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Pleural Fibrocalcific Plaques and Asbestos Exposure

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In a number of serial investigations an association has been demonstrated between the development of benign calcific pleural plaques or malignant diffuse mesothelioma and slight inhalation of asbestos dust, often some 20 or 30 years previously. As the industrial use of asbestos has increased enormously during the last few decades, a rise in the frequency of mesothelioma—which has hitherto been rare—is anticipated in the near future (Thomson, 1962). From the standpoint of epidemiological research concerning asbestos exposure, the demonstration of calcific plaques on roentgenograms has proved a useful criterion. So far, only an association has been disclosed, however, not an obvious causal relationship. Other pathogenetic factors, still unknown, have to be taken into account either as a contributory or the sole cause. The occurrence of bilateral calcific plaques does not yet imply the presence of asbestosis-pneumoconiosis. In the majority of subjects who have not been occupationally exposed to asbestos, pleural calcification is not combined with pulmonary changes or signs of pneumoconiosis.

Occupational Exposure to Asbestos and Pleural Plaques

In roentgenographically visible form, pleural calcification is relatively rare. The most common causes are hemothorax, pleurisy (usually tuberculous) and chronic empyema. In extensive roentgenological series the frequency of pleural calcification has been reported to be about 0.2% (Floyd and Hepburn, 1939). It has been estimated that the lesions are bilateral in every fifth or eighth case (Claus, 1962).

Bilateral pleural calcification attracted more general interest when Siegal *et al.*, in 1943, reported that they had observed this condition in 6.3% of talc miners in the northern areas of New York State (St. Lawrence County). The theory of a causal relationship with talc in this region, in the form of a fibrous, asbestiform mineral, tremolite, was advanced. It was not until 12 years later, however, that bilateral pleural calcification was again described, this time by Jacob and Bohlig (1955) in 5% of asbestos workers in Dresden. Independently of these authors, the Danes, Frost *et al.*, in 1956 directed attention to the association of asbestos exposure and pleural calcification. In a series of 31 insulation workers they detected 11 cases of pleural calcification, 8 of which were bilateral. In the insulation materials used, asbestos constituted an essential element. In many later investigations an association between pleural calcification and exposure to asbestos has been demonstrated. The most important statistics on pleural plaques and asbestos exposure are listed in Table I.

It has been found that the more severe the degree of pneumoconiosis observed among asbestos workers, the higher is the frequency of pleural calcification.

Müller (1962) detected pleural calcification in 6% of a group of workers who showed the slightest roentgenographic degree of asbestosis, while the corresponding figure was 38% in a group who had pulmonary changes of the severest degree. Among 1117 members of the Heat and Frost Insulators and Asbestos Workers Union in New York, Selikoff (1965) found 150 cases of pleural calcification. Of these, 145 were in a group of 393 workers with a history of more than 20 years' exposure to asbestos. Among those who had been a shorter time on the job, only 5 exhibited pleural calcification. Selikoff observed, moreover, that calcification rarely occurred without fibrosis of the lung parenchyma—asbestosis—being present as well.

The majority of investigators hold the view that roentgenographically discernible pleural calcification is a sign of asbestosis (1) if the lesion is bilateral, and (2) if there is no previous history of hemothorax, tuberculous or other pleurisy, or empyema (Frost *et al.*, 1956; Hurwitz, 1961; Anspach, 1962; Lawson, 1963; Oosthuizen *et al.*, 1964).

Under the last-mentioned conditions Selikoff (1965) regards unilateral calcification, as well, as strongly suggestive. The association with asbestos is brought out by the fact that not even in large groups of workers in gold, coal, copper, iron, chrome, and manganese mines was any typical case of pleural calcification discovered by Hurwitz (1961), who investigated the chest roentgenograms of workers at different mines in South Africa. Those subjects showing calcification were invariably asbestos workers.

Glasswool and rockwool, which are commonly used as insulation material in the building industry in addition to asbestos, also occur in disintegrated form as fibrous dust. However, such data as are available suggest that they do not seem to cause pleural calcification even after protracted exposure (Bjure *et al.*, 1964).

On the other hand, it is noteworthy that asbestosis and pleural calcification by no means invariably occur in conjunction. Of 36 patients with pleural calcification described by Hourihane *et al.* (1966) from the London Hospital, only 7 exhibited asbestosis—pulmonary fibrosis. Further, these authors found only 8 cases of pleural calcification among 36 patients with asbestosis. Cartier (1965), also, mentions that the majority of Canadian industrial asbestos workers with pleural calcinosis showed no signs of asbestosis, and that in most cases of asbestosis, pleural calcification was not detected. Moreover, Cartier drew attention to the fact that of 126 Canadian asbestos workers exhibiting pleural calcification, 90% had worked at one or the other of four smaller mines, while only 10% came from a larger mine with 1600 workers, and no case of calcification was observed among 1800 workers employed at the biggest mine. From this Cartier concluded that the factor causing asbestosis is not the same as the factor that leads to pleural calcification. Fehre (Müller, 1958), too, stated that regional factors or contributory factors relating to the particular industry may be of importance to the development of pleural calcification, since some investigators see these lesions in abundance while others observe none. He suggested that different composition of the dust involved might afford an explanation to the irregular occurrence of calcification. Nevertheless, it may be regarded as es-

TABLE 1

RECENT STATISTICS ON PLEURAL PLAQUES AND ASBESTOS EXPOSURE

Authors	Population type	Country	Number cases	Plaques		Asbestos exposure			Lung fibrosis		Mesothelioma (if mentioned)
				Number	Percent	Occupational	Environmental	None	Number cases	Percent cases	
Siegal *et al.* 1973	Talc workers	U.S.A.	221		6.3	+				11	—
Smith, A. H. 1952	Asbestos workers	U.S.A.	201	0	0	+					—
[illegible] Mohlig 1953	Asbestos workers	Germany	343		5	+					—
Frost *et al.* 1956	Insulation workers	Denmark	31	11		+					—
Felix, W. 1956	Steel-pot moulders	Germany	33	7		+					—
Kivisto, R. 1960	Hospital cases from asbestos areas	Finland		126			+			24	—
Müller, H. 1962	Asbestos workers	Germany	651		0–38	+					—
Angerer, M. 1962	X-ray mass survey	Germany		244		59	118	67			—
Hornek, J. 1962	X-ray mass survey	Czechoslovakia	9871	273		–	–	+		0	—

Lawson, J. P. 1963	Asbestos workers	England		7		+			5		+
Garavaglia, C. 1963	Asbestosis	Italy	63	14	21.5	+				100	—
Nest, W. 1963	X-ray mass survey	Germany	111,060	33		4		20			—
Oosthuizen *et al.* 1964	Asbestos workers	South Africa	2383	59		+					—
Marková, D. 1964	X-ray mass survey	Czechoslovakia	41,549	241		—	—	241		0	—
Cartier, P. 1965	Asbestos workers	Canada		125		+				14	—
Selikoff, I. J. 1965	Insulation workers	U.S.A.	1117	150		+			"Most"		—
Meurman, L. 1966	Autopsy cases	Finland	425	172	39.3	—					—
Hourihane *et al.* 1966	X-rays of hospital cases	England	27,500	30					7		2
Hourihane *et al.* 1966	Autopsy cases	England		56	4.2				24		13
Kleinfeld *et al.* 1966	Asbestos workers	U.S.A.	21	5		+					—
Raunio, V. 1966	X-ray mass survey	Finland	631,000	1510		2	Many		1		—
Zolov *et al.* 1967	X-ray mass survey	Bulgaria	3429	175		43	132		7		—

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tablished that all types of asbestos may be associated with pleural calcification since it has been detected in both serpentine and amphibole asbestos workers and in workers exposed to tremolite talc dust. Calcification has been described in workers from the Canadian chrysotile asbestos mines (Cartier, 1965), in workers from the South African crocidolite mines (Sleggs *et al.*, 1961), and in subjects exposed to dust from the Finnish anthophyllite asbestos mines (Kiviluoto, 1960).

In this connection it seems appropriate to emphasize the fact that except, perhaps, under laboratory conditions, asbestos dust exposure is never "pure." The dust is always mixed in various degrees with other dusts, as other mineral dusts. At present, we do not know whether and to what extent these other minerals cause pleural calcification. But it should be recalled that pleural calcification was first described in talc workers who had been exposed to dust composed of tremolite-talc, asbestos, and anthophyllite. Furthermore, in the studies performed by Smith (1952), calcified pleural plaques were found not only in tremolite workers but also in certain groups who had handled various other talc mixtures.

Nonoccupational Pleural Calcification

In the population living in the limited area comprising the Finnish anthophyllite asbestos deposits, typical bilateral pleural calcification is common without occupational exposure to the dust having occurred (Kiviluoto, 1960).

In a commune (Tuusniemi) in which an asbestos mine and mill have been worked since 1919, calcifications were detected at roentgenological mass surveys in 9% of the adult population. In the neighboring commune (Kuusjärvi) the corresponding figure was 6.5%. In the remainder of the Finnish population pleural calcifications are a rare roentgenographic finding, the frequency being estimated at only 0.5 per thousand of population (Raunio, 1966).

Kiviluoto discovered 126 cases of pleural calcification in a series from the asbestos area from which those who had worked at the asbestos mine or mill had been omitted. The lesion was bilateral in 85% of cases.

By analyzing samples of snow, small amounts of asbestos dust have been demonstrated as far as 27 km from the anthophyllite asbestos mine mentioned earlier (Laamanen *et al.*, 1965). It has thus been proved that the population living in the surroundings of the mine are exposed to asbestos dust. The source of exposure, however, need not necessarily be precisely the asbestos mine. Certain observations seem to indicate that scattered asbestos rocks and stones occurring in great numbers in this area may be a source of asbestos dust. It is a well-known fact that these incombustible stones have been used by the local population for the construction of fireplaces and stoves, and especially for the heated stones in the Finnish bath ("sauna") on which water is thrown in order to produce steam. It is also known that the children like playing with such stones, fascinated by the way they split into fan-like pieces when cut. Consequently, the asbestos exposure of the inhabitants of this area may have commenced in early childhood. In Raunio's (1966) roentgenological study of pleural calcification, the age distribution of the calcification cases from this region indicates that the asbestos exposure of the older age groups, in any event, must have begun before the exploitation of the asbestos deposits was started.

Similar endemic pleural calcification has recently been described in Bulgaria,

where a high frequency of pleural calcification was noted in the population (consisting mainly of farmers) living about a small asbestos mine. In this case, too, it was suggested that the asbestos content of the soil was a more likely source of exposure than atmospheric pollution derived from the mine (Zolov *et al.*, 1967).

Endemic pleural calcification in an urban population residing near an asbestos factory is described in Anspach's (1962) roentgenological study in the city of Dresden. Among 241 subjects with pleural calcification 177 had a history of exposure to asbestos dust due either to working at the asbestos factory or to living within a radius of 1800 m from the factory.

Endemic pleural calcification without known exposure to asbestos dust has also been described. In two areas in Czechoslovakia, i.e., in the district of Pacov (western section of the former Jihlava region) (Hromek, 1962) and in the district of Pelhrimov in south Bohemia (Marsová, 1961), bilateral plaque-like pleural calcifications were found in relative abundance during roentgenological mass surveys of the rural population. Neither fibrosis nor any other disease of the lung was observed in these cases. Hromek was unable to trace any asbestos exposure, and Marsová succeeded in suggesting only uncertain exposure to tremolite talc. The soil of the district of Pelhrimov being poor in calcium, farmers import, from the neighboring district of Chynov, a fertilizer called "Kalcofen," which contains small amounts of tremolite talc. Marsová later studied the occurrence of calcification in the district of Chynov; the frequency was only 0.3%, while it was as high as 4.3% in certain areas of the district of Pelhrimov.

At roentgenological mass surveys in the area of Leipzig, Neef (1963) detected 33 typical cases of bilateral plaque-like pleural calcification. The whole series comprised 111,069 subjects. Calcified pleural plaques were more frequent in women than in men, a phenomenon which also was noted by Marsová in Czechoslovakia. No changes justifying a diagnosis of pneumoconiosis were observed in Neef's cases, either, and only four subjects had a history of occupational exposure to asbestos or talc. Neef regarded bilateral pleural calcinosis as merely a change of old age.

It may thus be considered established that although pleural calcification is frequently seen in workers exposed to asbestiform dust the majority do not show this condition (Müller, 1962; Cartier, 1965; Hourihane, 1966). Furthermore, it may be stated that the longer the time that has elapsed since the beginning of occupational dust exposure, the higher is the frequency of pleural calcification (Selikoff, 1965). However, plaque-like bilateral pleural calcification cannot be regarded as identical with asbestosis, since in unselected material from roentgenological mass surveys the latter has almost been mostly involved only the pleura. In the majority of cases the changes are not associated with demonstrable fibrosis of the lung, nor do they cause any subjective or objective symptoms or signs of asbestosis (Kivilnoto, 1960; Raunio, 1966). In some series of nonoccupational, endemic plaque-like pleural calcification, exposure to asbestos has been uncertain (Marsová, 1961), or even absent (Hromek, 1962). On the other hand, it should be pointed out that the role possibly played by asbestos cannot be definitely eliminated as long as the lungs have not been histologically examined for asbestos fibers or bodies.

Comparative autopsy studies on the relative frequency of pleural plaques and

the content of asbestos dust (asbestos bodies) in the lungs have been performed only in England (Homburger *et al.*, 1966) and in Finland (Meurman, 1966). In an autopsy series from the London Hospital, plaque-like pleural thickenings were observed in 4.2–11.2%. In all these cases small amounts of asbestos bodies were recovered from the lungs. At consecutive autopsies performed in the same hospital asbestos bodies were detected in 24.3%.

The Finnish investigation was performed on a total of 438 consecutive autopsy cases at three central hospitals situated far from each other in different parts of the country (Meurman, 1966). One central hospital district includes anthophyllite asbestos deposits. The frequency of pleural plaques was 39.3% in the whole material, the range being from 13 to 57%. The lungs were examined for asbestos bodies at those two hospitals where plaques were most frequently seen. This series comprised 229 cases. Pleural plaques were observed in 124. In 79% of these, asbestos bodies were found in the lungs in varying, mostly small amounts. Accordingly, asbestos was not demonstrated in the lungs in all cases showing plaques, and on the other hand, plaques were not invariably found in the cases exhibiting asbestos bodies. In the whole material asbestos bodies were observed in 57.6%.

The series from London and Finland thus differ in certain respects. In the Finnish study the frequency both of cases showing plaques and cases with asbestos in the lungs was higher. Moreover, in a proportion of the cases with plaques (21%), asbestos was not demonstrated in the lungs, while in the London series asbestos was found in the lungs in all cases showing plaques.

In respect to anatomic structure, the plaques were identical in the two series. They also usually showed calcification varying in degree in both. In the majority of cases calcification was not heavy enough, however, to make the plaques visible on routine chest roentgenograms.

Another noteworthy difference between the Finnish series and that from London is that in the latter almost half the cases with plaques showed clinical, or in any event histologically demonstrable, asbestosis (pulmonary fibrosis). In the Finnish series pleural plaques were not associated with fibrosis or any other chronic disease of the lung. Consequently, although in the Finnish series cases showing both pleural plaques and asbestos bodies were highly significantly more frequent than cases in which this relationship was not observed, the conclusion cannot be drawn that an uncomplicated causal relationship is involved. The possibility remains that pleural plaques are due also to other, unknown factors. The same is suggested by statistics derived from autopsy material from the two largest hospitals in Milan. Asbestos bodies were found in 51% of cases, pleural

The Roentgenographic Appearance of Pleural Calcifications

In roentgenograms, pleural calcifications appear as patches and sometimes as streaks or plaques forming a variety of differing patterns, which have been described as bizarre, [illegible], curvilinear, or lace-like (Fig. 1). In actual fact this [illegible] that in most cases [illegible] the lesions in question [illegible]

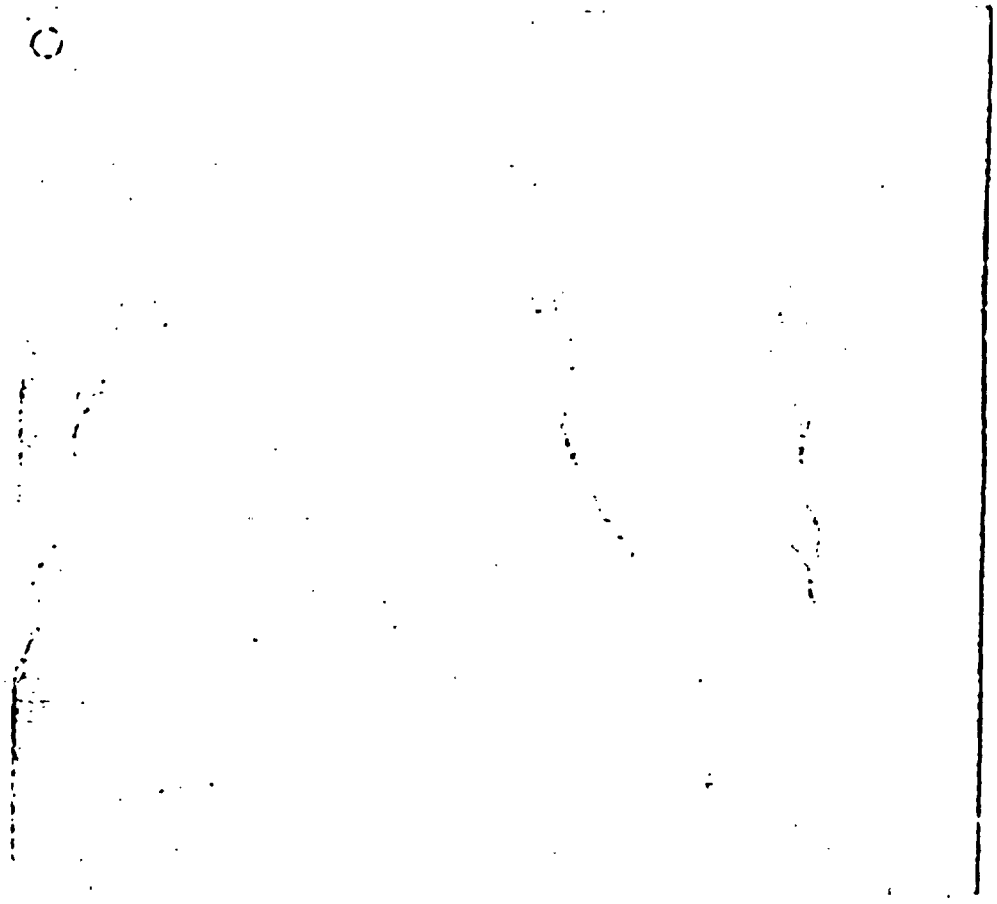

FIG. 1. Roentgenogram of a 70-y. old farmer showing bilateral calcific pleural plaques. He had never been an asbestos worker, but he had all his life lived in a region containing asbestos deposits, at a distance of 1 km from one asbestos mine and 12 km from another.

other calcific pleural changes (Unruwitz, 1961; Raunio, 1966). Bilateral, symmetric involvement is very characteristic (Kivilnoto, 1960; Marsová, 1964; Selikoff, 1965; Raunio, 1966). The left side is more heavily affected, and in unilateral cases it is the side more often involved (Kivilnoto, 1960; Selikoff, 1965; Raunio, 1966). The lateral portions of the middle and lower fields and the central portion of the diaphragm are the areas of predilection, but in more advanced cases calcifications are also found on the pleural surfaces of the pericardium. It has been stated that the calcifications show a tendency to form streaks following the direction of the ribs in the lateral portions of the chest (Kivilnoto, 1960).

Calcific plaques are mostly found on the parietal pleura, as has also been established anatomically (Smith, 1952; Fehre, 1956; Kivilnoto, 1960, Winkler, 1961; Marsová, 1964). The pleural cavity is usually unfused in any event to the area of plaque formation (Fehre, 1956; Müller, 1958; Kivilnoto, 1960, Meurman, 1966).

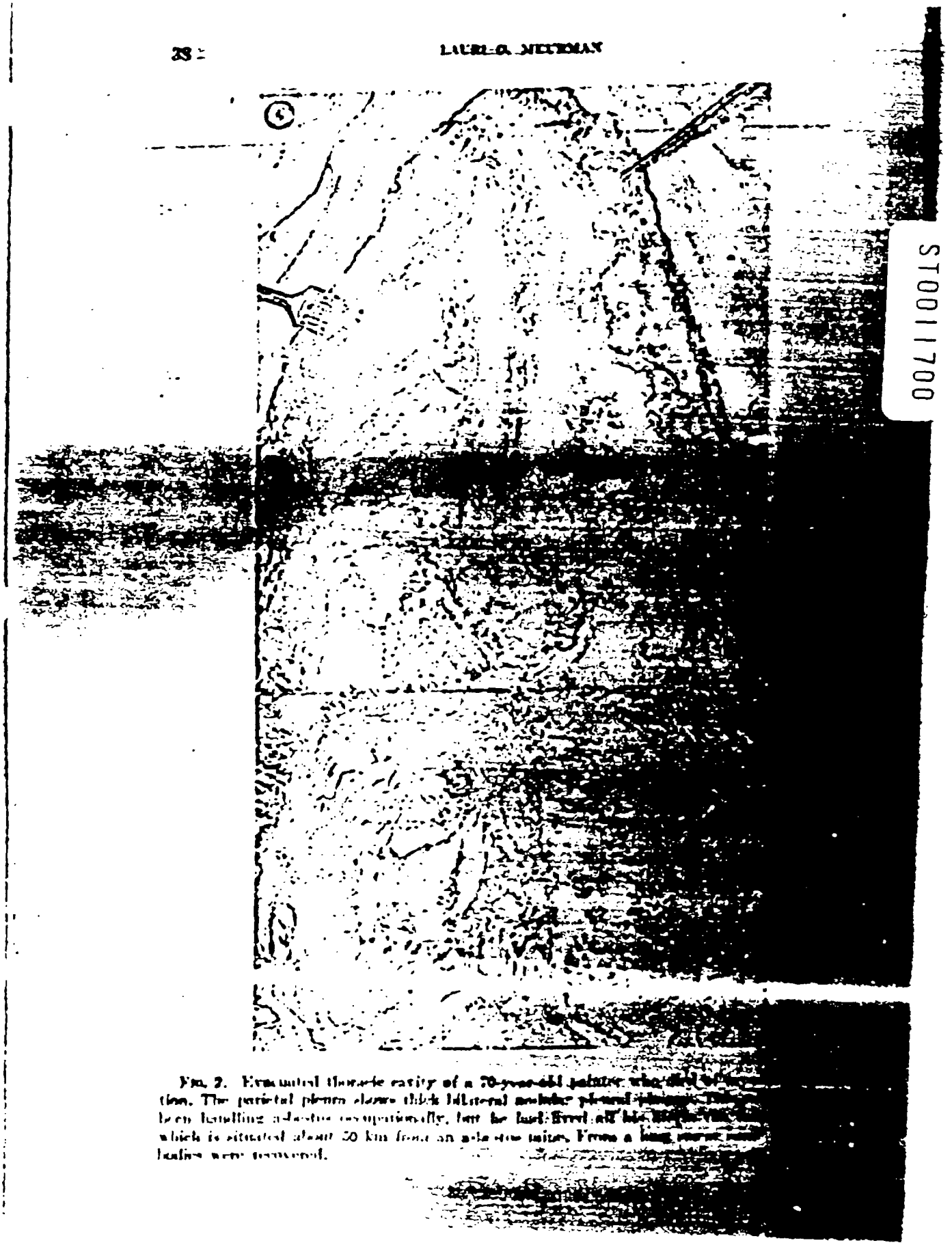

FIG. 2. Extramural thoracic cavity of a 70-year-old patient who died of [illegible]. The parietal pleura shows thick bilateral [illegible] pleural plaques. [illegible] been installing asbestos occupationally, but he had lived all his life in [illegible] which is situated about 30 km from an asbestos mine. From a [illegible] lesions were removed.

Pathological Anatomy of Pleural Calcifications

Grossly, the calcific plaques seen in the parietal pleura, and sometimes in the visceral pleura as well, are porcelain-like thickenings with a shiny surface. They are pearly white or ivory in color and often project more or less abruptly, like a plateau, over the surrounding tissue (Figs. 2 and 3). Their surface may be either smooth or nodular, as if packed with split peas. The plaques show wide variations in thickness, the range being from about 0.3 mm to 10 mm or larger. The variation in extent is also considerable, from small specks about 0.5 cm in diameter to almost continuous plaques covering the parietal and visceral pleurae. It is noteworthy, however, that the plaques seem to "avoid" the corners of the chest, since lesions are not found in the phrenicocostal sinus or in the area opposite the apices of the lungs (Meurman, 1966).

Histologically, it has been established that the calcified plaques consist of collagenous, hyaline, sclerotic connective tissue poor in cells, in which calcium has secondarily accumulated in varying amounts (Figs. 4 and 5) (Smith, 1932; Fehre, 1950; Müller, 1953; Meurman, 1966). The calcium concentration shows wide variation in different plaques in the same case and also in different parts of the same lesion. The calcium content, but not the thickness of the plaques, is decisive for their visibility on routine roentgenograms. A heavily calcified plaque appears yellowish gray and transparent, and if it is peeled off from the inner surface of the thorax, which is readily done, it feels lime-hard and fractures when bent. Plaques with a lower calcium content feel like cartilage and bend like leather.

Patho-anatomically the plaques correspond to the changes that have long been known by pathologists under the name of "sugar icing" or "frosting" (German: Zuckerguss) (Meurman, 1966). These lesions, the etiology of which has remained obscure, have mostly been encountered on the peritoneal surface of the liver and spleen, but also on the pleura and pericardium, and occasionally on the intestinal serosa (Borrmann, 1927).

Pleural plaques of the type described above, as well as "sugar icing," seem to develop as primarily chronic lesions, i.e., without any inflammatory, acute fibrinous stage followed by a granulation-tissue stage (Meurman, 1966). In no case of plaques so far investigated has an acute primary stage been observed. Also the thinnest plaques have been found to consist of collagenous hyaline sclerotic connective tissue.

The accumulation of calcium in the plaques is obviously a late, secondary [illegible] roentgenologically demonstrable calcific plaques have so far not been found in subjects younger than 30 years (Kiviluoto, 1960), while well-developed, weakly calcified pleural plaques have been observed at autopsy in an 18-year-old subject (Meurman, 1966). It is a well-known fact

FIG. 3. Thoracic cavity of an 81-year-old agricultural worker who died of hepatic coma due to liver cirrhosis. There are typical, thick bilateral pleural plaques with low calcium concentration, not visible on roentgenograms. This subject had lived at a distance of about 50 km from any asbestos mine, outside of the area containing asbestos deposits. He had not handled asbestos occupationally. No asbestos bodies were recovered from a lung smear, but in thick lung sections two typical asbestos bodies were found.

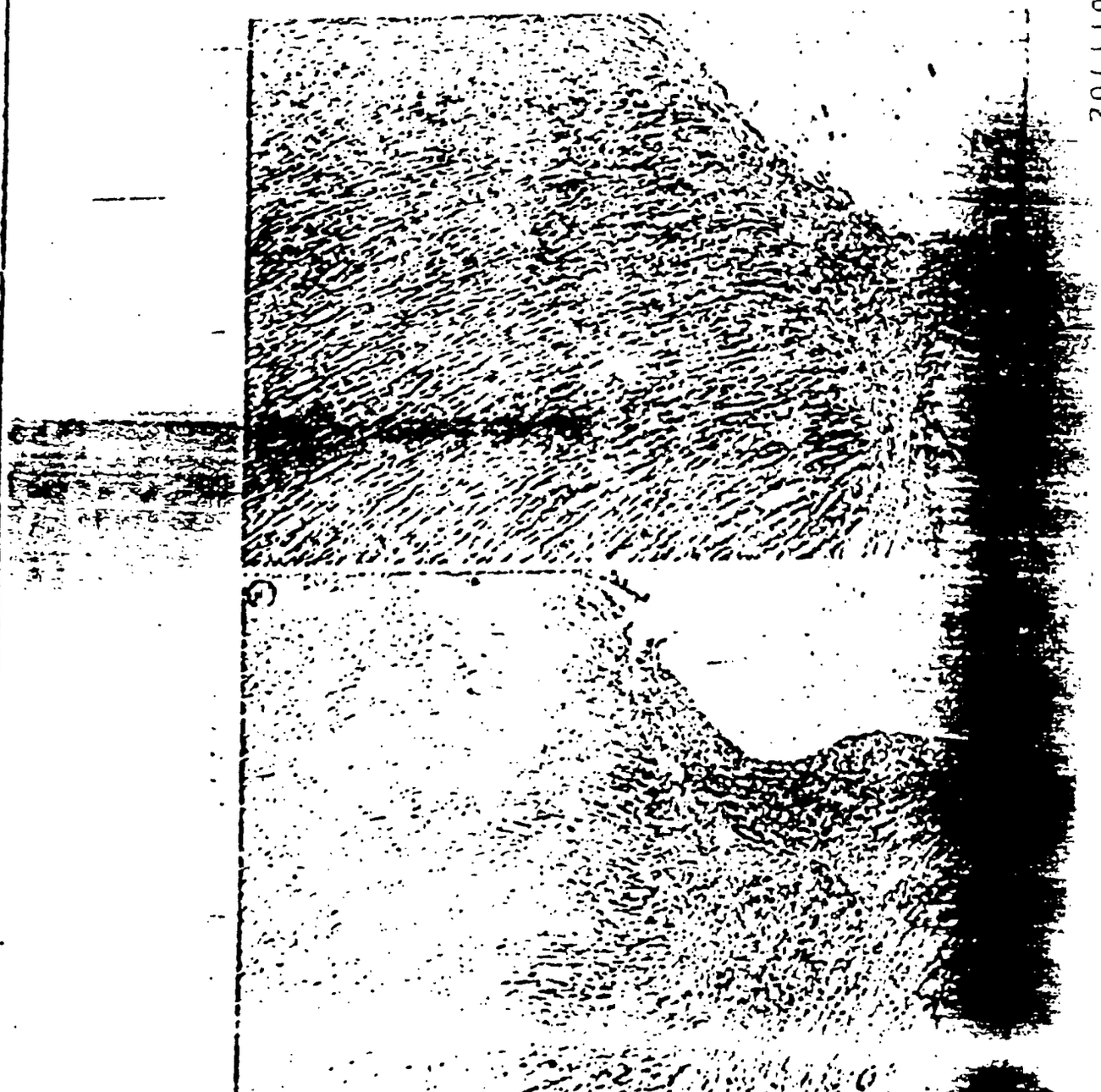

FIG. 4. Photomicrograph of a histological section from the margin of a typical [illegible] plaque showing transition from ordinary wavy collagenous connective tissue to [illegible] arborific, basket-weave-like tissue. van Gieson staining. ×15.

FIG. 5. Photomicrograph of a histological section from the margin of a pleural plaque. In the thickened area to the left calcium deposits are seen as densely packed black [illegible] the normal tissue to the right does not contain calcium. Alizarin red staining. ×15.

that hyaline connective-tissue degeneration, like necrosis, offers very favorable conditions for the accumulation of calcium deposits (Boyd, 1953).

Clinical Features in Cases of Pleural Calcification

In general, it appears that the presence of calcific plaques in the pleurae does not as such cause any subjective or objective symptoms or signs. Since in the majority of cases the lesions are not associated with any pathological changes in the lungs or any other organs, clinical disease proper does not seem to be involved (Kiviluoto, 1960; Marsová, 1961; Meurman, 1966; Raunio, 1966). Pulmonary fibrosis is a relatively common accompaniment, however, in particular when the plaques are so heavily calcified as to be visible on roentgenograms. In the 126 cases described by Kiviluoto, slight pulmonary fibrosis was detected in 12% and marked fibrosis in a further 12%. All subjects who had been occupationally exposed to asbestos dust at asbestos mines or mills were omitted from this series. Of the 53 subjects with pleural calcifications more thoroughly studied by Raunio, only two showed roentgenographically discernible fibrosis of the lung, and these subjects had been working at an asbestos mine. Raunio states, however, that in cases in which extensive pleural calcifications are present on the roentgenogram, fibrosis of the lung may be difficult to distinguish because it may be masked by the calcification.

On the other hand, in Selikoff's (1965) extensive series comprising insulation workers in New York, pleural calcification was almost invariably associated with pulmonary fibrosis varying in degree. The discrepancies may thus obviously be due to differences in composition of the series, i.e., whether they consist of occupationally or environmentally exposed subjects.

Calcific Pleural Plaques and Diffuse Mesothelioma

It is striking that an association between asbestos exposure on the one hand and on the other two different kinds of pleural lesion, i.e., benign calcific disseminated plaques in one study and malignant diffuse mesothelioma in another, was observed at roughly the same time by investigators working independently of each other in different parts of the world (Jacob and Bohlig, 1955; Wagner, 1959). Both these lesions are often associated with nonoccupational, obviously very slight asbestos exposure. Another feature in common seems to be that the conditions only became manifest after several decades have elapsed since the first exposure to asbestos dust (Kiviluoto, 1960; Wagner *et al.*, 1960). Moreover, both lesions have been observed in one and the same case (Weiss, 1953; Wagner, 1960; Lawson, 1963; Enticknap *et al.*, 1964; Steel *et al.*, 1965; Hourihane *et al.*, 1966; Castleman, 1967). From the histological standpoint attention may, in addition, be drawn to the structural resemblance between the stroma of benign hyaline sclerotic pleural plaques and diffuse mesothelioma of the second main group, the fibrotic type (Hourihane, 1966).

Numerous studies published in different parts of the world argue in favor of a significant correlation between the development of mesothelioma and asbestos exposure. In South Africa, Wagner *et al.* (1960) were the first to draw attention to this relationship, and somewhat later similar results were reported by Thomson

(1962). Convincing evidence has moreover been produced by Owen (1961); Hourihane (1961), and Newhouse and Thomson (1965) in England; Elmes *et al.* (1965) in North Ireland; Selikoff *et al.* (1965) in U.S.A.; König (1960) and Roitzsch (1965) in Germany; and McNulty (1962) in Australia.

On the other hand, a retrospective study of a 10-year autopsy series from the Malmö Hospital, performed by the present author in co-operation with Swedish pathologists (Högstrand *et al.*, 1968), gave no definite proof of an association between exposure to asbestos dust and the development of diffuse mesothelioma. This neoplasm was detected in 31 cases. In 18 of these, asbestos bodies were found in the lungs, in 6 cases in relative abundance. However, in a control series from the same hospital with the same composition as regards age and sex, asbestos bodies were found in the lungs in 12 cases, in 3 in large amounts. Since small numbers of asbestos bodies in the lungs are a frequent finding according to available statistics from different parts of the world, these results cannot be regarded as clear evidence of an association between asbestos exposure and mesothelioma. The same material was later roentgenologically examined by Kiviluoto (personal communication 1967). Among the cases with mesothelioma, two showed obvious and one uncertain pleural calcification.

The results concerning the relationship between asbestos exposure and diffuse mesothelioma are thus somewhat contradictory, and the same applies to asbestos exposure and pleural plaques. It seems obvious that asbestos plays an essential part in the development of both these lesions, but it also appears that other, as yet unknown factors, possibly environmental, may be involved. These factors may, moreover, be responsible for the development of benign (polyserositis fibrosa, Gosserjé, cited by Borrman, 1927) or malignant changes of the pleura or peritoneum, perhaps even without exposure to asbestos. Cartier's (1963) statement that the factor that causes asbestosis is not identical with the factor causing calcific pleural plaques therefore seems to hold good. But this unknown factor very frequently appears to be associated with exposure to asbestos dust.

Theories Concerning the Pathogenesis of Pleural Plaques

The calcification of pleural plaques is readily accounted for by their histological structure. Hyaline sclerotic collagenous connective tissue is precisely the kind of tissue with low vitality that favors the precipitation of calcium ions as phosphates. With increasing age the fluid concentration in the tissues is lowered, with the result that calcium salt precipitates in the sclerotic tissue gradually increase. It is much more difficult to understand why and how hyaline sclerotic connective tissue develops precisely in some irregularly shaped areas of the parietal and sometimes visceral pleura.

On the assumption that asbestos dust is the only cause of plaque formation, it might be suggested that the causative mechanism consists of direct mechanical friction (Siegal *et al.*, 1943; Kiviluoto, 1959). This theory presupposes that the asbestos fibers penetrate the visceral pleura and scratch the surface of the parietal pleura as a result of the respiratory movements, thus causing a fibrinous exudation in the pleural cavity. From the plaque granulation tissue would then grow into the fibrous tissue and gradually develop into hyaline sclerotic con-

nective tissue in the manner typical of scar formation. This hypothesis is compatible with the predominant location of the plaques in those areas of the parietal pleura where the respiratory movements are strongest (Kiviluoto, 1960). Although asbestos dust is found under the visceral pleura in only relatively small amounts in advanced cases of asbestosis, penetration of the pleura by asbestos dust is by no means impossible, since asbestos bodies protruding into the pleural cavity have been recovered from the surface of the lungs (Meurman, 1966). Likewise, asbestos fibers, though no asbestos bodies, have been found in parietal pleural plaques (Hourihane, 1966).

On the other hand, the presence of asbestos fibers in the parietal pleura does not necessarily mean that these fibers have migrated from the lungs through the pleural cavity. Asbestos dust has been recovered from many organs, e.g., the kidneys, bone marrow, liver, adrenals, spleen, and gastrointestinal tract (Selikoff *et al.*, 1965). Hence it seems possible that asbestos fibers are transported to the parietal pleura with the blood stream or via the lymphatics. Another argument against the mechanical injection theory is that the latter presupposes a preliminary stage of fibrinous exudation, and according to patho-anatomical experience fibrinous exudation as a rule leads to obliteration of the pleural cavity. So far, no evidence has been produced of either fibrinous exudation or any other preliminary stage of plaque formation preceding the hyaline sclerotic connective-tissue stage. In addition, plaques occur admittedly when the pleural cavity is unfused or, if it is obliterated, as a rule at those sites where it has remained open.

Of purely chemical theories regarding the pathogenesis of plaques, that offered by Lawson (1963) seems to be the most precise. Lawson suggests that the magnesium contained in asbestos and talc may be responsible for calcification by activating alkaline phosphatase.

A combined effect of physical and chemical factors is presupposed by the theory advanced by the present author (Meurman, 1966), according to which the sites of predilection of the plaques are those areas of the parietal pleura where the greatest amount of stretching is caused by the respiratory movements. The effect of asbestos as a contributory factor would consist of altering the composition of the fluid passing from the lungs to the pleural cavity. This change would be due to intrapulmonary damage caused by the asbestos fibers, comparable with microhemorrhages. And hemothorax is known to be the most common cause of pleural calcification.

So far no conclusive evidence has been advanced in support of any theory concerning the pathogenesis of plaque formation.

SUMMARY

This paper is a review of recent literature concerning calcific pleural plaques. It is established that multiple calcific pleural plaques are a rare roentgenographic finding in all population groups except miners and industrial workers who handle asbestos or talc. A noteworthy concentration of cases showing plaques has also been observed in populations living in the vicinity of asbestos mines. However, in certain areas a high frequency of pleural calcification has been noted without any asbestos exposure being demonstrable. Pleural plaques are a common

autopsy finding, and a certain regularity has been observed in their location. Anatomically and histologically, the plaques correspond to fibrotic [illegible] although in most cases their calcium content is so low that the lesions [illegible] visible on roentgenograms.

In industrial workers occupationally exposed to asbestos dust, pleural [illegible] tion is often associated with pulmonary fibrosis. By contrast, in those [illegible] which slight exposure to asbestos dust results from living in an area [illegible] asbestos deposits, or in the neighborhood of asbestos factories, ca[illegible] not as a rule associated with pulmonary fibrosis. If this condition is [illegible] is so mild that it cannot be demonstrated roentgenographically and [illegible] manifest itself as respiratory insufficiency. In addition to asbestos dust [illegible] some unknown endogenous or exogenous contributory factor seems to be [illegible] ble for pleural plaque formation. The presence or absence of this fa[illegible] viously decisive in respect to the development of plaques. In some [illegible] certain areas this hypothetical factor appears to be capable of produ[illegible] pleural plaques even without exposure to asbestos dust. The pat[illegible] pleural plaques is as yet obscure.

REFERENCES

ANSPACH, M. (1962). Sind Pleuraverkalkungen pathognomonish für eine Asb[illegible] *Arch. Gewerbepathol.* 19, 108-120.

BJURE, J., SÖDERHOLM, B., AND WIDIMSKY, J. (1961). Cardiopulmonary functi[illegible] workers dealing with asbestos and glasswool. *Thorax* 19, 22-27.

BORRMANN, A. (1927). Über Polyserositis chronica fibrosa und verwandte Z[illegible] *chows Arch. Pathol. Anat. Physiol. Klin. Med.* 201, 700-729.

BOYD, W. (1933). "A Text-Book of Pathology," sixth edition, Kimpton, Lond[illegible]

CARTIER, P. (1965). *Discussion in* Section VI. "Clinical studies of pulmonar[illegible] *Ann. N.Y. Acad. Sci.* 132, 387-388.

CASTLEMAN, B., AND FLETCHER, F. G. (1967). Case records of the Massach[illegible] Hospital. Case 4-1967. *New Engl. J. Med.* 276, 230-237.

CLAUS, H. G. (1962). Eine ungewöhnliche doppelseitige Pleuraverkalk[illegible] *Roentgenstr.* 97, 812-815.

ELMES, P. C., MCCAUGHEY, W. T. E., AND WADE, O. L. (1965). Diffuse meso[illegible] the pleura and asbestos. *Brit. Med. J.* 1, 350-353.

ENTICKNAP, J. B., AND SMITHER, W. J. (1964). Peritoneal tumours in asbest[illegible] *Ind. Med.* 21, 20-31.

FEHRE, W. (1956). Über doppelseitige Pleuraverkalkungen infolge beruflich[illegible] wirkungen. *Fortschr. Roentgenstr.* 85, 16-25.

FLOYD, C., AND HEPPLES, R. H. (1939). Calcification of the pleura. *Am. Rev. [illegible] Pulmonary Diseases* 40, 215-224.

FROST, J., GEORG, J., AND MØLLER, P. F. (1956). Asbestosis with pleural calcifi[illegible] insulation workers. *Dan. Med. Bull.* 3, 202-204.

GARAVAGLIA, C. (1963). Le calcificazioni pleuriche nelle pneumoconiosi. *Med. L[illegible]* 279-288.

GHEZZI, I., MOLINARI, G., AND PICCETTI, U. (1967). Asbestos bodies in the lung[illegible] habitants of Milan. *Med. Lavoro* 58, 221-227.

HAEGERHOLM, L., MEURMAN, L., AND OLSEN, R. (1968). Asbestos bodies in the lungs and and mesothelioma. *Acta Pathol. Microbiol. Scand.* 72, 177-191.

HOURIHANE, D. O'B. (1964). The pathology of mesotheliomata and an analysis of their association with asbestos exposure. *Thorax* 19, 268-278.

[illegible], L., and [illegible], P. C. (1956). Hyaline and calcified [illegible] of exposure to asbestos. *Brit. Med. J.* 1, 1070-1074.
[illegible]. Hromadný výskyt charakteristických pleurálních změn a obyvatelstva [illegible] kraje Jihlava. *Rozhledy Tuberk.* 22, 103-111.
[illegible]. Roentgenologic aspects of asbestosis. *Am. J. Roentgenol. Radium Therapy* [illegible] 85, 296-302.
[illegible] (1956). Die röntgenologischen Komplikationen der Lungenasbestose. *Fortschr.* [illegible] 83, 515-525.
[illegible]. Pleural calcification as a roentgenologic sign of non-occupational [illegible]-asbestosis. *Acta Radiol. Suppl.* 194, 1-67.
[illegible], J., and Shapiro, J. (1956). Clinical, radiological and physiological [illegible]. *Arch. Internal Med.* 117, 813-819.
Klein, [illegible]. Über die Asbestose. *Arch. Gewerbepathol. Gewerbehyg.* 18, 159-201.
[illegible], and Rauste, V. (1955). Observations on atmospheric air pollution caused by [illegible]. *Ann. N.Y. Acad. Sci.* 132, 240-245.
Lawrence, J. P. (1955). Pleural calcification as a sign of asbestosis. *Clin. Radiol.* 14, 111-117.
Mansori, D. (1951). Beitrag zur Ätiologie der Pleuraverkalkungen. *Z. Tuberk.* 121, 329-334.
Meurman, L. (1956). Asbestos bodies and pleural plaques in a Finnish series of autopsy cases. *Acta Pathol. Microbiol. Scand. Suppl.* 131, 1-107.
McNulty, J. C. (1952). Malignant pleural mesothelioma in an asbestos worker. *Med. J. Australia* 2, 863-864.
Müller, H. (1956). Über schwere Formen der Asbestose. in "Die Staublungenerkrankungen" (K. W. Jötten and W. Klosterkötter, eds.), Vol. 2, pp. 501-504. Steinkopff, Darmstadt.
Müller, H. (1957). Pleuraverkalkungen bei der Asbeststaublunge. *Radiol. Diagn.* 3, 33-38.
Nizze, W. (1953). Beiderseitige Pleuraverkalkungen im Alter. *Fortschr. Roentgenstr.* 99, 632-638.
Newhouse, M. L., and Thomson, H. (1965). Mesothelioma of pleura and peritoneum following exposure to asbestos in the London area. *Brit. J. Ind. Med.* 22, 261-269.
Oosthuizen, S. F., Theron, C. P., and Sluis-Cremer, G. K. (1961). Calcified pleural plaques in asbestosis. *Proc. Mine Med. Officers Ass.* 10, 196-201.
Owen, W. G. (1964). Diffuse mesothelioma and exposure to asbestos dust in the Merseyside area. *Brit. Med. J.* 2, 211-213.
Raunio, V. (1956). Occurrence of unusual pleural calcification in Finland. *Ann. Med. Intern. Fenn., Suppl.* 47, 1-61.
Rotzsch, A. G. (1953). Über die Koinzidenz von Asbestose und Mesotheliom. *Zbl. Allg. Pathol. Anat.* 103, 110.
Selikoff, I. J., Churg, J., and Hammond, E. C. (1964). Relation between exposure to asbestos and mesothelioma. *New Engl. J. Med.* 272, 560-565.
Selikoff, I. J. (1963). The occurrence of pleural calcification among asbestos insulation workers. *Ann. N.Y. Acad. Sci.* 132, 351-367.
Shaw, W., Smith, A. R., and Greenburg, L. (1953). The dust hazard in tremolite talc mining. *Am. J. Roentgenol. Radium Therapy Nucl. Med.* 69, 11-20.
Simons, C. A., Marchand, P., and Wagner, J. C. (1961). Diffuse pleural mesotheliomas in South Africa. *S. African Med. J.* 35, 25-34.
Smith, A. R. (1952). Pleural calcification resulting from exposure to certain dusts. *Am. J. Roentgenol. Radium Therapy Nucl. Med.* 67, 375-382.
Steel, S. J., and Reid, J. (1963). Pleural calcification and mesothelioma following exposure to asbestos. *Brit. J. Diseases Chest* 59, 130-132.
Thomson, J. G. (1962). Mesothelioma of pleura or peritoneum and limited basal asbestosis. *S. African Med. J.* 36, 759-760.
Wagner, J. C. (1960). Some pathological aspects of asbestosis in the Union of South Africa. in "Proceedings of the Pneumoconiosis Conference" (A. J. Orenstein, ed.) Johannesburg 1959, pp. 373-382. Churchill, London.
Wagner, J. C., Sleggs, C. A., and Marchand, P. (1960). Diffuse pleural mesothelioma and asbestos exposure in the North West Cape Province. *Brit. J. Ind. Med.* 17, 260-271.

Weiss, A. (1953). Pleuraktels bei Lungenasbestose, in vivo morphologisch gesich
Medizinische 3, 93-91.
Wenker, A. (1961). Die Talkstaublunge. in "Handbuch der gesamte Arbeitsmedizin" (
W. Rauder, ed.), Vol. II Berufskrankheiten 2nd subvol. Urban & Schwarzenberg, Münch
Zorov, Chr., Borissov, T., and Ivanov, L. (1967). Pleural asbestosis in agricultur
workers. *Environ. Res.* 1, 287-293.

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