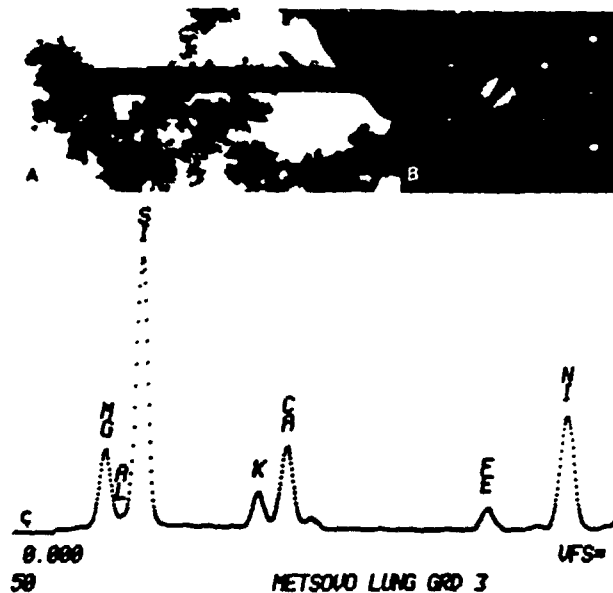


FIG. 3. Diagnostic criteria used in the identification of fiber in tissues: (A) morphology, including diameter (fiber is $\sim 0.25 \mu\text{m}$ diameter) and internal structure; (B) selected area electron diffraction pattern (pattern obtained on fiber shown in (A) indicates a lattice repeat of 0.53 and 1.8 nm, representing values for an amphibole structure; (C) chemistry of fiber shown in (A) indicating a tremolite composition. Potassium is a residue artifact of the KOH reactant.

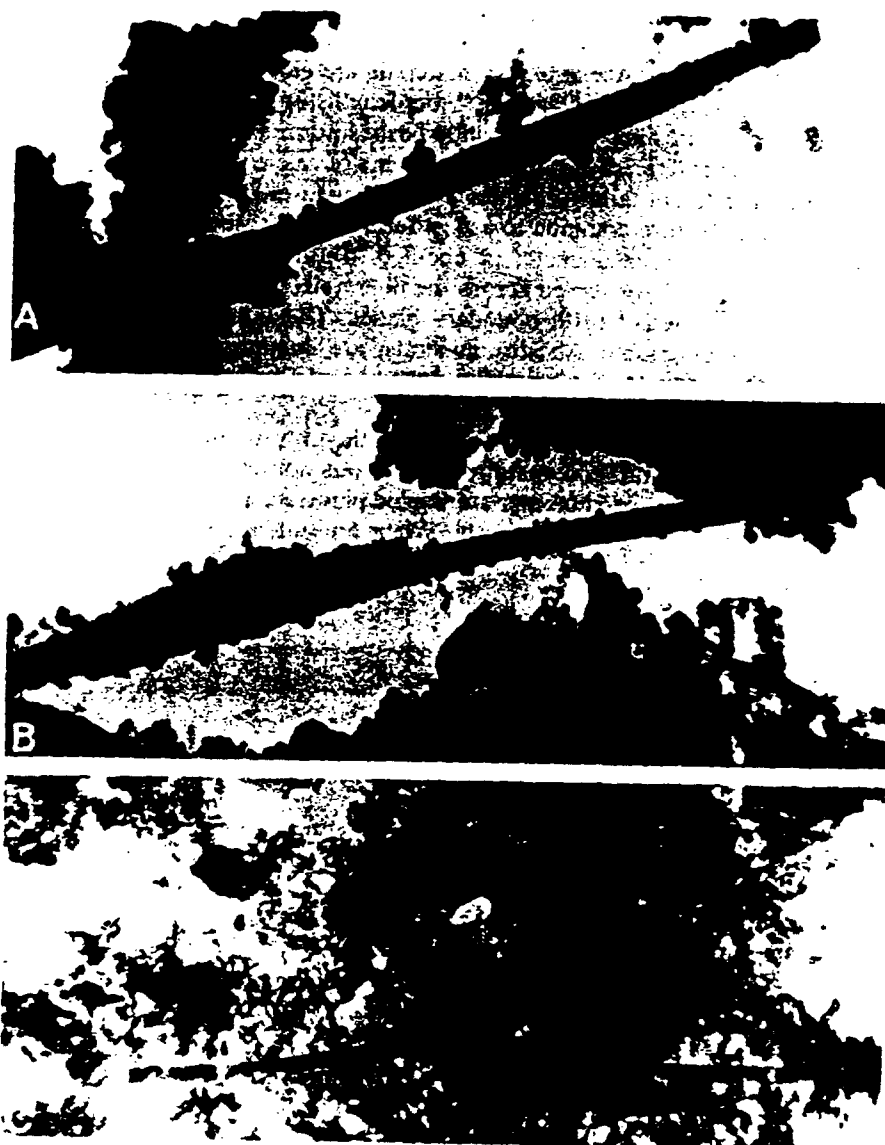


FIG. 4. Fibers extracted from biopsy specimens. (A) Fiber $\sim 0.25 \mu\text{m}$ diameter; length:width ratio is greater than 28:1; fiber composition is of aluminous tremolite. (B) Fiber $\sim 0.20 \mu\text{m}$ in diameter; length:width ratio is greater than 26:1; composition, aluminous tremolite. (C) Fiber $\sim 0.15 \mu\text{m}$ diameter; length:width greater than 48:1; composition, silicate mineral (obscured by tissue debris; X-ray signal contaminated).

corded and the reflection (b^*), which conform

Chemical analyses obtained on standard tremolites, electron spectra. Na:Si, Mg:S fiber found in "Met" standard tremolite and magnesium (14- suggesting possible compositions not quite rich and silica poor, cleavage fragment.

In qualitative terms included both rare amphibole minerals occur phibole fibers tended uncommon asbestiform in only five of eight tissue available. Platy micas, were common

Clinical Studies

Roentgenographic showed pleural calcification (27.3%) from Votone distant villages and in the Metsovo area. Vlachi, like the vast only four non-Vlachi most of their life there calcification was 29.28.6% in the 30- to 70+ age group (Table 2).

Age group
30-39
40-49
50-59
60-69
70+
All ages

corded and the reflections measured. Values of 0.53 nm (c^*) and 1.83–2.06 nm (b^*), which conform to an amphibole structure, were obtained (Fig. 3).

Chemical analyses of seven "clean" fibers were compared with five sets of analyses obtained on tremolite standards (iron rich and iron poor). For the standard tremolites, elemental ratios were calculated from background corrected spectra. Na:Si, Mg:Si, Al:Si, Ca:Si, and Fe:Si ratios have been matched with the fiber found in "Metsovo lungs." Several fibers were in good agreement with standard tremolite composition; three fibers were apparently "low" in calcium and magnesium (14–17% Ca:Si, rather than $25 \pm 3\%$ Ca:Si) and high in aluminum (suggesting possible Al substitution in both X and Y structural sites). Others had compositions not quite similar to the common hornblende, apparently aluminum rich and silica poor, but not sufficiently high in Ca:Si ratio to suggest a pyroxene cleavage fragment.

In qualitative terms, the mineral fibers observed within the tissue debris included both rare chrysotile fibrils and several varieties of amphiboles. The amphibole minerals occurred with much greater frequency than chrysotile; the amphibole fibers tended to be tremolitic and morphologically asbestiform. Additional uncommon asbestiform fibers were considered as well. These fibers were found in only five of eight specimens studied perhaps because of the small amounts of tissue available. Platy particles, consistent in chemistry with serpentine, talc, and micas, were common.

Clinical Studies

Roentgenographic profile. Of the persons from Metsovo, Anilio, and Milea 116 showed pleural calcifications on X ray (47.2%) (Table 1). Also, 6 of the 22 persons (27.3%) from Votonosi showed similar signs. None of the 30 Vlachi persons from distant villages and none of the 73 inhabitants of the three neighboring villages in the Metsovo area showed calcification. All 122 persons with calcifications were Vlachi, like the vast majority of the inhabitants of these villages. We examined only four non-Vlachi from these four villages (mean age 41 years) who had spent most of their life there. None had calcifications. The youngest person with pleural calcification was 29 years old. The incidence of calcifications increased from 28.6% in the 30- to 39-year-old group to 81.0% in individuals older than 70 (Table 2).

TABLE 2
INCIDENCE OF CALCIFICATION BY AGE

Age group	Number of each group	Plaques (% positive)
30–39	21	28.6
40–49	56	44.6
50–59	58	65.5
60–69	42	71.4
70+	37	81.0
All ages	214	

ameter; length:width ratio
 $\approx 0.20 \mu\text{m}$ in diameter
 (C) Fiber $\sim 0.15 \mu\text{m}$ di
 ured by tissue debris; X



FIG. 5. Examples of plaque development: (A) Development of plaques as small meniscus on diaphragm (see arrows, stage II). (B) Development of plaques as large coalesced extensive lesions (stage IV).

The plaques appear first on the diaphragmatic pleura, or as an irregular node elsewhere that cannot be differentiated from a parenchymal lesion (Fig. 5a). Plaques increase in size and extent until 40–50 years of age, after which time they cover most of the thorax (Figs. 5b, 6).

The overall percentage of roentgenograms with calcifications in the three main villages ranged from approximately 42% in women to 58% in men (Table 1). There was fairly equal sex distribution except for the 10 women of Votonosi (mean age 37.9 years) only 10% of whom had abnormal chest roentgenograms instead of approximately 23% "expected" for their age. With such limited experience definitive explanations concerning this observation cannot be made at this time.

Clinical profile. Clinical information was obtained concerning 98 inhabitants of the four villages where calcifications were noted: 37 had negative X rays (group



FIG. 6. Plaque development in the same individual, with time: (A) 1971, (B) 1977, (C) 1983.

A) and 61 showed pl. in group A and 8 in account for any patt (56%) had respirato. cough, expectoratio asthma, tuberculosis group B was larger (in terms of age (A, 4

Spirometric profile and 32 from group B B, because of known Therefore, 18 and 29 FVC and FEV₁ in gr. tively. Group B incl. fifteen with stage III. were 87.8 and 95.0% in stage IV, showing with advancing age a

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The general pattern patterns reported from has been implicated (



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as an irregular nodular lesion (Fig. 5a). After which time

in the three main men (Table 1). There Votonosi (mean age 50 years) instead of 10 years experience demonstrated at this time. In 1983 98 inhabitants of Votonosi X rays (group



(B) 1977, (C) 1983.

A) and 61 showed plaque development (group B); there were only 14 smokers (6 in group A and 8 in group B); there was no apparent occupational factor to account for any pattern of respiratory disease; 20 of the 37 persons of group A (56%) had respiratory symptoms or history of respiratory disease (dyspnea, cough, expectoration, wheezing, history of frequent "colds," pneumonia, asthma, tuberculosis, bronchogenic carcinoma); the incidence of symptoms in group B was larger ($52/61 = 85\%$). However, the two groups are not comparable in terms of age (A, 45.0 years; B, 62.0 years) or sex.

Spirometric profile. Spirometry was attempted in 55 persons, 23 from group A and 32 from group B (5 persons were excluded from group A and 3 from group B, because of known pulmonary or cardiac problems that interfered with testing). Therefore, 18 and 29 persons, respectively, were evaluated. The mean values of FVC and FEV₁ in group A were 92.3 and 96.6% of the predicted values, respectively. Group B included one with stage I roentgenogram, four with stage II, fifteen with stage III, and ten with stage IV. The mean values of FVC and FEV₁ were 87.8 and 95.0% in stage II, 81.0 and 88.3% in stage III, and 75.5 and 80.5% in stage IV, showing a slight decrease of lung volume (restrictive lung disease) with advancing age and plaque development.

DISCUSSION

Pleural calcifications are reported here in inhabitants of four villages from a small area in northwestern Greece. These changes occur in both sexes, with equal frequency, and increase in prevalence with age. This pattern suggests a common environmental factor as an etiological agent. As of now, only persons of Vlachi ethnicity living in Metsovo, Anilio, Milea, and Votonosi have been affected. Neither Vlachi from distant villages nor inhabitants of these four villages who are not Vlachi have been affected. We stress ethnicity at the present time not so much to suggest immunologically controlled patterns of response, but rather to suggest the possibility of some social or cultural factor which controls this cluster phenomenon.

In the past, agents of an infectious nature (e.g., tuberculosis, histoplasmosis) were thought responsible for this disease pattern. Many individuals within this area have been treated in the past few years for these diseases. No positive chemotherapeutic results have been observed so that the "infectious agent hypothesis" is suspect. Further, the appearance of the X rays is not consistent with either tuberculosis or histoplasmosis.

There are also reports of *mesothelioma* and benign *pleural effusions* in this population. These findings caused us to focus on mineral fiber as a factor in the etiology of the pleural calcification and restrictive pulmonary function observed. Similar patterns have been observed in other parts of the world and mineral agents account for the entire spectrum of the diseases observed, i.e., pleural calcification, malignant mesothelioma, and pleural effusion. This pattern is similar to that observed in the Karain area of Turkey.

The general pattern described in this part of Greece has striking similarities to patterns reported from central Turkey, where the fibrous zeolite mineral erionite has been implicated (Artvinli and Baris, 1979). In the past 2 years, three patients

from the Metsovo area were hospitalized with clinical, roentgenological, and pathological findings compatible with mesothelioma. Moreover, a number of inhabitants of this same area died with mesothelioma in the past several years in other hospitals. All of these patients were Vlachi.

Five cases of pleural mesothelioma, in a population of some 5000 people, in 2 years appears to be a much higher annual incidence than expected. Data for the annual incidence of mesothelioma for the area of Greece are currently unavailable. The incidence can be compared with reports in other parts of the world: one case per million people in Pennsylvania (Lieben and Pistawka, 1967); one case per million in Finland (Nurminen, 1975); two to three cases per million in Great Britain (Greenberg and Davies, 1967). The prevalence of this disease in this area of Greece is strikingly higher (five cases per 5000 in 2 years).

There are further anomalies in this pattern. It is of special interest that none of the 5 patients with diagnosed mesothelioma had pleural calcification. Yet, the incidence of previous, unexplained, pleural effusion was significant. Of the 98 persons whose clinical histories were known, 26 had had episodes of benign pleural effusion. This percentage was higher in individuals with pleural plaques than in the control group.

The mineralogical studies of the settled dust and tissues suggest mineral fiber as at least one of the agents in the etiology of these diseases. Some of the fibers identified possess the morphological, structural, and chemical characteristics of fibers with demonstrated biological activity. The following caveat should be mentioned: the analysis of the transbronchial biopsy reflects mineral dust deposited in and proximate to the airways. These mineral fibers may or may not, either qualitatively and quantitatively, reflect the fiber population at the pleura, the site of tissue injury.

Several features of this disease pattern require further explanation. The occurrence of pleural plaques in this ethnic group may be related to some common social habit, practice, or "life-style," confined to this particular group, which exposes them to mineral fiber in concentrations considerably different from others living in the same area. The Vlachi people tend to work in the fields, as shepherds, where they are more likely to encounter dust. Whether this is critical to the development of disease remains to be elucidated. The overall pattern of pleural calcification and pleural disease, and the occurrence of what appears to be asbestiform amphiboles and traces of chrysotile in pulmonary tissues, is consistent with the appearance of these changes. A quantitative case-control study of pulmonary tissues is warranted for the future. For the present we propose the term "Metsovo lung" to describe this interesting association.

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