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Pleural calcification, pleural mesotheliomas, and bronchial cancers caused by tremolite dust

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ABSTRACT Around the town of Çermik in south-east Turkey there are many deposits of asbestiform minerals, some of which are used to make whitewash or stucco. A sample of 7000 of the population revealed 461 (6·5%) with pleural thickening and calcification, of whom 103 (1·47% of the total) had evidence of interstitial pulmonary fibrosis. Forty-one patients with respiratory cancer were admitted to the Diyarbakir Chest Hospital from around Çermik and from a comparable area of equal population (but without asbestos deposits) in 1977–8. Of these 23 were mesotheliomas, 22 coming from around Çermik. In addition, 11 of the 18 primary bronchial cancers came from around Çermik. A similar excess of mesothelioma and bronchial cancer had been admitted from the Çermik area in previous years. The whitewash or stucco material has been shown to contain fibrous tremolite and non-fibrous antigorite/lizardite, chlorite, and talc. A lung biopsy of a patient from Çermik contained large numbers of tremolite fibres, both free and forming asbestos bodies. There were only occasional chrysotile fibres.

Çermik is a town in south-east Turkey. Since 1973 we have been reporting on investigations into the cause of "Çermik disease."[1–6] In the present report we add new mineralogical and epidemiological information and discuss the significance of the pleuropulmonary disease in the district.

Around the town of Çermik are numerous outcrops of asbestiform minerals which are used to make whitewash and stucco for the walls and roofs of the houses. The first pulmonary abnormality to be noted was a high prevalence of pleural thickening with calcification. Subsequently it was noted that, compared with other

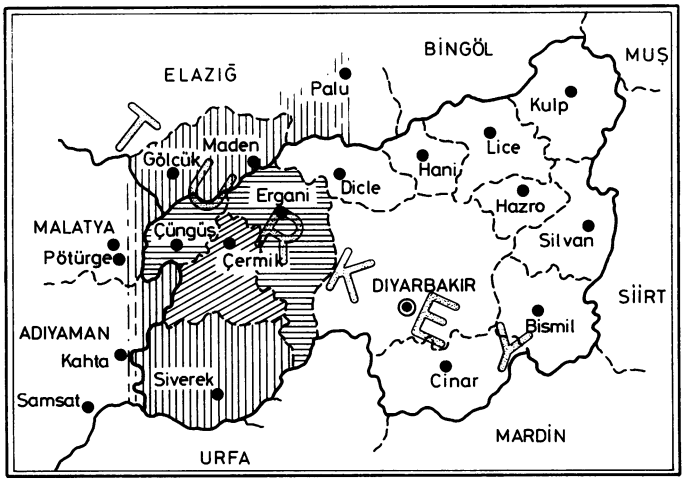

Fig 1 *Map of south-east Turkey showing the districts served by the Diyarbakir Chest Hospital. The districts hatched horizontally and obliquely show the highest incidence of Çermik disease." Cases have also been reported from the districts hatched vertically. Asbestos deposits occur and are worked in all these districts, but do not occur in the unhatched districts.*

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districts in the area served by the Diyarbakir Chest Hospital, there was a very high incidence of pleural mesothelioma and a relatively high incidence of primary lung cancer. There were also cases of benign fibrosing pleurisy. The clinical picture was similar to that reported from further west in Turkey (Karain).[7 8]

The investigations were undertaken to determine the cause of this local excess of pleural and pulmonary disease in part of Turkey.

Methods

Figure 1 shows a map of this part of Turkey. The districts where outcrops of asbestiform minerals occur are shaded. Those with vertical shading were not investigated in detail. The outcrops are both most frequent and most frequently exploited in the three districts around Ergani, Çermik, and Çüngüş which are shaded obliquely and horizontally. The population of these three districts is 100 800.

Three thousand, seven hundred men and 3300 women over the age of 20 years were selected from these three districts and investigated with chest radiography. These individuals were those who could be persuaded to attend from villages in which fibrous minerals were known to be used, and do not represent a random sample (table 1). The films were all read by three chest physicians working independently.

Diyarbakir Chest Hospital serves these three districts as well as the others shown on the map. The population of the five asbestos districts listed in table 2, 227 000, is approximately equal to that of the seven non-asbestos districts, 217 000. During the period of the survey (1977 and 1978) there were 86 admissions to the Chest Hospital for neoplasms of the lung and pleura. These were analysed and only those 41 patients coming from the five asbestos districts and seven non-asbestos districts were considered. The diagnoses were established by the usual techniques and the frequency with which each diagnostic procedure was used is listed in table 3.

Table 1 *Age and sex distributions of pleural calcification and pulmonary fibrosis among 7000 individuals screened by chest radiography*

Age groups (yr)	*Sex*	*Numbers*	*Pleural calcifications*		*Pulmonary fibrosis*	
			Number	*%*	*Number*	*%*
21–30	M	774	4	0·51	—	—
	F	740	2	0·27	—	—
31–40	M	1169	30	2·56	3	0·25
	F	1052	28	2·66	1	0·09
41–50	M	1062	49	4·61	7	0·65
	F	960	58	6·04	6	0·62
51–60	M	632	89	14·08	22	3·48
	F	441	81	18·36	18	4·08
61–70	M	94	70	74·46	20	21·27
	F	54	32	59·25	16	29·63
70+	M	13	11	84·61	6	46·15
	F	9	7	77·77	5	55·55
Totals	M	3724	253	6·79	57	1·53
	F	3276	208	6·34	46	1·40
Totals		7000	461	6·58	103	1·47

Table 2 *Distribution of 41 patients with malignant mesothelioma and bronchogenic carcinoma between asbestos and non-asbestos districts*

Town	*Population**	*Pleural neoplasms*		*Pulmonary neoplasms*		*Total*	
		Number	*Rate*	*Number*	*Rate†*	*Number*	*Rate†*
Asbestos districts							
Çermik	34 297	5	14·57	1	11·66	9	26·24
Ergani	50 766	9	17·72	3	5·90	12	23·63
Çüngüş	15 738	3	19·06	1	6·35	4	25·42
Maden	36 594	2	5·46	1	2·73	3	3·19
Siverek	90 027	3	3·33	2	2·22	5	5·55
Totals	227 422	22‡	9·67	11§	4·83	33	14·50
Non-asbestos districts							
Lice	38 422	—	—	1	2·60	1	2·60
Kulp	35 761	—	—	3	8·38	3	8·38
Dicle	28 737	—	—	1	3·47	1	3·47
Hani	18 192	—	—	1	5·49	1	5·49
Silvan	52 196	—	—	1	1·91	1	1·91
Hazro	16 310	—	—	—	—	—	—
Çinar	28 344	1	3·52	—	—	1	3·52
Total	217 962	1‡	0·45	7§	3·21	8	3·67

* Data from 1970 census
† Per 100 000 inhabitants
‡ $\chi^2 = 16·55$ highly significant
§ $\chi^2 = 0·38$ not significant

Table 3 *Diagnostic procedures carried out on the 41 patients with malignant tumours of lung and pleura*

Diagnostic procedure	*Number of cases*
Bronchoscopy	28
Bronchial biopsy	26
Needle biopsy (lung)	6
Needle biopsy (pleura)	10
Pleural biopsy at thoracoscopy	13
Cytological examination of pleural effusion	23
Regional node biopsy	4
Thoracotomy	2
Cytological examination of sputum	41
Radiological examination	41

Results

POPULATION SURVEY

There were 451 cases of pleural calcification and thickening among the 7000 individuals selected (6·5%, table 1). There was no significant difference between the sexes but there was an increase in frequency with age. Few cases were seen in the 21–30 year age group but 69% were affected before the age of 70. The probability of developing pleural changes appeared to be normally distributed about an average of 50% at 65 years in this population.

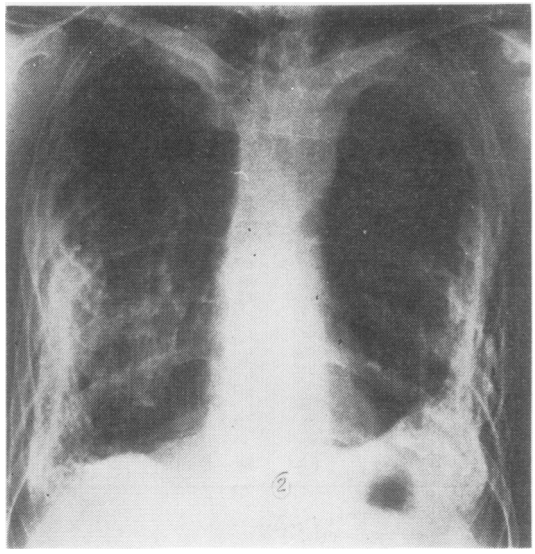

Fig 2 *Chest radiograph of a man aged 36 years from Çermik with shell-like calcification of the parietal and diaphragmatic pleurae. There is also thickening of the pleura at both apices.*

Pulmonary changes appeared about 10 years later than the pleural changes and affected about 50% of the population over the age of 70 (table 1). The pleural change was sometimes very extensive. Figure 2 shows advanced pleural calcification in a man of only 36 years also from Çermik.

Only six cases of pulmonary tuberculosis were detected in the population survey, rather fewer than was expected for the general population of this region.

ADMISSIONS TO HOSPITAL

Of the 86 patients with primary tumours of the lungs and pleura admitted to Diyarbakir hospital in 1977–8, 33 came from the asbestos exposed districts and only eight from the control districts (table 2).

There were 23 patients with malignant pleural mesotheliomas, of whom only one came from the non-asbestos districts. The incidence appeared highest in the three districts where the radiological survey had been carried out (Çermik, Ergani, and Çüngüş). In these villages there were 17 cases during the period from a population of 100 000. The rate in Maden and Siverek was less than a third of this. Figure 3 shows a hydropneumothorax with tumour on the chest wall in a man of 65 years from Ergani. The fluid contained hyaluronic acid. Bilateral pleural calcification is also present. Men and women were affected in equal numbers although the three patients under 40 years of age were all women (table 4). All the men and none of the women smoked cigarettes.

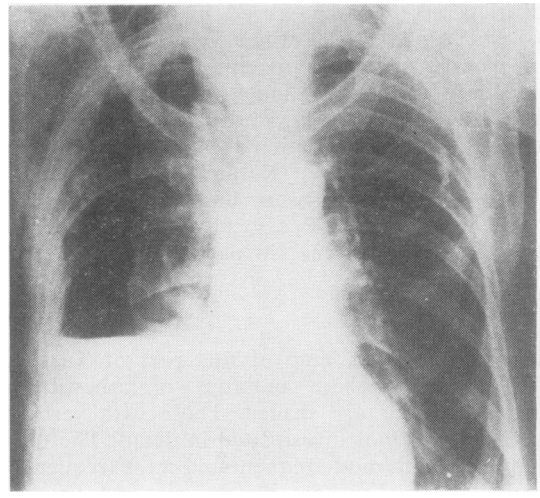

Fig 3 *Chest radiograph of a man aged 65 years from Ergani showing a right hydropneumothorax. Tumour (mesothelioma) is seen on the parietal wall on the right side. The fluid contained hyaluronic acid. Bilateral calcified pleural plaques are present.*

Primary bronchial cancer occurred in both asbestos and non-asbestos districts (table 2), 11 cases from the former, and seven from the latter. The difference is not statistically significant but when the figures are combined with those for the

Table 4 *Age and sex distribution of 41 patients with pleural and pulmonary malignant tumours*

Age groups (yr)	*Pleural tumour*			*Pulmonary tumour*			*Total*
	Male	*Female*	*Total*	*Male*	*Female*	*Total*	
21–30	—	—	—	1	—	1	1
31–40	—	3	3	4	1	5	8
41–50	1	5	6	1	2	3	9
51–60	4	1	5	5	1	6	11
61–70	5	2	7	2	1	3	10
71+	2	—	2	—	—	—	2
Totals	12	11	23	13	5	18	41

Table 5 *Pleural and pulmonary cancers from abestos and non-asbestos districts in this and previous studies*

Years covered	*Asbestos centres*		*Non-asbestos centres*	
	Pleural tumours	*Pulmonary tumours*	*Pleural tumours*	*Pulmonary tumours*
1968–76	24 (10·55)	32 (14·07)	2 (0·92)	12 (5·50)
1977–8	22 (9·67)	11 (4·83)	1 (0·45)	7 (3·21)

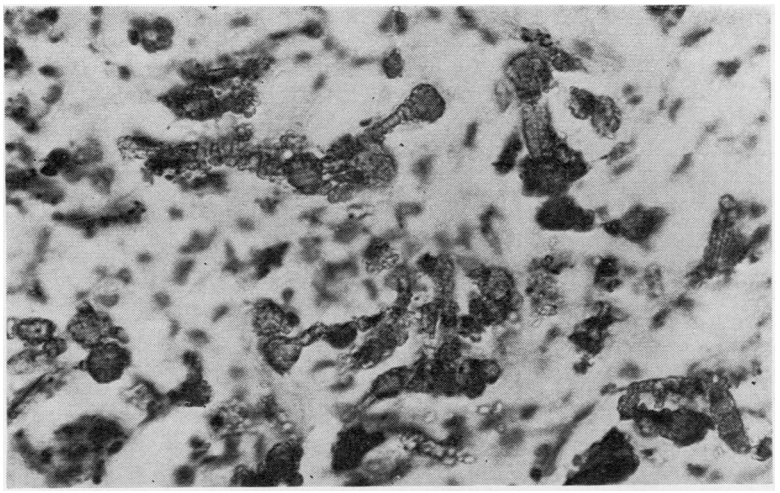

Fig 4 *Photomicrograph of lung tissue from a man aged 42 years from Çermik who was shown to have a bronchogenic adenocarcinoma by needle biopsy of a mass in the left lung and biopsy of the regional lymph nodes. The lung contains numerous typical haustrated, bulbous-ended asbestos bodies. Original magnification H and E ×600.*

years 1968–76 the difference is significant (χ^2= 7·58 $p<0·001$ (table 5).

The age at which these cancers developed appeared to be lower than for mesothelioma and they appeared to be more frequent in men (who all smoked) than women (who did not) but these differences were not statistically significant (table 4). Examination of the lung biopsies for dust in the patients from the asbestos area showed numerous asbestos bodies (fig 4).

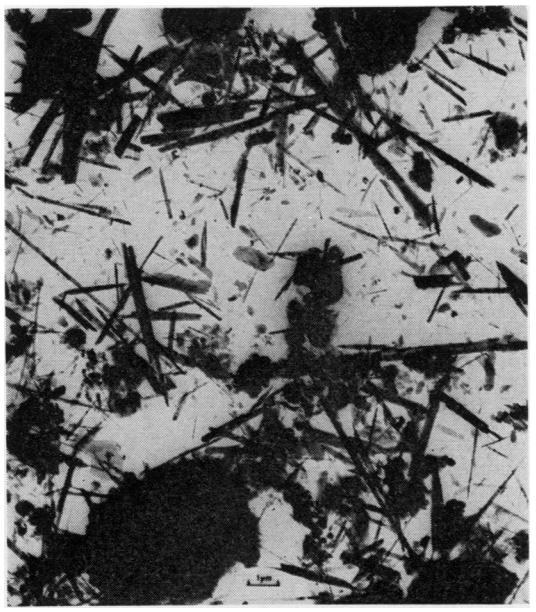

Fig 5 *Electron micrograph of stucco whitewash material from Çermik district. Long straight fibres of tremolite asbestos of varying lengths and thicknesses. Original magnification ×10 000.*

MINERALOGICAL INVESTIGATIONS

During earlier investigations the whitewash and stucco material had been examined at the State Institute of Mineralogical Research and shown by x-ray analysis to contain serpentine minerals and talc. It was assumed that the fibrous element was chrysotile because of the presence of the serpentine. On this occasion new samples of both whitewash or stucco from Çermik and lung material from the patient whose lung is shown in fig 4 were sent for more detailed analysis including electron microscopy and probe analysis of individual fibres.

The stucco was shown to consist of three non-fibrous phases—chlorite, talc, and a serpentine (antigorite/lizardite). The fibrous mineral was an amphibole, tremolite (fig 5). The serpentine mineral did not include chrysotile fibres. In the biopsy specimen most of the fibrous particles were tremolite with a very small percentage of chrysotile (fig 6). The elemental analyses of the fibres of tremolite in the stucco and the biopsy were found to be very similar, suggesting a common source.

Discussion

The use of stucco material containing a fibrous mineral appears to be the cause of the pleural reactions, pulmonary fibrosis, and malignant tumours of the lungs and pleura in the Çermik area. The inhabitants of Çermik and neighbouring communities are unaware that this material causes these diseases. While initial analysis suggested that the fibrous mineral was chrysotile,

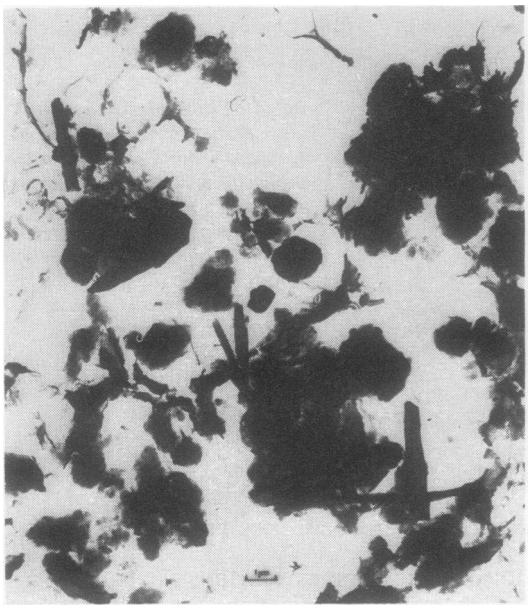

Fig 6 *Electron micrograph of dust obtained from the histological section shown in fig 5, showing short straight fibres which on probe analysis had the same elemental composition as the tremolite fibres shown in fig 6. Original magnification* × *12 000.*

more detailed analysis showed it to be the amphibole tremolite. The material also contains talc and non-fibrous serpentine but the detailed composition may vary from place to place within the area.

The material is quarried from the mountains by the male population both for local use and for sale elsewhere. It is used as a whitewash for the walls and floors of the houses. The application is usually done by women who grind the material to a powder and suspend it in water. The process is repeated each year. Consequently householders are repeatedly exposed from an early age, and this exposure can be described as both environmental and occupational but not industrial. The exposure leads to the diseases usually associated with exposure to asbestos.[9-11] The first obvious sign is the development of "geographic" calcified plaques in the pleura.[12-14] Radiographic changes of pulmonary fibrosis develop later in a proportion of the population as described by Meurman[10] and Selikoff.[11]

Table 6 *Results of radiological surveys*

Survey	*Number of individuals*	*Pleural calcification*		*Pulmonary fibrosis*	
		Number	*%*	*Number*	*%*
Previous studies	15 239	389	2·55	52	0·34
This study	7000	461	6·50	103	1·47
Totals	22 239	850	3·82	155	0·69

In this environment the exposure is lifelong, from birth to death, as long as the individual remains in the area. Probably for this reason the radiographic changes appear early and are very extensive. We have encountered many cases of non-malignant pleural effusions associated with these changes similar to the cases described by Chretien[15] and Lemanager.[16] There is also thickening of the apical pleura in many cases which has not been described previously.

Although the prevalence of the non-malignant changes increases with age, it is variable in extent. Unless further study indicates wide variations in levels of exposure this suggests an inherent difference in susceptibility between individuals. The incidence of tuberculosis in this community is relatively low but further work is needed to see whether exposure to asbestos carries any protection against tuberculosis.

Individuals have been detected who spent their infancy in the asbestos area and then moved away. With no further exposure they have developed radiographic changes 20 to 25 years later and some have subsequently developed a respiratory neoplasm. This emphasises the relative importance of childhood exposure and of the long latent interval between critical exposure and the first detectable signs of disease. On the other hand adult exposure can also be significant as is exemplified by the wife of a government official who lived for only three years, from the age of 22 to 25 years, in Çermik and yet was found to have pleural calcification when she developed bronchial cancer 35 years later.

A similar clinical picture has been described in patients outside the areas of the present survey in Palu and Adiyaman to the North and West (fig 1). The population of the whole area which appears to be at risk is over half a million. So far the investigation covers about half the area and the numbers of people examined is only a small fraction of the total. Although support has been provided by the Tuberculosis Units of the Turkish Ministry of Health and Welfare it has only been possible to take radiographs of about 5% of the population at risk.

More important than the benign changes in the lungs and pleura are the related neoplasms. The malignant mesotheliomas are both the most frequent and most clearly related to asbestos exposure. This has been widely reported elsewhere.[17-23] The bronchial cancers are not only slightly less frequent but only a proportion (perhaps one-third) can be attributed to the

asbestos exposure. Whereas mesotheliomas have been produced experimentally with asbestos fibres, it has been less easy to show that asbestos can cause primary bronchial cancers experimentally.[24 25] In the case of both mesothelioma and bronchial cancer the relatively low frequency of these tumours in comparison with the benign changes suggests that individual susceptibility is also important.

As there is no effective treatment for these diseases it is imperative that efficient preventive measures are taken immediately. They should be aimed at protecting the whole population and not just the men while they quarry the material and the women while they apply the whitewash.

The work was carried out with the continuous help of Hamdi Acan MD, General Director of the Tuberculosis Unit, Ministry of Health and Welfare, Turkey. The special analysis of the stucco material and the dust in the lung biopsy was carried cut by Dr FD Pooley, Department of Mineral Exploitation, University College, Cardiff, Wales.

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