

should wish to do so. The problems now posed by motor-cars and drugs are in many ways similar. We must ensure that the price of advance is not too high and that accidents are reduced to a minimum by foresight and care. Both are examined, licensed, and periodically reviewed. Roads and lines of communication of information are improved. The manufacturers are exhorted to introduce the latest safety devices and tests. However, in the final analysis, most depends on the driver and prescriber.

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PLAINTIFF'S EXHIBIT

CAP-242

Hyaline and Calcified Pleural Plaques as an Index of Exposure to Asbestos

A Study of Radiological and Pathological Features of 100 Cases with a Consideration of Epidemiology

D. O'B. HOURIHANE,* M.D., M.R.C.P.I., D.C.P.; LEILA LESSOF,† M.B., B.S., D.M.R.D.
 P. C. RICHARDSON,‡ M.B., B.S., B.SC., M.R.C.P.

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Benign collagenous pleural thickening is a common finding at necropsy in cases of asbestosis (Gloyne, 1933), and calcification may occur within the thickened serosa (Gloyne, 1938). Focal pleural calcification may be noted radiologically in asbestosis (Hurwitz, 1961; Lawson, 1963), but may also be seen in those who work with asbestos or other silicates without evidence of pulmonary disease (Smith, 1952). There is strong evidence from Finland (Kiviluoto, 1960) that environmental—that is, non-industrial—exposure to asbestos leads to the relatively common finding of focal pleural calcification (calcified pleural plaques) in a community.

This paper is concerned with the association between pleural plaques as seen at necropsy or in routine chest radiographs and exposure to asbestos, and we wish to emphasize the potential epidemiological value of radiology in assessing the prevalence of these lesions in a population.

There were 56 cases in which pleural plaques were found at necropsy, and 50 cases in which pleural calcification was seen on x-ray examination. Six of the patients from the radiological series had the presence of plaques confirmed at necropsy, so that the total number of cases with pleural plaques is 100.

Pathology

Hyaline pleural plaques occur as discrete elevated grey-white areas, usually involving the parietal layer and without associated effusion or adhesions (Fig. 1). The plaques vary greatly in size and shape, and the intervening pleura and unaffected visceral layer show a slight, diffuse thickening (Fig. 1). The cut surface is of a uniform glistening grey colour unless focal

calcification is present, when yellow spots or laminae may also be seen. Focal calcification within plaques is shown in x-ray films of parietal pleura in Figs. 2 and 3. Plaques are usually bilateral, most prominent in the lower halves of the pleurae, and tend to follow the lines of the ribs (Figs. 1, 2, and 3). Although their consistency is that of cartilage, histologically they are composed of laminated hyaline collagen and often show either spotty or massive focal calcification (Fig. 4). There is no suggestion of vascularity or of granulation tissue when examined *post mortem*, although surface fibrin incorporated into a plaque was observed in one case.

We could detect no other histological difference between plaques with some calcification and those with none, and we have used the term "hyaline pleural plaques" to refer to all of them.

Necropsy Prevalence

From 1 January to 31 December 1964 a personal examination of each necropsy at the Bernhard Baron Institute was attempted, and 16 cases with these plaques were found. There was no tuberculosis in the chest in any case, and after histological examination only two cases could be defined as "asbestosis" (pulmonary fibrosis due to asbestos). The total number of necropsies during 1964 was 381.

* Lecturer in Pathology, London Hospital Medical School. Present address: School of Pathology, Trinity College, Dublin.

† Late Senior Registrar in Radiology, London Hospital.

‡ Senior Medical Registrar, Department of Medicine, London Hospital. Reprints from Dr. D. O'B. Hourihane, School of Pathology, Trinity College, Dublin.

The incidence of these plaques is therefore at least 4.2% of all necropsies here. This is a minimal figure, as many necropsies were not in fact personally examined, and it is a simple matter to overlook these lesions in the post-mortem room unless care is taken to clean the pleura and examine all its surfaces. During 1965 a vigorous effort was made to attend all necropsies, including those performed by the Department of Forensic Medicine. The incidence during January–March was 15 of 134 necropsies (11.2%). Several of the plaques had tumours at their edges, either metastatic or primary diffuse mesothelioma, so it seemed that these lesions often interrupted the otherwise continuous spread of tumour on the pleural membrane, or that the lymphatics in these areas were blocked, and, consequently, trapped neoplastic cells preferentially. The presence of aggregates of carbon at the edges of many plaques also suggests lymphatic obstruction.

In addition to these 31 cases detected during routine necropsies at the Bernhard Baron Institute of Pathology nine cases were received from other pathologists during 1964; and plaques were found *post mortem* in an additional 16 subjects with clinical asbestosis who had been cared for at the London Hospital.

Association of Pleural Plaques with Asbestos

A sensitive and quick method for detecting asbestos bodies was found to be histological examination of routinely processed

basal lung tissue, cut at 30 μ and mounted unstained (Hourihane, 1965a). With this technique the lungs from 115 routine necropsies were examined, and classical asbestos bodies were found in 28 (24.3%). The number of blocks examined from positive and that from negative cases were comparable.

The lungs from each case in which pleural plaques were present were similarly examined, and, without exception, asbestos bodies were found in all 56. This was to be expected in the 16 cases of clinical asbestosis and the eight cases in which only histological evidence of asbestosis was found, consisting of pulmonary fibrosis associated with asbestos bodies and fibres. In the remaining 32 cases there had been no pulmonary reaction to the asbestos. The association between the plaques and asbestos bodies in the lungs is statistically significant ($P < 0.01$) when compared with the control series, whether the cases of asbestosis are included or not.

Attempts were made to identify asbestos within some of the plaques by means of a technique of incineration and phase-contrast microscopy which had already proved successful in dealing with mesotheliomata (Hourihane, 1965b). Histological preparations from 12 cases were incinerated, and asbestos fibres were found in four of them.

The mode of origin of these lesions is uncertain; they may be formed by the incorporation of fibrin into the pleura and its subsequent alteration to stain as collagen (Heard and Williams, 1961), or by the formation of collagen *de novo*. Either mechanism might be initiated by the presence of asbestos fibres in the pleural tissues; possibly the parietal pleura is predominantly affected, because the lymphatics here are subjected less to the milking movements of the chest viscera.

Tuberculosis has always been accepted as a cause of these plaques, and we have excluded any such from this study. We have in fact seen one case with a tuberculous lesion of the pleura in which there was a hyaline plaque of the parietal pleura of identical histology to those already described. No asbestos was found in the lungs of this case. No radiograph was available.

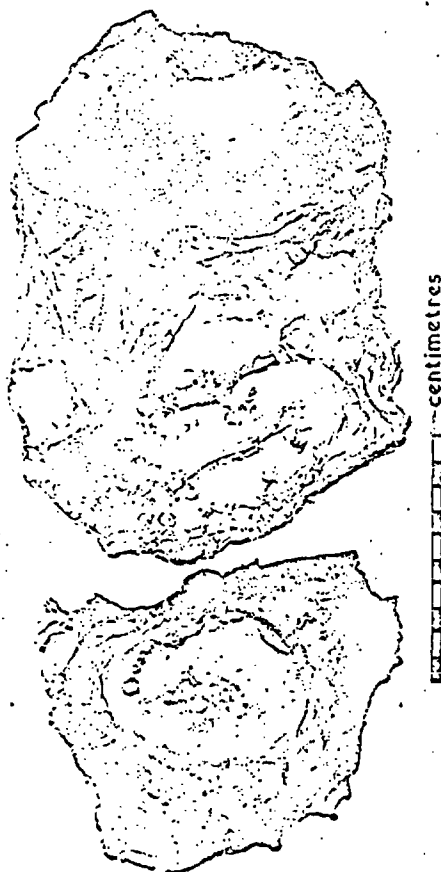


FIG. 1.—Left parietal pleura (upper) and left dome of diaphragm. The plaque in uppermost part is unusually large; the smooth oval plaques below it are of the type commonly seen. Note the tendency to follow the direction of the ribs, and the small nodular projections in the lower part of specimen and on the surface of the diaphragmatic plaques. No history of exposure to asbestos, but asbestos bodies in sputum and lung. Patient died with peritoneal mesothelioma.



FIG. 2.—X-ray film of parietal pleura shown in Fig. 1. Irregular calcification in largest plaque, with very little in others. Note the central "spot" of calcification within the nodules in lower part of photograph.

The majority of plaques (75%) were found in men, and most of the subjects died between 50 and 60 years of age. Apart from one woman of 35 who died with a mesothelioma and asbestosis, the youngest patient with a pleural plaque was aged 45 at death. The age and sex incidence correspond to those seen in the radiological series.

Pleural Calcification

When calcium is present in sufficient amounts, radio-opaque lesions can be detected on chest radiography. During routine reporting of chest radiographs at the London Hospital in the nine-month period beginning June 1964 36 cases of pleural calcification were seen in patients who had no history of pulmonary tuberculosis or other radiological evidence that might suggest this diagnosis. During this period approximately 27,500 chest radiographs were reported, but a systematic search for these calcific lesions was not carried out. Calcification was usually unassociated with evidence of a parenchymal lung lesion, but in seven cases there was radiological evidence of asbestosis (Hurwitz, 1961), and two others had a pleural effusion, which later was found to be associated

with mesothelioma. Usually, but not always, the calcification was bilateral and was found to affect all zones of the lung field, though commonly sparing the apices. Plaques were often noted on the diaphragm, presumably because of its tangential position in regard to the x-ray beam. The calcification often had an

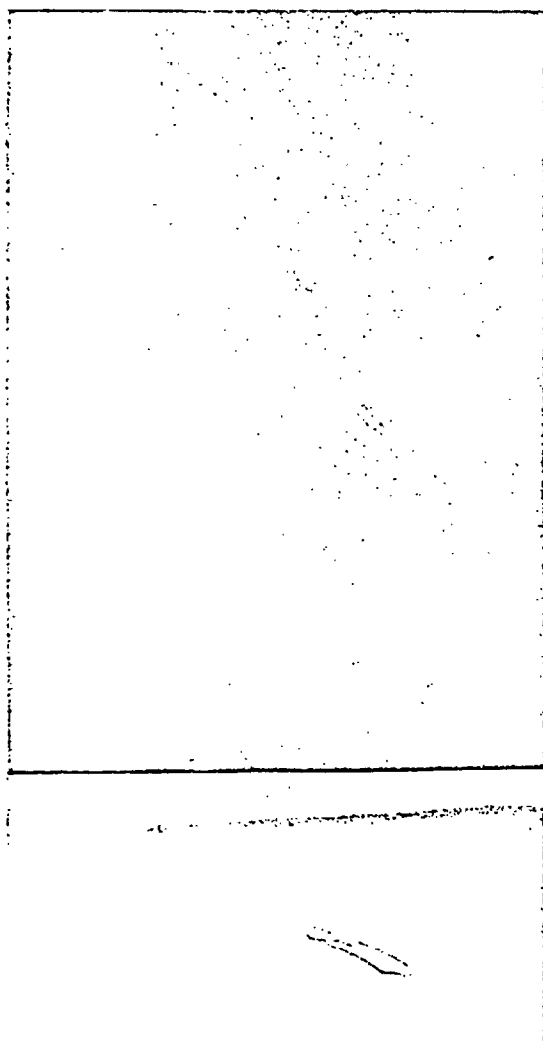


FIG. 3.—X-ray film of parietal pleura showing numerous plaques but very little calcification. Lower inset shows a dense zone of calcification within a diaphragmatic plaque in the same patient—a boiler-lagger for 30 years; he died with peritoneal mesothelioma.



FIG. 4.—Laminated hyaline collagen; the black spots and streaks are calcium salts. (Haematoxylin and eosin. $\times 90$.)

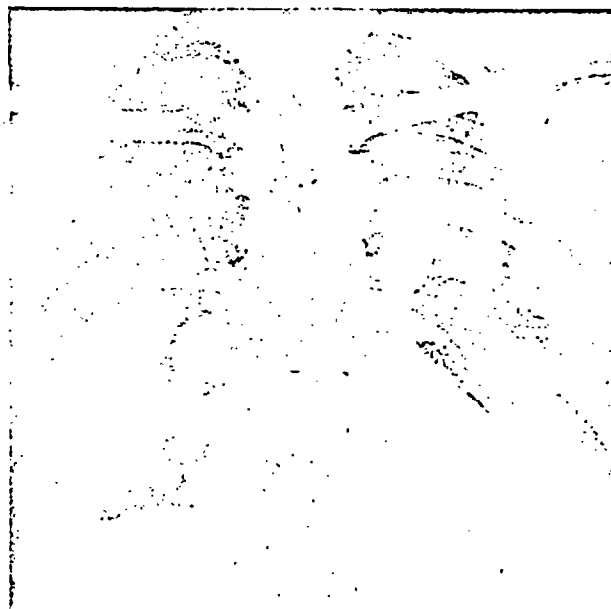


FIG. 5.—X-ray film showing speckled "holly-leaf" calcification overlying both lung fields; there are also plaques of calcium on both diaphragms. Exposure: patient's garden backed on to an asbestos factory and he lived there until aged 20. Moved from this address 27 years ago. Previous M.M.R. in 1954 was apparently normal.

uneven or speckled appearance, with irregular outlines like those of a holly leaf (Fig. 5). In one case the calcification was thought to be intrapulmonary, but the occurrence of a partial pneumothorax during aspiration clearly showed the calcification to be pleural (Fig. 6).

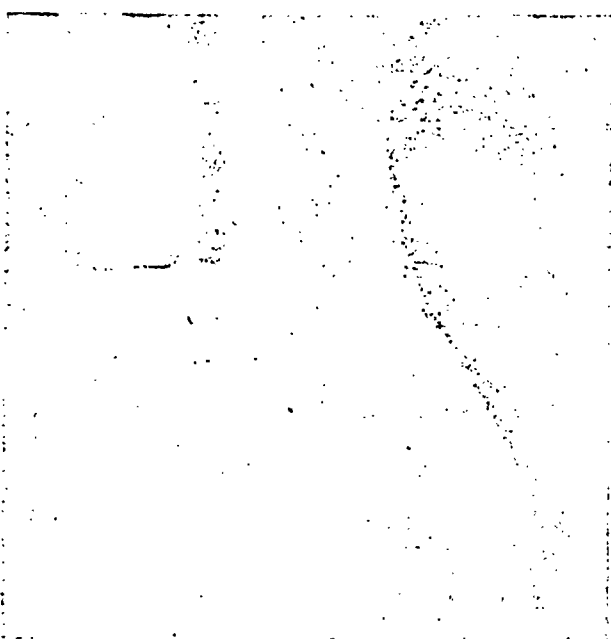


FIG. 6.—X-ray film showing calcification overlying left lung field. The right hydropneumothorax following aspiration shows the calcification to be in the parietal pleura. The patient had a mesothelioma of the right pleura, confirmed at necropsy. Exposure was two months in an asbestos factory over 40 years previously.

These findings are at striking variance with the experience of one of us at x-ray departments of two other London hospitals. The pleural calcification found in the seven cases with classical radiological evidence of asbestosis was indistinguishable from the calcification present in other cases in the series, including the cases of pleural mesotheliomata. This led to a wider survey, in which the radiographs of 36 cases of clinical asbestosis were examined and pleural calcification was found in eight. A previously published series of 65 cases of mesothelioma (Hourihane, 1964, 1965b) was also examined and six further cases of pleural calcifications were found, making a total of 50 patients in the radiological series. The association of calcified pleural plaques with other radiological abnormalities was not a constant finding. In 29 out of 36 cases discovered at routine sessions pleural calcification was the only abnormality which might suggest exposure to asbestos. In one case serial chest radiographs were available over a period of nine years. Initial radiographs showed one or two small opacities in the right upper zone. Nine years later there were extensive plaques of calcification in both upper lung fields.

Association of Pleural Calcification with Asbestos

An important failure to identify the lesions in the antemortem chest radiographs became apparent during this study. Only the most dense pleural calcification appeared to be detectable in routine chest x-ray films. Radiographs were available from 51 of the 56 subjects in whom plaques had been found at necropsy, and only seven of these had evidence of pleural calcification in life, associated in one with radiological appearances of asbestosis. All seven had histological evidence of asbestosis at necropsy.

In the total radiological series of 50 cases (33 males and 17 females) the ages ranged from 41 to 81 years, with a maximum incidence in the sixth decade. A history of exposure to asbestos was obtained in 43 (86%). Of the 16 tested eight had asbestos bodies in the sputum.

The evidence that pleural calcification, detected radiologically in 36 cases in the absence of a mesothelioma or known asbestosis, was associated with exposure to asbestos is summarized in Table I. A control group of 36 patients, with normal chest x-ray films and no history of pulmonary tuberculosis, was

TABLE I.—Types of Asbestos Exposure in 36 Cases of Pleural Calcification. (Previously Diagnosed Asbestosis or Mesothelioma Excluded from this Group)

Form of Exposure	Pleural Plaque Series	Control Group: with No Pleural Plaques
Employed at one asbestos factory ..	11	1†
Living within 1-mile (800 m.) radius of an asbestos factory, but no other contact ..	6	1
Insulators and ladders ..	6	0
Relative worked with asbestos or asbestos dust at home ..	2	2
Dockers or lorry-drivers handling asbestos cargoes ..	5	0
No history of exposure to asbestos ..	6*	32
	36	36

The difference in asbestos exposure between these two groups is statistically significant ($P < 0.01$).

* 1 patient had asbestos bodies in sputum and in lungs.

† Employed at asbestos factory for 1½ days: left "because of dust."

investigated similarly. The patients were matched for age and sex, care being taken to match for in-patient and outpatient status, and all had attended the same x-ray department within two months of the group with pleural plaques. A detailed history was taken from each group covering industrial, domestic, and environmental exposure to asbestos, and 4 out of the 36 control subjects gave a history of such exposure. The difference between the test series (83% positive history) and the control (11%) is statistically significant ($P < 0.01$).

The exposure to asbestos in the 36 cases in Table I varied considerably. One woman, who had calcified plaques on x-ray examination and who died of a malignant melanoma, had been exposed 25 years previously when she had held asbestos sheets intermittently over a period of six weeks while her husband sawed them to make rabbit hutches. Other patients, especially those employed as boiler-ladders, had been exposed for periods of up to 40 years.

Data concerning the exposure to asbestos in the entire radiological series of 50 cases and the causes of death among the 29 cases with no radiological evidence of asbestosis or mesothelioma are given in Tables II and III.

TABLE II.—Asbestos Exposure in Radiological Series of 50 Cases

Average time since first exposure to asbestos (known in 37 cases) ..	34.6 years (range 12–59)
Mean duration of exposure in 10 boiler-ladders ..	29.9 years (range 6–40)
Mean duration of exposure of 23 cases in other occupations ..	5.7 years (range 1½–30)

The following is an example of a case history.

A 67-year-old man had a laparotomy for generalized abdominal pain. At operation carcinomatosis peritonei was diagnosed, and this was supported on histological examination. In view of the finding of calcification on the diaphragms, in an otherwise normal chest x-ray picture, the histological slide was re-examined and a

TABLE III.—Pleural Plaques as Sole Radiological Abnormality in 29 Cases. Analysis of Causes of Death

	No. of cases
Subsequently died ..	7
Necropsy ..	5
Histological asbestosis ..	5
Causes of death:	
Malignant mesothelioma (3 peritoneal) ..	4
• Carcinoma of bronchus ..	1
Malignant melanoma ..	1
Respiratory failure ..	1

One additional patient has had a pleural mesothelioma diagnosed at thoracotomy and confirmed histologically, and is still alive.

* Necropsy not performed.

been shown not to be peritoneal mesotheliomata, since the clinical course and macroscopic appearances of these neoplasms can be very similar (Hourihane, 1964).

While necropsy and radiological surveys of other populations would be of great interest, and while the hazards of asbestos exposure are in need of more detailed analyses, the preventive and legal aspects of industrial, domestic, and environmental exposure require urgent consideration. Once pleural plaques have developed the dangers of supervening malignancy are great and the possibility of successful treatment is remote.

Summary

A close association between exposure to asbestos and the development of pleural plaques has been shown. A cause-and-effect relationship is probable. The most extensive lesions are radiologically detectable, and the disease asbestosis is then also present, despite the absence of any other radiological abnormality.

The sources of asbestos are considered and evidence is presented to suggest that there is a widespread non-industrial community exposure. Mesotheliomata are common in patients with pleural plaques, and it is suggested that there is a dose-response relationship between the asbestos and the development of these neoplasms.

The question of a relationship between lung cancer and asbestos is left open, but the value of radiological surveys for pleural plaques is emphasized in any study of this problem.

Asbestos is not the sole cause of pleural plaques, but it is certainly the most common.

We should like to thank the physicians and surgeons of the London Hospital who allowed us to refer to cases under their care, and the registrars of the x-ray department who helped us to collect the radiological series. We are grateful to Professor I. Doniach, Dr. N. Lloyd-Rusby, and Dr. L. J. Rae for encouragement and assistance. We are indebted to Mr. Moss and the film store for their help in tracing a large number of films, to Miss R. L. Cresswell for secretarial assistance, and to the photographic department for the illustrations.

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Effect of Aggregating Agents on the Electrophoretic Mobility of Human Platelets

J. R. HAMPTON,* M.A., B.M., M.R.C.P.; J. R. A. MITCHELL,† M.D., D.PHIL., M.R.C.P.

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In the presence of very low concentrations of adenosine diphosphate (A.D.P.), adenosine triphosphate (A.T.P.), 5-hydroxytryptamine (5-HT), and the adrenalines (Gaarder *et al.*, 1961; Mitchell and Sharp, 1964) platelets in a citrated plasma system adhere together to form aggregates, but the mechanism of this type of aggregation is unknown. Platelets carry a negative surface charge (Abramson, 1928), and they would normally be expected to repel each other; during aggregation the electrostatic forces must be overcome. The surface charge on cells can be measured by determining their electrophoretic mobility, and we considered that a study of the effect of the various aggregating agents on platelet charge might yield information on the nature of the clumping process. This paper reports the results of these studies.

Methods

Blood samples were obtained from healthy volunteers and from medical and surgical patients who did not have acute inflammatory conditions. Platelets from subjects with a variety of inflammatory states (pneumonia, phlebitis, pericarditis, and temporal arteritis) and with recent myocardial infarctions or

pulmonary emboli behave abnormally and will be described separately (Hampton and Mitchell, 1966b).

Platelet-rich and platelet-poor citrated plasma were prepared, and the platelets were brought into contact with glass, as described previously (Hampton and Mitchell, 1966a). Platelet-rich citrated plasma was diluted 1 in 10 with platelet-poor citrated plasma or with the other media specified below, and the electrophoretic mobility of platelets was measured in the horizontal capillary apparatus developed by Bangham *et al.* (1958). All measurements were made at 25° C. with a potential gradient of 2.66 V/cm. The mobilities are expressed as $\mu/\text{sec.}/\text{V/cm}$.

Effect of A.D.P. and Noradrenaline on Mobility

The post-contact mobility of platelets in a platelet-rich/platelet-poor citrated plasma mixture was measured. A.D.P. or noradrenaline (both from Sigma) was dissolved in 0.85%

* Junior Lecturer, Department of the Regius Professor of Medicine, the Radcliffe Infirmary, Oxford.

† First Assistant, Department of the Regius Professor of Medicine, the Radcliffe Infirmary, Oxford.