MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

by

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I. Introduction and Aims

The combined sex age-adjusted mesothelioma incidence rate for Connecticut was reported in 1977 to have increased ten-fold since 1935. Although available statistics might be subject to diagnostic error, the apparent rise was attributed to the increase in the State's 'cumulative asbestos consumption'. Complete occupational histories for the cases of mesothelioma were not presented. A detailed review of the available pathological material by an independent pathologist to investigate the degree of diagnostic certainty was not undertaken (Bruckman 1977; Bruckman 1978). The present study attempts to determine the role of various etiological factors, such as occupational and environmental asbestos exposures, and includes a review of available pathological material.

II. Methodology

The CTR has identified 229 cases of malignant mesothelioma as well as 38 other pleural tumors, not mesothelioma, which were diagnosed in the state between 1935 and 1977 ([redacted]).

Medical, demographic, and occupational data have been collected for the cases and for the respective spouses of cases diagnosed 1955-1977. Similar information has been gathered for a random sample of approximately 700 decedents (1935-75) aged 20 to 98 years from the Division of Health Statistics of the Connecticut Department of Health Services.

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Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. The case-control comparisons will comprise cases (215) diagnosed after 1954 ([redacted]), and controls (604) whose deaths occurred during this same time period. This procedure yields a case-control ratio of approximately 1:3, while reducing sources of error resulting from the limited occupational and medical data prior to 1955 and the lack of awareness of mesothelioma associated with this earlier time period (1935-1954). City Directories were searched for job title and name of specific employer or industry for cases, controls and spouses at 1, 10, 20, 25, 30, 40 and 50 years prior to date of diagnosis, death or until the subject was less than twenty years old (The Price and Lee Company, 1890-1977). An occupational history search was attempted for spouses to coincide with these intervals for their corresponding cases.

1970 U. S. Census industrial and occupational codes (U. S. Dept. of Commerce, Bureau of the Census, 1971) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. A computerized list of job and industry titles has been developed for all cases, spouses, and controls (1955-1977). This will form the basis for classification of study subjects into asbestos exposure categories for future case-control comparisons (Fig. 1).

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III. Results

Descriptive Epidemiology

The following descriptive results are based upon available CTR information and will require adjustment following the completion of the slide review. Using the 1950 U.S. population as a standard, the age-adjusted incidence rate for mesothelioma in Connecticut is 2.1/million for the years 1935-1977. Rates per 100,000 population increased for both sexes, but there was a rapid rise from about 1960 for males (Fig. 2). The male-female ratio is approximately 2:1; the mean age at diagnosis is 59 years. Average survival time from date of diagnosis to date of death is ten months.

10 cases were reported in New London Labor Market Area (LMA) where shipyards are located, and 5 of these were identified between 1975 and 1977 (Fig. 3). The geographical distribution of mesothelioma shows evidence of urban clusters in the 5 largest cities (Bridgeport, Hartford, Waterbury, Stamford, New Haven) where 30% of the cases resided at time of diagnosis (Fig. 3). Since these locations have comprised 20-30% of Connecticut's population (1940-1977), the suggested urban effect may reduce to a factor of population density. These 5 large cities and New London are all centers for LMA's. All 6 areas exhibit a similarly increasing age-adjusted incidence rate for males. The Stamford LMA's mesothelioma rate shows an unexplained sharp increase since 1965 (Fig.4).

SLIDE REVIEW

Malignant mesothelioma is a very rare disease with only 2 cases per million population expected annually. Resistance to the acceptance of mesothelioma as a disease entity persisted until the late 1960's. Wagner's widely publicized association of mesothelioma with Cape Crocidolite asbestos exposure created the potential for the introduction of diagnostic bias (Wagner, 1960).

Positive diagnosis of mesothelioma is often complicated by its confusion with other forms of cancer. It is important to differentiate between mesothelioma and metastatic carcinoma. Autopsy findings in such cases are extremely helpful in this regard. The use of special stains such as Alcian Blue with and without hyaluronidase, PAS with and without Diastase and to a lesser extent Mucicarmine and corrective tissue stains on surgical materials are valuable as well in this regard. The controversy over criteria for positive diagnosis is well documented in the literature (Kannerstein, 1977). Most experts agree, however, that a full autopsy is required to positively distinguish diffuse mesothelioma of the pleura or peritoneum from other primary or secondary neoplasms.

We examined, for all CTR reported cases of mesothelioma and for all plueral tumors other than mesothelioma (1935-77), the histological basis for diagnosis (Tables 2, 3). Whitwell has pointed out that the most striking histologic character of diffuse mesothelioma is the remarkable structural variation that occurs from area to area even

in the same case. For 12% (32) of the cases, no tissue was examined at time of diagnosis, while the origin of available material varied. Overall (1935-77) only 44% (105) of the 238 deceased cases are known by the CTR to have been autopsied, but only 83 (79%) of the autopsied cases were microscopically confirmed. The percentages for all categories, except peritoneal mesothelioma, are low ranging from 33% to 40% autopsied.

These results suggested the advisability of a case review. Dr. Romeo Vidone, chief pathologist of St. Raphael's Hospital, is presently studying the available clinical records in the CTR (except occupational data) and slides we have obtained for cases diagnosed after 1954. Cooperation was sought from 37 hospitals, of which 30 have thus far provided us with the materials requested.

The object of the case review will be to classify the cases relative to the certainty of diagnosis using well-defined criteria for the diagnosis of mesothelioma. In the first phase of the review the pathologist will have no knowledge of the occupational history or environmental exposure to asbestos. As the study progresses this data will be analyzed in relation to these factors.

On first review the cases in this study are being placed in one of six categories (Table 4), which represent the relative certainty of the diagnosis of mesothelioma using anatomic criteria. This is being carried out on all available materials, including cytologic preparations, surgical pathology and autopsy reports and slides. In all cases the

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diagnostic classification is based on autopsy materials, or surgical pathology material, in no case was cytology alone used to place a patient in category 1, 2 or 3. As the study progresses, attempts will be made to obtain the original blocks for additional special stains such as PAS with and without Diastase , Alcian Blue with and without hyaluronidase, Mucicarmine, Reticulin and Masson stain as indicated. It should be mentioned that in a number of the cases already reviewed some of the above mentioned stains were available.

The preliminary results of the primary review of the first 106 cases are shown in Table 5. 22 cases were considered to be mesothelioma, 38 probable mesothelioma and 28 possible mesothelioma. The 28 possible mesotheliomas, based on the material reviewed, might also possibly be some other condition such as metastatic carcinoma. Also on the basis of this first review, 6 cases were considered probably not mesothelioma and 5 were considered definitely not mesothelioma, 7 were considered unknown since no diagnostic classification could be arrived at based on the materials reviewed.

Classifications 1 and 2 were added together since these represent probable or definite mesotheliomas. Classifications 4 and 5 were also added together since these were considered not to be mesotheliomas. Thus 56.6% are thought to be mesothelioma, 26.4% are possibly mesothelioma and 10.4% not mesothelioma or excluded from the study. 6.6% are still classified as "unknown".

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IV. Discussion

Although this study was initially undertaken to discover whether it would be feasible to identify the environmental factors responsible for the increase of malignant mesothelioma in the State of Connecticut, it has suffered from lack of detail in available records. Major deficiencies in the data are the low autopsy rate for the pleural mesotheliomata and the inadequacy of some of the pathological material available and used for diagnostic purposes.

Felton has pointed out several reasons for post-mortem review. A problem may arise in workers' compensation adjudication where a decision has to be made, years to decades after initial work exposure, in those instances where death has resulted from pulmonary cancer or a thoracic or peritoneal mesothelioma. It is therefore important, in such cases, to be able to confirm by the presence of asbestos related effects that there has been exposure to respirable asbestos fibers (Felton, 1980).

A further need for autopsy arises to confirm the diagnosis of malignant mesothelioma made on limited biopsy material obtained during life. This is important for workers' compensation purposes and also to improve the epidemiological data required to investigate the etiological factors involved with this disease.

It has been our experience that occupational histories are not routinely obtained and included in hospital records. Although job information was obtained for 99% of the cases from all three sources (City Directory, Death Certificates, CTR), our search through records

stored at the CTR (i.e., hospital records) produced job titles for only 17% of the mesothelioma cases. If we exclude from this group those designated as "retired", "housewife", or "student", the figure is reduced to 12%. We were only able to ascertain type of industry in 7% of these cases. The sample size for these statistics was 220 cases diagnosed between 1955 and 1977. A recently passed Connecticut Statute, (Public Act 80-143) whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

Two other areas of epidemiological interest which are not routinely recorded for patients admitted with suspected malignant disease are smoking habits and hobbies or part-time activities.

In any retrospective review of mesothelioma it is essential to include an objective review of all anatomic pathology material. This review should include all available reports and slides including cytology, surgical pathology and autopsy materials. It should be conducted by an experienced pathologist thoroughly familiar with the gross and microcsopic characteristics of mesothelioma and with special expertise in the surgical pathology of tumors.

Another problem has been recognized which should be addressed. There is variation in the literature on the classification of these tumors. The lines between localized and diffuse mesothelioma are not always clear cut and the separation of benign from malignant is not always as readily apparent as one would be lead

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to believe by review of the literature. In fact, there are discrepancies between some of the classic papers in this field regarding characteristics of these neoplasms, both gross and microscopic. This is not limited to growth patterns such as that in the pleura or peritoneum, but includes such important characteristics such as metastatic patterns and certainly applies to histologic descriptions which are not uniform from paper to paper. It is hoped that as an outgrowth of this study some clarification of this aspect of the problem will be forthcoming.

It is evident that until the physicians investigating cases of malignancy appreciate the importance of occupational and environmental factors (lifestyle, habits, hobbies, part-time activities, detailed job histories), attempts to apportion blame to any particular factor for disease causation or promotion will be severely hampered. It is particularly essential in the case of a rare tumor, which may present diagnostic difficulties, to obtain sufficient tissue for study before a diagnosis is made. Whenever a tumor is found and an association is suspected with a particular occupational or environmental factor, every attempt should be made to document all relevant facts and to subsequently verify the diagnosis by means of a full autopsy.

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Table 1. Sex, age and diagnostic characteristics of 229 cases of malignant mesothelioma and 38 other pleural tumours diagnosed in Connecticut, 1935-1977

Diagnosis[a]	Males		Females		Total		Mean age	
Pleural mesothelioma	102	(94)[b]	45	(37)	147	(131)	61	(62)
Pleural tumour (other than mesothelioma)	24	(12)	14	(8)	38	(20)	62	(63)
Peritoneal mesothelioma	20	(18)	13	(11)	33	(29)	58	(59)
Mesothelioma at other sites & at unknown sites	29	(21)	20	(14)	49	(35)	52	(54)
Total	175	(145)	92	(70)	267	(215)	59	(60)

[a] WHO (1976)

[b] Numbers in brackets refer to the period 1955-1977

Table 2: Basis for Diagnostic Evaluation
for cases of Malignant Mesothelioma
and Pleural Tumors other than
Mesothelioma Diagnosed in Connecticut, 1935-1977

Diagnosis[a]	Tissue[b] Available	%	No Tissue Available	%	Total	%
Pleural Mesothelioma	136	(93)	11	(7)	147	(100)
Pleural Tumor (other than mesothelioma)	27	(71)	11	(29)	38	(100)
Peritoneal Mesothelioma	31	(94)	2	(6)	33	(100)
Mesothelioma at other sites and unknown sites	41	(84)	8	(16)	49	(100)
Total	235	(88)	32	(12)	267	(100)

[a] WHO (1976)

[b] specimen from biopsy, frozen section, surgery, autopsy, D and C

Table 3: Frequency of Autopsy for Cases of Malignant Mesothelioma and Pleural Tumors other than Mesothelioma Diagnosed in Connecticut, 1935-1977

Diagnosis[a]	(1) Autopsy, Microscopic Evidence of Cancer	(2) Autopsy, Gross Evidence of Cancer	(3) Autopsy Gross Evidence, Unknown Whether Cancer	(4) Autopsy, but only Indirect Evidence of Cancer	(5) Autopsy, no Report	(6) No Autopsy	(7) Unknown	(8) Number Dead	Autopsy[b] %
Pleural Mesothelioma	43	3		1	7	82	18	134	40
Pleural Tumor (other than mesothelioma)	8	1	1		3	13	11	37	35
Peritoneal Mesothelioma	21	4				2	1	28	89
Mesothelioma at other sites and unknown sites	11				2	21	5	39	33
Total	83	8	1	1	12	98	35	238	44%

[a] WHO (1976)

[b] $\frac{\text{cols(1) + (2) + (3) + (4) + (5)}}{\text{Col (8)}}$

Table 4

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION OF CASES

(Based on Review of Anatomic Pathology Material)

1. Mesothelioma
2. Probably Mesothelioma
3. Possible Mesothelioma (+ or -)
4. Probably Not Mesothelioma
5. Not Mesothelioma
6. Unknown

Table 5

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION BASED ON ANATOMIC PATHOLOGY REVIEW

PRELIMINARY RESULTS (106 Cases)

Classification	No.		No.	%
1. Mesothelioma	22	>	60	56.6%
2. Probably Mesothelioma	38			
3. Possible Mesothelioma	28	—	28	26.4%
4. Probably Not Mesothelioma	6	>	11	10.4%
5. Not Mesothelioma	5			
6. Unknown	7	—	7	6.6%
Total	106		106	100. %

Figure 1

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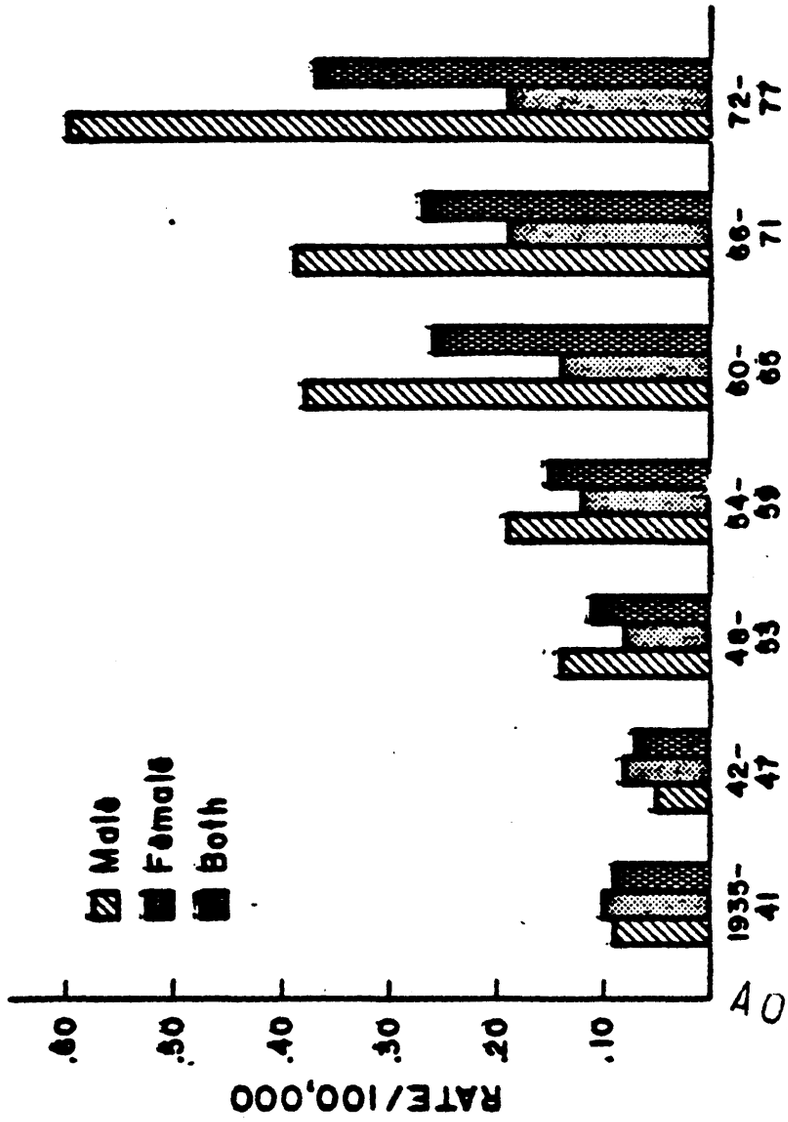

Figure 2

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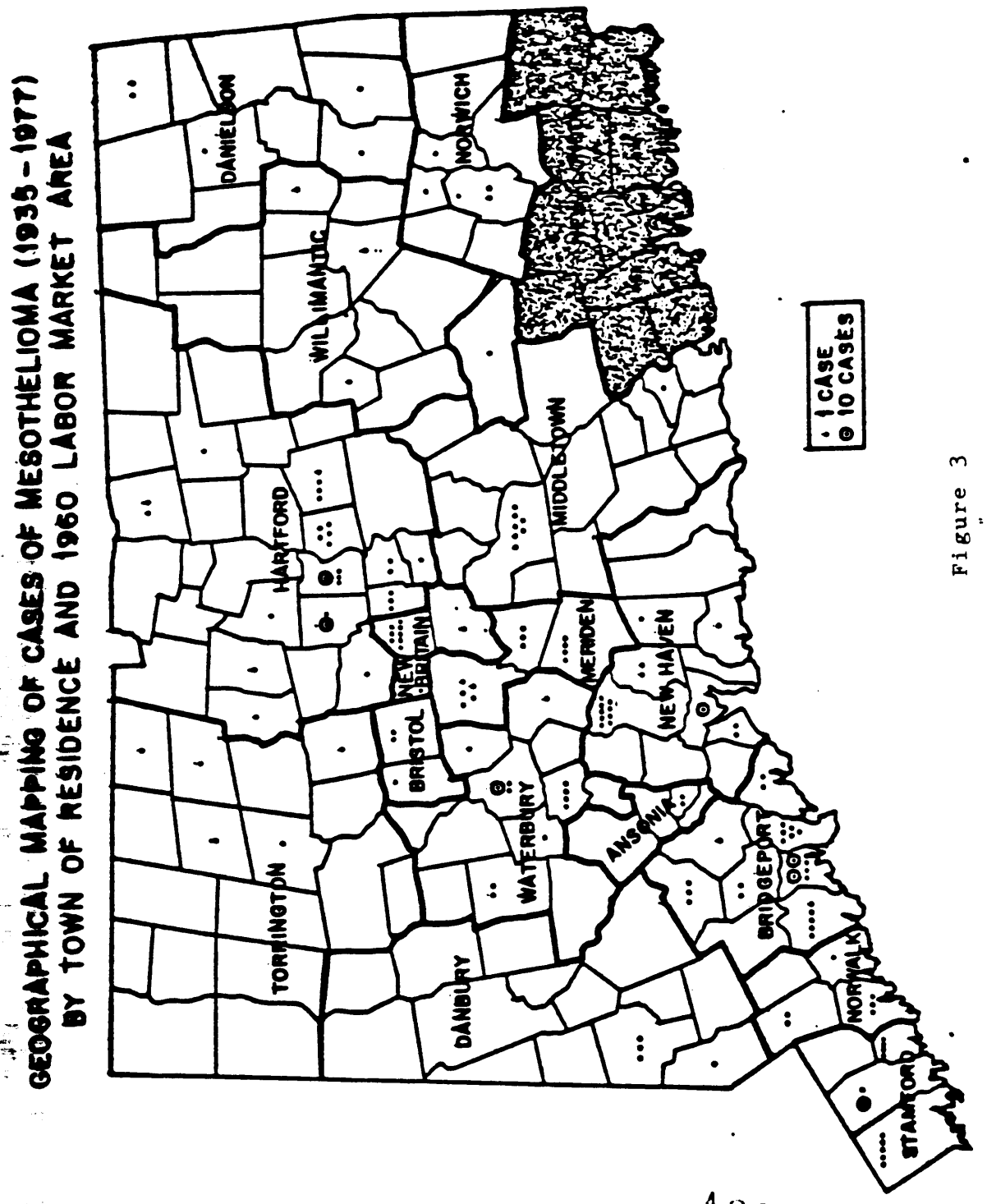

Figure 3

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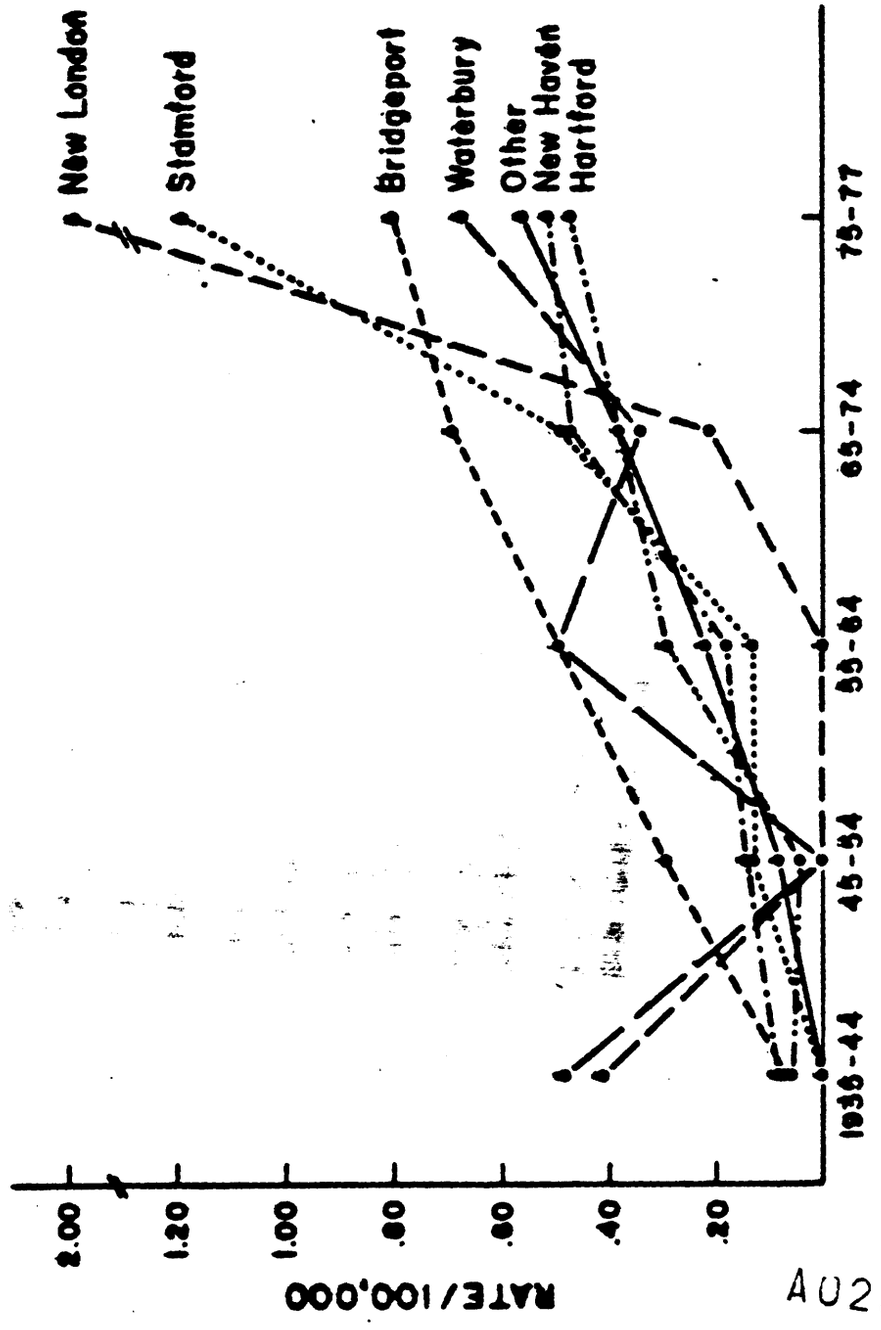
AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA
FOR CONNECTICUT MALES BY YEAR OF DIAGNOSIS
AND LABOR MARKET AREA
New London
Stamford
Bridgeport
Waterbury
Other
New Haven
Hartford
1935-44
45-54
55-64
65-74
75-77
RATE/100,000
2.00
1.20
1.00
.80
.60
.40
.20
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Figure 4

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THE INFLUENCE OF OCCUPATIONAL AND ENVIRONMENTAL ASBESTOS EXPOSURE ON THE INCIDENCE OF MALIGNANT MESOTHELIOMA IN CONNECTICUT

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INTRODUCTION

The combined sex age-adjusted mesothelioma incidence rate for Connecticut was reported recently to have increased ten-fold since 1935. Although available statistics might be subject to diagnostic error, the apparent rise was attributed to the increase in the state's 'cumulative asbestos consumption'. Complete occupational histories for the 133 cases of mesothelioma were not presented. An ambient air standard of 30 ng/m^3 measured over a 30-day interval was proposed and was justified by the reported rise in the state's mesothelioma incidence (Bruckman, 1978).

In the present study, the cases of mesothelioma recorded in the Connecticut Tumor Registry (CTR) were re-examined to determine the role of occupational and environmental exposures and to consider possible diagnostic errors through review of available histological material.

MATERIAL AND METHODS

The 229 cases of malignant mesothelioma identified by the CTR occurred at the following sites: pleura (147), peritoneum (33) and other sites (49); pleural tumours other than mesotheliomas were also recorded (38) (Table 1). Medical, demographic and occupational data were collected for the cases and for their respective spouses from hospital records, death certificates and City Directories (The Price and Lee Company, 1890-1977). Similar information was gathered for a random sample of decedents in Connecticut aged 20 to 98 years. The 1970 US Census Industrial and Occupational Codes (US Department of Commerce, Bureau of the Census, 1971) were assigned to the employment information obtained. Those cases with occupations associated in the literature with malignant mesothelioma were selected for study from all those with occupations in which there was probable asbestos exposure (Hutchison, 1976; Levine, 1978; McDonald, 1979; Weston, 1976).

Table 1. Sex, age and diagnostic characteristics of cases of malignant mesothelioma and other pleural tumours diagnosed in Connecticut, 1935-1977

Diagnosis[a]	Males	Females	Total	Mean age	Percent 'positive' histology[b]	Percent autopsied[c]
Pleural mesothelioma	102 (94)[d]	45 (37)	147 (131)	61 (62)	93 (95)	40 (38)
Pleural tumour (other than mesothelioma)	24 (12)	14 (8)	38 (20)	62 (63)	71 (85)	35 (37)
Peritoneal mesothelioma	20 (18)	13 (11)	33 (29)	58 (59)	94 (97)	89 (88)
Mesothelioma at other sites & at unknown sites	29 (21)	20 (14)	49 (35)	52 (54)	84 (86)	33 (41)
Total	175 (145)	92 (70)	267 (215)	59 (60)	88 (93)	44 (45)

[a] World Health Organization (1976)

[b] SEER, 1976 Code/Field Number 19 (US Department of Health, Education, and Welfare, National Cancer Institute, 1976)

[c] (No. autopsied/no. deceased) × 100

[d] Numbers in brackets refer to the period 1955-1977

Descriptive epidemiology for this research pertains to the time interval 1935-1977. Case-control comparison and statistical modelling include 215 cases diagnosed after 1954 and 605 controls (1955-1977). Information from 1935-1954 was inadequate for such comparisons due to limited occupational and clinical data and to the lack of awareness of mesothelioma.

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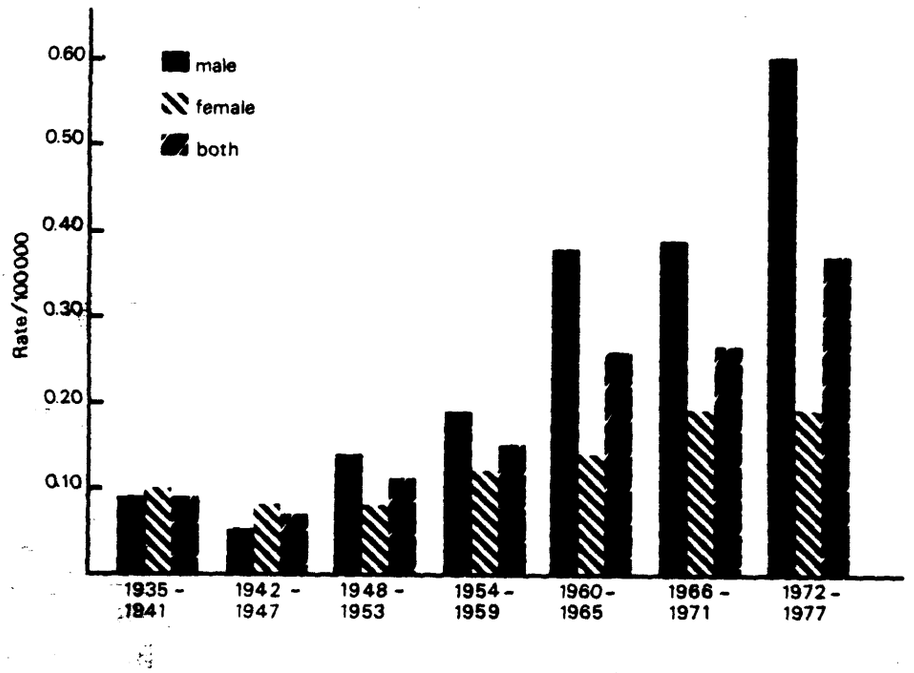
RESULTS

The crude incidence rate for mesothelioma in Connecticut is 2.2/ million for the years 1935-1977. Age-adjusted incidence rates per 100,000 population (using the 1950 US population as a standard) increased for both sexes, but there was a rapid rise from about 1960 for males (Fig. 1). Of the 229 cases, 195 were reported after 1954. The mean age at diagnosis was 59 years. The geographic distribution of these cases reveals a clustering in dense urban areas. Ten cases were reported (1955-1977) in an area where shipyards are located, and five of these were identified between 1975 and 1977.

FIG. 1. AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA IN CONNECTICUT BY YEAR OF DIAGNOSIS AND SEX



A logistic regression model was fitted to examine the incidence of pleural mesothelioma (1955-1977) as a function of time, age and sex. Connecticut population figures were used for denominator data in the

estimate of disease probability. The main effects model provided a reasonably good fit ($P > 0.10$). Relative risks (here approximated by the odds ratio) over time intervals, age categories and sex groups were estimated. Persons alive in 1975-1977 had a 3.5 times greater risk of developing pleural mesothelioma than those alive between 1955 and 1964 (95% confidence intervals (CI): 2.25, 5.48). With progression across the age intervals 45-54, 55-64, 65-74..., the individual risk of this disease is 1.5 times greater than in the preceding ten-year age group (95% CI: 1.13, 1.31). Males have 3.0 times the risk of females (95% CI: 2.10, 4.22).

These descriptive and analytical results assume completeness and accuracy of case identification. A sizeable proportion (56%) of the 267 cases were not autopsied; and autopsy percentages for pleural tumours other than mesothelioma and for mesotheliomas at other or unknown sites are low - 35% and 33%, respectively. The unknown site group had a mean age of only 52 years (Table 1). The differentiation of cases of malignant pleural tumours into mesothelioma and other pleural tumours is suspect. A discriminant function analysis of these two groups of cases (diagnosed after 1954) on the basis of age, sex, survival time, stage and number of tumours yields a 60% misclassification. These results suggest possible misdiagnosis and the advisability of a case review, which is made feasible by the large proportion of patients diagnosed on the basis of available histological material (Table 1).

When the mesothelioma incidence has been adjusted for diagnostic weaknesses and misclassifications and when the occupationally exposed cases, controls and spouses have been identified, it may be possible to determine the role of environmental asbestos exposure, if any, in the remaining cases.

SUMMARY

Medical, occupational and demographic data were collected for 229 cases of malignant mesothelioma and 38 other pleural tumours, their spouses, and 605 controls. Methods were developed for classifying subjects into probable asbestos exposure categories. Although disease incidence rates exhibited a rapid increase from 1955 to 1977, there remains a serious question of diagnostic reliability. A case review is being undertaken.

RESUME

Les auteurs ont recueilli des données médicales, professionnelles et démographiques sur 229 sujets atteints de mésothéliome malin et 38 d'autres tumeurs pleurales, leurs conjoints et 605 témoins. Ils ont mis au point des méthodes permettant de classer les individus en catégories d'exposition probable à l'amiante. Bien que les taux d'incidence de la maladie accusent une rapide augmentation de 1955 à 1977, il subsiste un sérieux problème de fiabilité diagnostique. Une étude de cas individuels est présentement entreprise.

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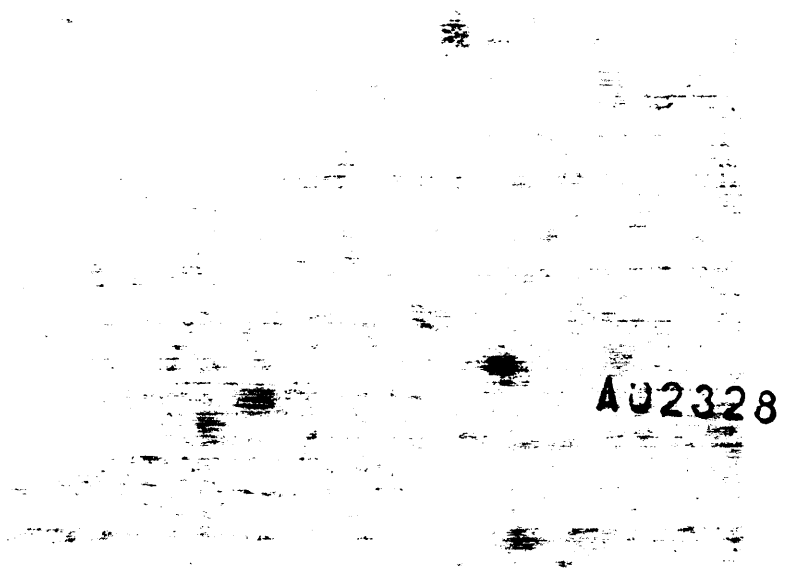

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EARLY MALIGNANT CHANGES IN PLEURAL PLAQUES DUE TO ASBESTOS EXPOSURE: A CASE REPORT

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PLEURAL lesions related to asbestos exposure are well documented (Meurman 1966; Mattson & Ringqvist 1970). The pathology has been described by Roberts (1971). Mattson and Ringqvist have studied 42 cases with radiological signs of pleural plaques at the Lung Clinic, Boras, diagnosed between 1961 and 1967. They define pleural plaques as 'bilateral, local, irregular thickenings of the parietal pleura which cannot be connected with haemorrhage, infection or injury'. These authors review the literature on the subject and point out Kiviluoto's (1960) conclusion that only amphibole asbestos can cause the development of pleural plaques. Two of Mattson and Ringqvist's patients have died of malignant mesothelioma during the 6-year period of observation. Fletcher and Edge (1970) have given an excellent description of the early radiological changes in pulmonary and pleural asbestosis. These authors prefer the latter term to pleural plaques in the title of their paper.

Case Report

A Caucasian male, born in 1907, died on 22 August 1970 after being absent from work for one week. He was born in the Channel Islands and worked as a farm labourer from 1921 to 1928. From 1928 to 1940 he worked in garages and was a truck and car driver. In 1940 he began his employment at a Rochdale asbestos textile factory, in an area now demolished. He worked on the disintegrators, crushing-machine, grit separators and was a member of the 'heavy gang' doing all sorts of dusty jobs which exposed him to chrysotile asbestos and occasionally also to crocidolite. In 1953 he changed his job to that of truck driver, delivering the bags of prepared asbestos fibre from the fiberizing plant to the factory for further processing. In 1960 he went to work in the company garage as a driver and garage-hand.

On engagement he was examined by the company Medical Officer but the records of this examination are no longer available. Medical records are available which show that he was regularly examined from 1950 onwards and that his chest was radiographed at approximately 2-yearly intervals until 1968 and annually thereafter. The medical records are brief. Rhonchi were first heard in his chest in July 1957. He was absent from work because of bronchitis during the winter of 1958–9 and thereafter was prone to annual winter

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bronchitis. In 1964 he was regarded as suffering from chronic bronchitis. In 1967 he began to complain of dyspnoea on effort and he became orthopnoeic, had Grade 1–2 effort dyspnoea and complained of occasional chest tightness after the 1967–8 winter. His symptoms of orthopnoea and dyspnoea on effort gradually increased. He was last examined in March 1970. He had stopped smoking in 1960 and never resumed. On examination in March 1970 he was cyanosed, had mild hypertension (BP 150/90) and physical signs compatible with chronic bronchitis. No finger-clubbing was noted.

Special investigations carried out (at work) consisted of serial chest radiography, lung function tests and an ECG in March 1968 and March 1970. No comment on these films appears in the medical records until 1969 when some enlargement of the cardiac outline was thought to have occurred.

He applied to the Pneumoconiosis Medical Panel for Industrial Injuries (Disablement) Benefit in March 1970, but was not accepted as it was considered that he was suffering from chronic airways obstruction and not asbestosis. In view of his rather sudden death, and his history of exposure to asbestos, the Coroner was informed and requested an autopsy examination. The autopsy was performed by the Coroner's Pathologist (Dr D. S. Lyon) on 24 August 1970.

Autopsy findings

The relevant autopsy findings relate to the thoracic cage and its contents. All the main airways were patent and mucoid secretions were present in large quantities. The lungs were distended and obviously emphysematous. They were congested on sectioning them. There was no pulmonary fibrosis present on naked eye examination.

On the left side, the chest wall and visceral pleural surface was studded with tumour nodules varying in size from 1–2 mm to 10 mm or more in diameter (Fig. 1). Calcified plaques were present on the left dome of the diaphragm and hyaline pleural plaques were seen on the chest wall. Similar pleural plaques were present on the right but no tumour nodules were seen.

TABLE 1. VENTILATORY CAPACITY AT VARIOUS AGES

	February 1968 (age 60 years)	*April 1968* (age 60 years)	*March 1969* (age 61 years)	*March 1970* (age 62 years)
FEV_1 (litres)	1·23	2·26 (4·06)	1·87 (3·67)	1·84 (3·68)
FVC (litres)	0·88	1·00 (3·08)	0·17 (2·67)	0·86 (2·65)
FEV_1/FVC %	49 (70–80)	44 (70–80)	46 (70–80)	46 (70–80)
Gas transfer factor (ml/min/mm Hg)	—	26·5 (22–5)	19 (24)	17 (24)
$Paco_2$ rebreathing	—	44·5 (36–40)	46 (36–40)	47 (36–40)

Figures in parenthesis indicate predicted normal values.
These results are compatible with restrictive and obstructive lung disease.

The mediastinal surface of the pericardium was studded with tumour nodules as was the outer wall of the oesophagus. The heart was enlarged due

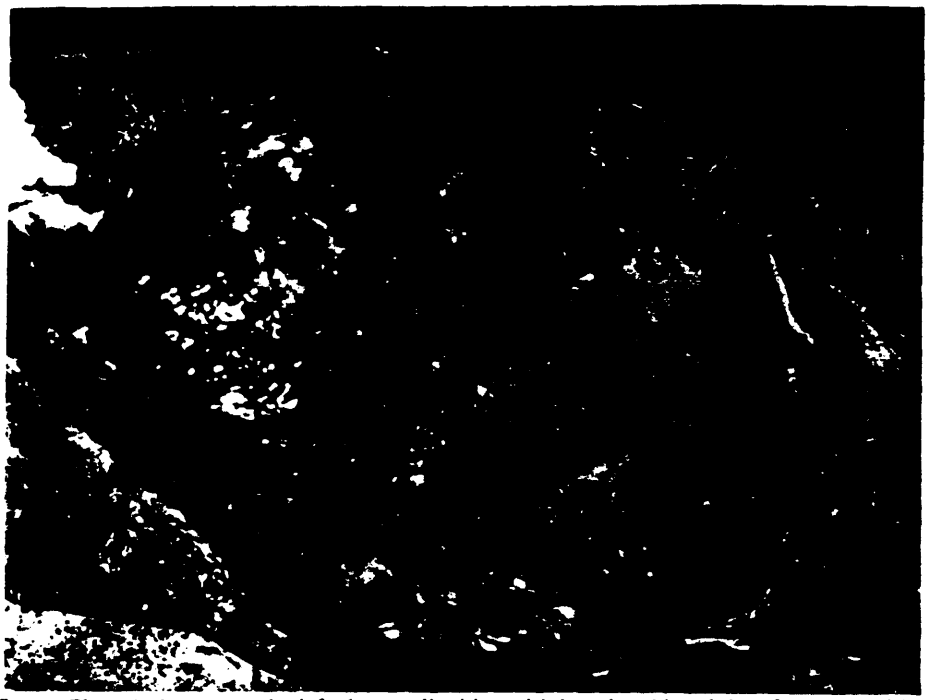

FIG. 1. Pleural plaques on the left chest wall with multiple polypoid nodules of tumour arising from them at post mortem

to left and right ventricular hypertrophy and dilatation. Patchy coronary atheroma was present and patchy myocardial fibrosis was found. The liver and spleen showed chronic venous congestion.

The diagnosis in this case was recorded by the Coroner's Pathologist, as 'mesothelioma due to exposure to asbestos'. Histological sections were also examined by the members of the U.I.C.C. panel of pathologists. The tumour was classified as a tubulopapillary type of malignant mesothelioma, with some areas showing sheets of undifferentiated cells but no sarcomatous elements. Asbestos bodies were found in the lungs and in places slight asbestosis as well.

Discussion

From the pathological point of view this case has several features of interest. Firstly, it shows discrete nodules of mesothelioma arising from both visceral and parietal pleural surfaces (Figs 2–5). While these may be the result of seedling deposition, it could also be argued that the diffuse mesothelioma is the result of confluence of a number of multifocal tumours, arising in both visceral and parietal pleural layers. The mesothelial cells lying adjacent to the tumour in Fig. 4 appear abnormally hyperplastic and suggest an unstable, pre-malignant state.

Secondly, this case illustrates that foci of mesothelioma can arise from the

FIG. 2. Mesothelioma arising in the cells overlying a hyaline parietal pleural plaque. The tumour arises from a narrow stalk and proliferates in a polypoid form to cover the adjacent pleura. × 48

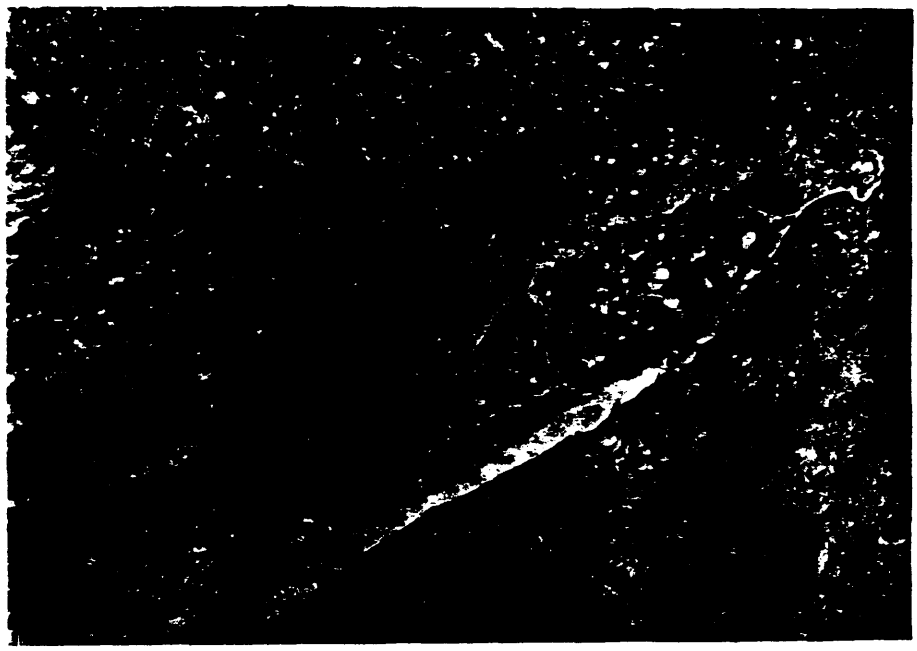

FIG. 3. Mesothelioma arising in the cells overlying a hyaline parietal pleural plaque. × 140

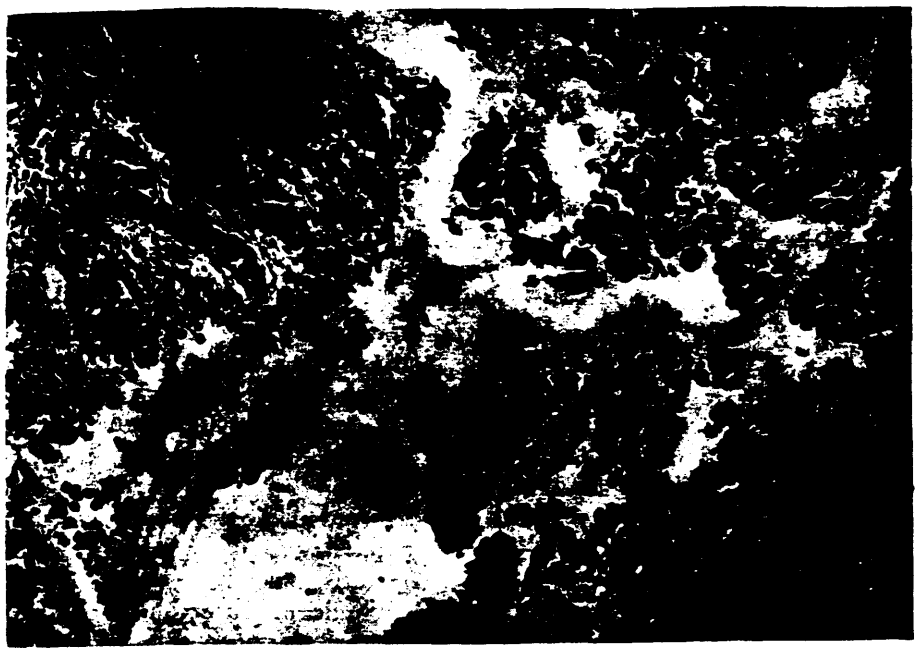

FIG. 4. Unstable mesothelial cells lining the parietal pleura adjacent to a focus of mesothelioma. The appearance suggests a diffuse origin of the tumour of multifocal distribution rather than multiple seedling deposits. × 200

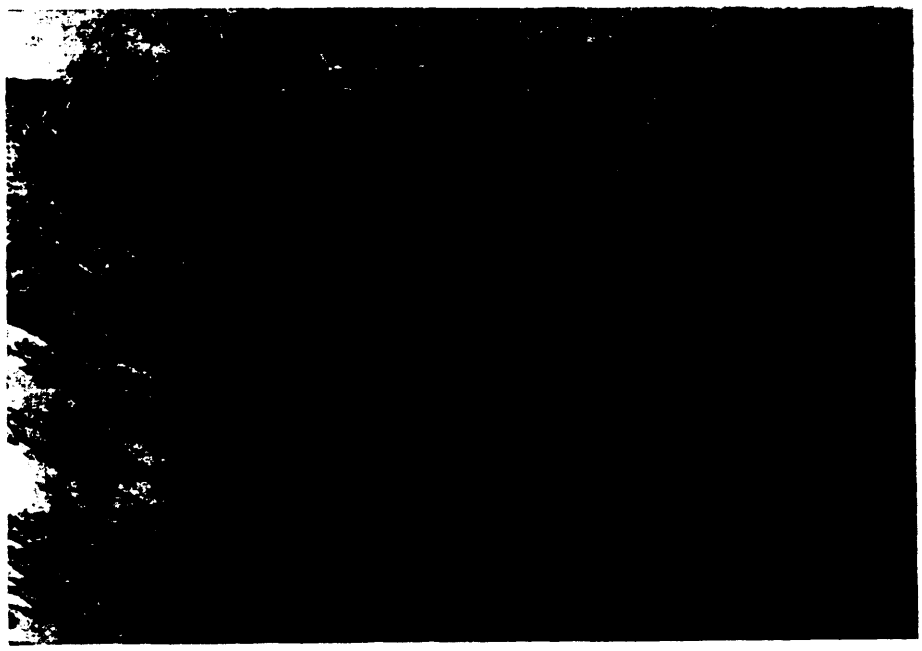

FIG. 5. A focus of mesothelioma in the visceral pleura of the lung. This could have arisen per se in the visceral pleural cells, but seedling deposition or lymphatic spread can not be excluded. × 48

pleural cells overlying a hyaline plaque (Fig. 3). This finding does not answer the question 'Are pleural plaques pre-malignant?' but it does demonstrate that the mesothelioma cells on the surface of a pleural plaque are able to give rise to a tumour.

Fletcher (1972), in a mortality study of 408 male shipyard workers with pleural plaques, has found 3 cases of mesothelioma and 16 bronchial carcinomas. He finds the occurrence of these 3 cases to be very significant considering the rarity of the disease in the general population.

The case report presented in this paper illustrates the possible origin of a mesothelioma in non-calcified pleural plaques. Eight chest radiographs are available dating back to June 1951—11 years after first exposure. Pleural thickening of the 'flange' type as described by Fletcher and Edge (1970) is first apparent on the right side of the radiographs dated January 1964. Subsequent films show definite 'hardening' of the pleural lesion. Fig. 6 illustrates the appearances noted on the last available film in March 1970. There is no evidence of underlying pulmonary fibrosis.

Dalquen et al. (1970) regard plaques as an epidemiological fossil, indicating an endemic asbestos exposure in certain populations. These authors believe that all observed cases of pleural plaques should be officially registered as they could provide the basis for further prospective studies on the aetiology of pleural mesothelioma. The case described tends to support this conclusion.

Sheers and Templeton (1968) have found that in workers exposed to asbestos

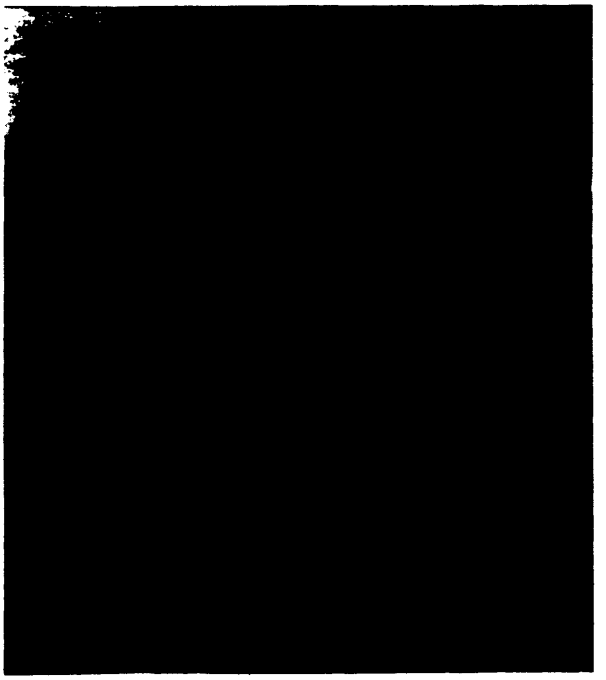

FIG. 6. A chest radiograph showing a pleural lesion in the right thorax (March 1970)

in the Royal Dockyard at Devonport, the prevalence of pleural fibrosis ranges from 28% in continuously exposed workers to 1·9% in those with least exposure. Mackenzie and Harries (1970) point out that in shipyards, as in the asbestos industry, there has been a changing pattern of disease due to better control of dust. This has resulted in a longer maturation period and hence they point out that not so much is seen of the florid, rapidly progressive interstitial pulmonary fibrosis which was so common 30 years ago. It is thus easier to see changes in the pleura where there is only very minor fibrotic change present. The uncertainty of the relationship of pleural reactions to the possible development of malignant disease is stressed, especially as they are encountering more extensive pleural reactions, often with effusion, in younger men than before but after long exposure of 20–25 years. These young patients have longer for the disease to progress and for possible malignant changes to develop.

Summary

Pleural plaques are generally accepted as an index to asbestos exposure. The occurrence of pleural plaques and other pleural lesions in workers exposed to asbestos must be carefully recorded to determine the precise prognostic value of this radiological sign in the study of the natural history of malignant mesothelioma of the pleura.

ACKNOWLEDGEMENTS

I should like to thank Dr D. S. Lyon for preparing the histological sections and allowing me to use them to illustrate this case. I should like to acknowledge the useful comments by Dr J. S. P. Jones on the histology in this case and to thank him for his help in producing Figs 2–5.

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Frequency of HLA antigens in asbestos workers with and without pulmonary fibrosis

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Summary

HLA antigens were determined in 37 patients with asbestosis and 37 matched controls with equivalent asbestos exposure but no pulmonary fibrosis, All had worked in the same textile factory. No significant differences in the prevalence of antigens were found between the two groups or between either group and controls who had not been exposed to asbestos. When the data were combined with findings from other pilot studies the previously suggested association between asbestosis and HLA-B27 was not confirmed. Subjects who were positive for HLA-B12 tended also to have advanced radiographic fibrosis. Asbestos workers without pulmonary fibrosis had an unexpectedly high frequency of HLA-BW5, which might indicate that this antigen protects against the development of pulmonary fibrosis.

Introduction

Merchant *et al* suggested, in a pilot study of 56 asbestos workers,[1] that the HLA antigen B27 might provide a useful marker of enhanced human susceptibility to the damaging effects of asbestos dust on the lungs. At a recent international conference it was reported[2] that 27% of 22 asbestos workers with alleged

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asbestosis had HLA-B27 compared with 9·8% of control workers without asbestosis. In neither series were the criteria for the diagnosis of asbestosis given, nor was the prevalence of all the HLA antigens in workers with asbestosis tabulated. We could not therefore perform a combined analysis of the results.

This paper reports the prevalence of HLA antigens in asbestos workers with and without pulmonary fibrosis, in white-collar workers from the same asbestos textile factory, and in a large group of healthy blood donors in a nearby city.

Subjects and methods

Forty-four asbestos textile workers, most of whom were retired, had been certified by the pneumoconiosis panel as having asbestosis. They had worked in carding, spinning, twisting, handling, and supervising asbestos textiles in the same factory and their relevant occupational history is summarised in table I. We subsequently diagnosed pulmonary fibrosis due to asbestos dust inhalation in 37 of the 44 workers. These workers were unrelated Caucasians, and we rejected others because they did not satisfy stringent criteria for the diagnosis of the disease—that is, dyspnoea on effort; persistent end-inspiratory crepitations with or without finger clubbing; reduction in forced vital capacity, forced expiratory volume in one second, and single breath transfer factor; and positive radiographic features using the ILO/UC/1971[3] classification of pneumoconiosis. By convention only small irregular pulmonary opacities were considered and pleural opacities were ignored. The following observations were recorded from the medical records: the age and year of entry into the factory, the number of years of exposure to asbestos dust, job title, smoking habits, and the age at which asbestosis was diagnosed. We then obtained from the medical records a group of employees with comparable occupational exposure who were not suffering from asbestosis. After the nature of the investigation had been explained to all 74 workers a new clinical examination was made, pulmonary function tests were repeated when possible, and the most recent chest radiograph was reviewed. A 20-ml sample of venous blood was taken into a heparinised container for tissue typing and into a plain tube for antinuclear antibody (ANA) and rheumatoid factor determinations. HLA typing was performed on fresh unfrozen lymphocytes by the two-stage microlymphocytotoxic method using 26 antisera specificities obtained from the National Tissue Typing Reference Laboratory, Bristol. ABO antigens were typed by standard methods and ANA and rheumatoid factor were estimated by the method of Soutar,[4] positive results being at a dilution of 1/8 or greater.

Forty volunteer white-collar workers at the same factory were tissue typed and their results were compared with those of 616 blood donors from Merseyside, who acted as controls.

Statistical analyses for pulmonary function were made with Student's t test and for other comparisons with Fisher's exact test.

Results

Table I summarises the clinical, physiological, serological, and radiological findings in 37 subjects with asbestosis (group 1) and the matched subjects free from pulmonary fibrosis (group 2). These subjects were closely matched for occupational exposure. Rheumatoid factor was present in almost as many controls as patients with asbestosis —a finding confirmed in the white collar workers (7 out of 40 (18%) had rheumatoid factor at a titre of 1/8 or greater).

Table II gives the prevalence of HLA antigens in the two matched groups, the 40 factory controls (group 3), and the 616 blood donors (group 4). There seemed to be an increased prevalence of HLA-B12 in group 1 and HLA-BW5 in group 2. No differences were observed in the prevalence of HLA-B27. No significant differences existed for any other antigens between any of the groups.

Table III shows statistical comparisons for the three HLA-B antigens 12, 27, and W5 between all the groups. There were no significant differences between the two control groups who had not been exposed to asbestos—groups 3 and 4. The prevalence of HLA-B12 was higher in group 1 than in group 4, whereas HLA-BW5 was more prevalent in group 2 than in group 4 and group 1. The relative risk of asbestosis in people with HLA-B12 was thus 2·37 when compared with that in healthy volunteers, but the probability was no more than that expected by chance (P ·0·05) when P was multiplied by the number of specificities tested. Except for B27 we would not perform a combined analysis of our results and those of the previous two studies.[1,2] The relative risk for people with B27, calculated from all three series, was, however only 1·87 ($\chi^2=1·96$; P ·0·05) (table IV).

When the three B series antigens were examined in relation to the radiographic category (table V) there was a definite but insignificant association between the presence of HLA-B12 and radiographically severe disease and BW5 and clear radiographs.

In neither group 1 nor group 2 were there any differences in respect of the presence or absence of these antigens when cross-tabulated with the length of exposure, year of first exposure, age of first exposure, or the presence or absence of ANA.

Discussion

Most doctors specialising in occupational medicine agree that differences exist in the severity of pulmonary reactions in people with similar exposure to asbestos dust. The finding of an increased frequency of ANA and rheumatoid factor in subjects with asbestosis[4] suggests that host factors may change an individual's response, and such autoantibodies raise the possibility of inherited differences in susceptibility to asbestosis. The major histocompatibility system in man is thought to be closely linked with genes controlling immunological responses, and associations with other disorders have been established.[6] The prior

TABLE I—*Occupational, clinical, physiological, serological, and radiological data on 74 textile workers who had been exposed to asbestos, half of whom had asbestosis*

	No of subjects	Sex (M:F)	Age (years)			Year entered			Age entered				Years exposed				No who smoked	No with clubbing	No with crepitations	% of predicted value			No with ANA	No with RF	Radiographic profusion category†		
			< 55	-59	60	< 1930	-1949	1950	< 20	-29	-39	40	< 20	-29	-39	40				FVC	FEV_1	T_{LCO}			0	1	2
Group 1	37	27:10	2	7	28	12	18	7	11	11	11	4	7	11	13	6	28	16	37	78·5 ± 16·5	76·8 ± 18·1	66·9 ± 13·7	12	9	2	22	13
Group 2	37	28:9	3	9	25	9	21	7	11	14	8	4	3	14	13	7	27	1*	1†	94·1 ± 17·3	87·1 ± 19·1	96·3 ± 19·8	1	7	30	7	0
χ^2 P																		14·97 < 0·001	66·26 < 0·001	< 0·001	< 0·05	< 0·001	9·33 < 0·01		45·26 < 0·001		

*Bronchiectasis.
†Profusion category 0 = 0/-, 0/0, and 0/1. 1 = 1/0, 1/1, and 1/2. 2 = 2/1, 2/2, and 2/3.
RF = Rheumatoid factor.

TABLE II—*Prevalence of HLA antigens in groups 1, 2, 3, and 4 and groups 1 and 2 combined*

HLA	Group 1 (n = 37)		Group 2 (n = 37)		Group 3 (n = 40)		Group 4 (n = 616)		Groups 1 and 2	
	No	%	No	%	No	%	No	%	No	%
HLA antigens A locus										
1	14	(37·8)	14	(37·8)	10	(25)	195	(31·7)	28	(37·8)
2	18	(48·6)	16	(43·2)	23	(57·5)	266	(43·2)	34	(45·9)
3	6	(16·2)	12	(32·4)	15	(37·5)	148	(24·0)	18	(24·3)
9	10	(27·0)	5	(13·5)	4	(10·0)	83	(13·5)	15	(20·3)
10	2	(5·4)	2	(5·4)	6	(15·0)	40	(6·5)	4	(5·4)
11	4	(10·8)	5	(13·5)	4	(10·0)	56	(9·1)	9	(12·2)
28	4	(10·8)	2	(5·4)	3	(7·5)	46	(7·5)	6	(8·1)
W29	2	(5·4)	3	(8·1)	3	(7·5)	NT		5	(6·8)
W32	2	(5·4)	4	(10·8)	7	(17·5)	NT		6	(8·1)
HLA antigens B locus										
5	2	(5·4)	6	(16·2)	3	(7·5)	37	(6·0)	8	(10·8)
7	6	(16·2)	7	(18·9)	16	(40·0)	151	(24·5)	13	(17·6)
8	10	(27·0)	10	(27·0)	7	(17·5)	157	(25·5)	20	(27·0)
12	18	(48·6)	10	(27·0)	13	(32·5)	185	(30·0)	28	(37·8)
13	2	(5·4)	2	(5·4)	0		18	(2·9)	4	(5·4)
14	4	(10·8)	3	(8·1)	2	(5·0)	46	(7·5)	7	(9·5)
15	1	(2·7)	0		0		NT		1	(1·4)
17	5	(13·5)	3	(8·1)	1	(2·5)	46	(7·5)	8	(10·8)
27	2	(5·4)	3	(8·1)	2	(5·0)	40	(6·5)	5	(6·8)
W5	1	(2·7)	9	(24·3)	3	(7·5)	49	(8·0)	10	(13·5)
W10	3	(8·1)	7	(18·9)	11	(27·5)	56	(9·1)	10	(13·5)
W15	4	(10·8)	3	(8·1)	8	(20·0)	40	(6·5)	7	(9·5)
W16	0		1	(2·7)	6	(15·0)	NT		1	(1·4)
W18	8	(21·6)	3	(8·1)	3	(7·5)	NT		11	(14·9)
W21	2	(5·4)	2	(5·4)	0		NT		4	(5·4)
W22	1	(2·7)	3	(8·1)	1	(2·5)	NT		4	(5·4)
TY	0		2	(5·4)	2	(5·0)	NT		2	(2·7)

NT = Not tested

identification of men at risk when handling asbestos is an obvious occupational health goal. Our investigation was justified by previous pilot studies that showed encouraging results but lacked adequate controls and numbers.

Our results have not confirmed these encouraging findings.[1 2] We found no association between HLA-B27 and the development and severity of asbestosis. There are several reasons for the discrepancy between our findings and those of the earlier studies. Merchant *et al*[1] studied 56 subjects referred to a pneumoconiosis panel, but they did not specify the criteria for establishing the diagnosis of asbestosis. When they reviewed the radiographs they found that HLA-B27 was present in six out of 19 subjects with radiographic profusion of 2/1 or greater (on UICC classification (1971)). They found that the length of exposure to asbestos was shorter and the first exposure more recent in the 10 workers who were positive for HLA-B27, although at least four of these probably did not have asbestosis and such small numbers are

not significant. Most of their subjects worked in the insulation industry or dockyards and might have had a mixed exposure to different types of asbestos. The dust levels in these occupations vary and have been high in the past. In contrast, our subjects all worked in a single asbestos textile factory and were predominantly exposed to chrysotile asbestos, although the older and longer-serving employees had once been exposed to much higher levels than those today, and small quantities of crocidolite may also have been present in the environment then.

Matej and Lange[4] studied 134 workers from a Polish factory and reported that HLA-B27 was 3·44 times more common among these workers than among the control population, but they gave no indication of the diagnostic criteria for asbestosis in the 22 workers deemed to be affected. Combining the data on HLA-B27 in the two previous reports and our study (table IV) shows that the association is not statistically significant.

TABLE III—*Comparison* of prevalence of HLA, B12, B27, BW5 in the four groups studied*

	HLA B12	HLA B27	HLA BW5
1 v 2	$\chi^2 = 2{\cdot}82$; P = 0·093	P = 1·0†	P = 0·014
1 v 3	$\chi^2 = 1{\cdot}47$; P = 0·23	P = 1·0†	P = 0·67
1 v 4	$\chi^2 = 4{\cdot}81$; P = 0·028	$\chi^2 = 0$; P = 1·0	$\chi^2 = 0{\cdot}72$; P = 0·40
2 v 3	$\chi^2 = 0{\cdot}076$; P = 0·78	P = 0·93†	P = 0·044
2 v 4	$\chi^2 = 0{\cdot}041$; P = 0·84	$\chi^2 = 0{\cdot}002$; P = 0·96	$\chi^2 = 9{\cdot}62$; P = 0·0019
3 v 4	$\chi^2 = 0{\cdot}023$; P = 0·88	$\chi^2 = 0{\cdot}002$; P = 0·96	$\chi^2 = 0$; P = 1·0

*"χ²" tests: DF = 1; Yates's correction.
†Fisher's exact test.

TABLE IV—*Prevalence of HLA, B27 in patients with asbestosis in this and other studies*

Study	No of subjects	Asbestosis		Controls	
		Positive for B27	Negative for B27	Positive for B27	Negative for B27
Marchant *et al*[1] ..	56	6	13	4	33
Matej and Lange[4] ..	134	5	17	11	101
Present study ..	74	2	35	3	34

Combined relative risk = 1·87. $\chi^2 = 1{\cdot}96$; P > 0·05.

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TABLE V—*Number of subjects exposed to asbestos with and without HLA antigens B12, B27, and BW5 and their radiographic categories as judged by ILO-UC profusion criteria*[5]

ILO-UC profusion category*	B12		B27		BW5	
	Positive	Negative	Positive	Negative	Positive	Negative
0	9	23	3	29	9	23
1	11	18	2	27	1	28
2	8	5	0	13	0	13
Total:	28	46	5	69	10	64

*See footnote to table I for definition of profusion categories.

If the association between a disease and the HLA system is strong only relatively small numbers of patients and controls are necessary to confirm it, but when the association is weak, problems of sampling and statistical errors assume greater importance. These have been reviewed,[7] and so far none of the reported associations between HLA antigens and asbestosis have achieved significance when the probability value has been multiplied by the total number of antigens tested. Ignoring the trend may, however, obscure the association, and further data should be obtained.

HLA-B12 was found in 18 of our 37 (49%) patients with asbestosis. This antigen was also found in 16 out of 20 (80%) patients with cryptogenic fibrosing alveolitis[8]—a disorder similar to asbestosis but without the history of occupational exposure—and in four out of eight children with the highly pathogenic strain of *Haemophilus influenza* serotype B.[9]

If HLA-B12 does increase susceptibility to the damaging effects of asbestos on the lung and to the development of cryptogenic fibrosing alveolitis, this would imply that in the HLA region of chromosome 6 in man a pulmonary fibrogenic gene is in linkage disequilibrium with HLA-B12. Since the external agent in asbestosis is known it may prove possible to elucidate further the pathogenesis of asbestosis and the significance of the interaction of the HLA antigens with environmental precipitating factors in general.

The high prevalence of HLA-BW5 (tables II-V) in exposed workers without asbestosis and with clear radiographs raises the possibility that possession of this antigen may protect against the development of pulmonary fibrosis. This is not an entirely new concept since it has been shown that progressive massive fibrosis (PMF) occurs in a low percentage of coalminers[10] with HLA-BW18. Moreover, patients with carcinoma of the bronchus survive longer after pneumonectomy[11] if they are positive for HLA-BW19 and B5.

When exploring HLA associations with disease, studies of

families offer confirmation of the findings,[12] but it is unlikely that this will be possible in asbestos workers, who, unlike coalminers and cotton workers, do not traditionally follow relatives into similar work.

If further studies of HLA antigens are made in this disorder we cannot emphasise too strongly the need for applying rigid criteria for the diagnosis.[13] Only in this way will meaningful results be obtained and those with an increased risk be recognised.

We thank Mrs A Knott for meticulous care in matching the controls and performing the pulmonary function tests and Dr M Perkin for collecting many of the samples. We also thank Mr C West, who gave valuable statistical advice.

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Corporate Health, Safety and Environmental Affairs Department

July 5, 1984

Raymond L. H. Murphy, Jr., M.D.
Faulkner Hospital, Inc.
1153 Centre Street
Boston, Massachusetts, 02130

Subject: Asbestos Criteria

Dear Ray,

Thank you for sending me the most recent draft of Part 1 of the Report entitled "Standardization of Criteria for the Diagnosis of Asbestos Related Diseases." I have read the report with interest and think that it is a concise summary of the diagnostic features of asbestosis. I have made a number of editorial changes in red ink on the pages indicated on the sheet attached to the report.

There are two comments I would like to make. The first is that you give no references to justify using "roentgenogram consistent with interstitial fibrosis of 1/2 or 1/1" as being diagnostic of asbestosis. As far as I am aware the profusion of irregular opacities on a radiograph does not necessarily correlate with the severity of the pathologic or physiologic lesions present and therefore the diagnostic value or 1/2 is probably no greater than that of 1/0 in the absence of other clincial features of disease. I would like to offer the suggestion that you modify the statement to read as I have indicated in the draft text as follows: "- - - and a roentgenogram consistent with interstitial fibrous or profusion of small irregular opacities greater than 1/0 (ILO U/C, 1980) are either impractical, - - - -."

My second comment is that the question of medical surveillance of persons potentially exposed to present day levels of asbestos or those exposed to far more hazardous conditions in the recent past needs to be addressed when considering the question of early diagnosis. Asbestosis is a dose-related disease dependent upon exposure (concentration) and time (length of time exposed) as well as the lapsed interval for manifestation of biological effects. Bearing this in mind, it is likely that early diagnosis, in persons exposed to past high levels of airborne asbestos fibers, is more likely to be

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made using the criteria suggested than it is in those whose entire working life has been spent in modern conditions (i.e., since 1972 in the USA). I would like you to emphasize the importance of obtaining an adequate work history including details of fiber types used and, whenever possible describing the job or industry in full so that a reasonable assessment of length of exposure and dose can be attempted. Since employers are required to inform employees of the results of their personal sampling for asbestos, the actual exposure measurements should be documented whenever known. Although it may seem obvious to state, surely the diagnosis of asbestosis is dependent upon proof that exposure to asbestos, over and above the normal amount present in the air we all breathe, has taken place.

In the discussion on lung function criteria, would it be at all appropriate to discuss disability and impairment?

I look forward to seeing the next draft and hope my remarks and editing efforts prove to be useful and acceptable.

Sincerely,

Hilton C. Lewinsohn, M.D.

HCL/pmb
Enc.

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STANDARDIZATION OF CRITERIA FOR THE DIAGNOSIS

OF ASBESTOS RELATED DISEASES

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DRAFT

June 4, 1984