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PLAINTIFF'S EXHIBIT
UC-2627

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935-1977

by

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Presentation to the Connecticut Thoracic Society, November 4, 1980

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Malignant Mesothelioma in Connecticut 1935-1977 by H C Lewinsohn, J.W. Meigs, and M.J. Teta

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.[1] Although available statistics might be subject to diagnostic error, the apparent rise was attributed to the increase in the State's 'cumulative asbestos consumption'.[1,3] 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. 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.

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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 (Table 1).

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.

Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. ~~Future~~ The case-control comparisions will ~~include~~ comprise cases (215) diagnosed after 1954 (Table 1), 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). The Price and Lee City Directories (4) 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. 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, 1971) (5) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. A computerized

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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) (c)

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

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1.3.6. A dose response relationship has been demonstrated between the extent of asbestos exposure and the radiological parenchymal changes. Parenchymal change correlates in general with an adverse effect on the long-term prognosis of an individual. However, in the absence of mesothelioma, there is no adverse prognostic significance associated with pleural changes unless they are unusually severe.

1.3.7. Since pleural changes may occur in the absence of parenchymal fibrosis, the use of the term "pleural asbestosis" is undesirable.

1.3.8. Other causes of radiological changes must be carefully excluded prior to making the diagnosis of asbestosis. This is important in the early stages of the disease when the radiological changes are slight.

1.4. Other Investigations. 1.4.1. Asbestos (Ferruginous) Bodies. When a productive cough is present asbestos fibres or ferruginous bodies in the sputum are evidence of exposure to asbestos but are not diagnostic of asbestosis.

1.4.2. Biopsy is very seldom justified as a diagnostic procedure for asbestosis. The effects of exposure should already have been recognised on the grounds outlined in the foregoing criteria. Biopsy is justified if it is thought that an asbestos-exposed patient may be suffering from some other potentially treatable lung disease. Any surgeon about to conduct a throacic operation on a person known to have been exposed to asbestos should be asked to obtain a specimen of lung tissue for histological examination.

1.5. Lung Function Abnormalities. The characteristic abnormalities are those of restrictive lung disease.

1.5.1. It is recommended that the FVC, FEV_1 and FEV_1/FVC ratio be recorded routinely in standard fashion. A comparison of periodic lung function testing over a number of years is of much greater value than a single observation compared to the standard "normal" values. In assessing the results, allowance must be made for certain ethnic differences and the effects of smoking habits.

1.5.2. While a restrictive pattern is consistent with the diagnosis of asbestosis, it is not specific to this disease. Asbestosis may develop with little or no detectable restrictive defect in the early stages. A predominantly obstructive picture is uncommon in the absence of a smoking history.

1.5.3. More sophisticated measurements in the assessment of restrictive lung disease (e.g. the measurement of transfer factor and lung compliance) are diagnostically helpful, but are not essential to the routine medical surveillance of a group of asbestos-exposed workers.

1.6. Differential Diagnosis. When there are clinical, radiological, or lung function abnormalities in asbestos workers, the exclusion of simulative disease is necessary for the correct management of the individual. This is increasingly important as, with improving occupational hygiene standards, asbestosis becomes less common.

1.7. Comment. The art of diagnosis, always a matter of weighing probabilities and looking at the total evidence, demands expert judgement based on the interpretation of the above criteria. Each of them is on a scale of severity and it is possible to find high values in some, low values in others, or any permutation or

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combination of criteria in the individual cases. According to the circumstances the elements of the decision and action will vary.

Section 2—Mesothelioma

2.1. Diffuse malignant mesothelioma of the pleura or peritoneum is a rare primary tumour in the general population. When attributable to asbestos the latent period between initial asbestos exposure and onset of the disease is usually 20 to 40 years or longer.

2.2. It must be emphasized that the definitive diagnosis of mesothelioma is not easy. In asbestos workers it may be associated with asbestosis though the level of fibrosis can be minimal. In some cases there is no evidence of fibrosis even at necropsy. Mesothelioma may occur after relatively brief but intense asbestos exposure. While pleural abnormalities are common in asbestos workers, there is no conclusive evidence that of themselves they predispose to mesothelioma. Early suspicion of the presence of pleural mesothelioma arises when pleural effusion or chest pain occurs in an asbestos worker. The tumour may completely encase the lung. Peritoneal mesothelioma may occupy a large amount of the abdominal cavity and produce ascites with or without abdominal pain. Metastases, although rare, can affect other organs, but local spread is the usual mode of progression. Hitherto no treatment has been successful, the outcome being invariably fatal.

2.3. Ideally, the diagnosis will be based on careful necropsy in which particular attention is given to excluding the possibility of a primary cancer at some distant site. Furthermore, the tumour tissue should be referred to one of the established mesothelioma reference panels so that histopathologists especially skilled in the diagnosis of this tumour may give their opinion. Such panels now exist in many countries.

2.4. While cases of mesothelioma may arise in the general population with no obvious cause, the majority of mesothelioma cases are related to asbestos exposure. The proportion of cases attributable to asbestos exposure varies; it is greatest in the more highly industrialised communities, especially those with a large shipbuilding or ship repairing industry. In industrial populations generally, most mesothelioma cases may be ascribed to asbestos although even in these communities no relationship with asbestos can be established in a proportion varying from 10% to over 30%. In other groups which have been adequately studied, the proportion of mesothelioma cases associated with asbestos exposure is lower but variable. Not all mesotheliomata are due to asbestos; e.g. endemic mesothelioma in some areas of Turkey is believed to be due to a fibrous form of zeolite.

2.5. Smoking habit plays no part in the genesis of mesothelioma as far as can be determined at the present time.

2.6. This tumour is relatively uncommon even among those who have had substantial asbestos exposure. Many believe that the risk of developing mesothelioma is greatest with crocidolite, less with amosite, and apparently less with chrysotile, while anthophyllite appears never to have caused mesothelioma in

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humans. This opinion, however, does not enjoy unanimous support and some authorities hold that there is no justification for differentiating between the various kinds of asbestos and their biological effects.

2.7. There is epidemiological and pathological evidence of an exposure-response relationship between inhaled asbestos and tumour formation. Recent work does not support the often stated idea that any slight, casual or brief asbestos exposure may lead to mesothelioma.

2.8. The long latency period between asbestos exposure and the development of the tumour makes elucidation of a dose-response relationship difficult. Thus, the effects of good dust control on the incidence of mesothelioma will only be determined in the future.

Section 3 — Lung Cancer

3.1. Cancer of the lung is the most common form of cancer in males in industrialised countries, and the primary cause is cigarette smoking. In asbestos workers who smoke, it is many times more common than in members of the general population who are not exposed to asbestos and who do not smoke.

3.2. Epidemiological studies have shown that the risk of bronchogenic cancer is greater at higher levels of asbestos exposure. Non-smoking asbestos workers under the conditions of past exposure appear to be at greater risk than non-smokers in the general population. Even so, these non-smoking asbestos workers are at less risk of bronchogenic cancer than cigarette smokers who have not been exposed to asbestos in the general population. There is also epidemiological evidence that the lower levels of past exposure to asbestos do not pose a detectable excess risk of bronchogenic cancer.

3.3. There are no specific pathological features by which an individual case of lung cancer can be attributed solely to asbestos exposure.

3.4. An adeno-carcinoma situated peripherally and particularly in a lower zone, is the type of tumour more likely to occur in a worker exposed to asbestos more than fifteen years previously. This is especially so in the presence of asbestosis.

Section 4 — Cancer of Other Sites

4.1. The evidence relating asbestos to cancer of other sites is equivocal and further data are awaited.

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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 (sample from listing Fig. 1).

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III. Results

Descriptive Epidemiology

The following ~~descriptive~~ results are based upon ~~the information~~ available ~~available from the~~ CTR and will require adjustment following ~~the~~ completion of ~~our~~ me slide review. Using the 1950 US 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 fifty-nine years. Average survival time from date of diagnosis to date of death is ten months.

~~Ten~~ New London Labor Market Area (LMA) ~~Ten~~ (10) cases were reported in ~~an LMA (New London)~~ where shipyards are located, and ~~five~~ 5 (50%) 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 ~~also~~ all centers for ~~Labor Market Areas (LMA's)~~ 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).

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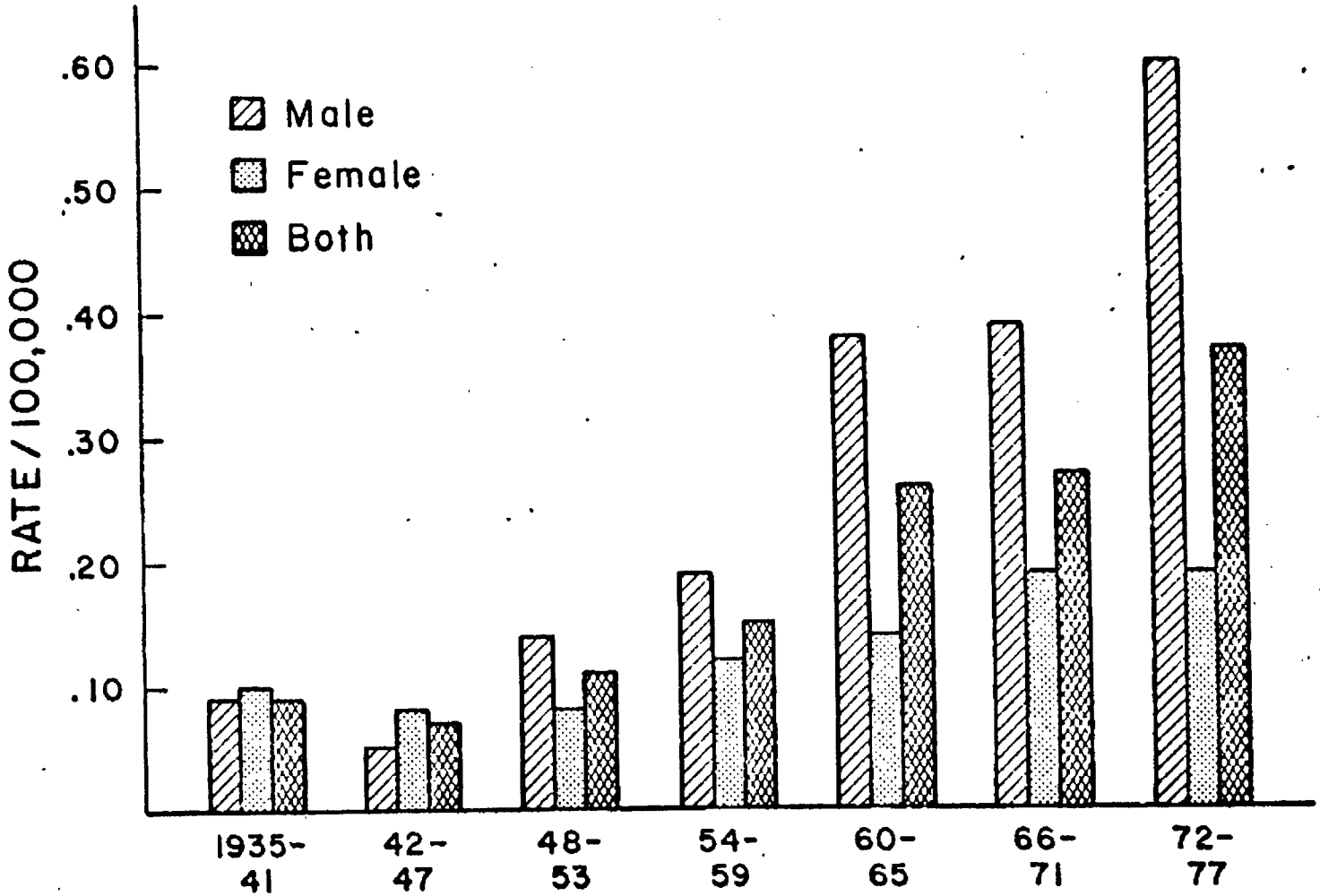
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Fig 2

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



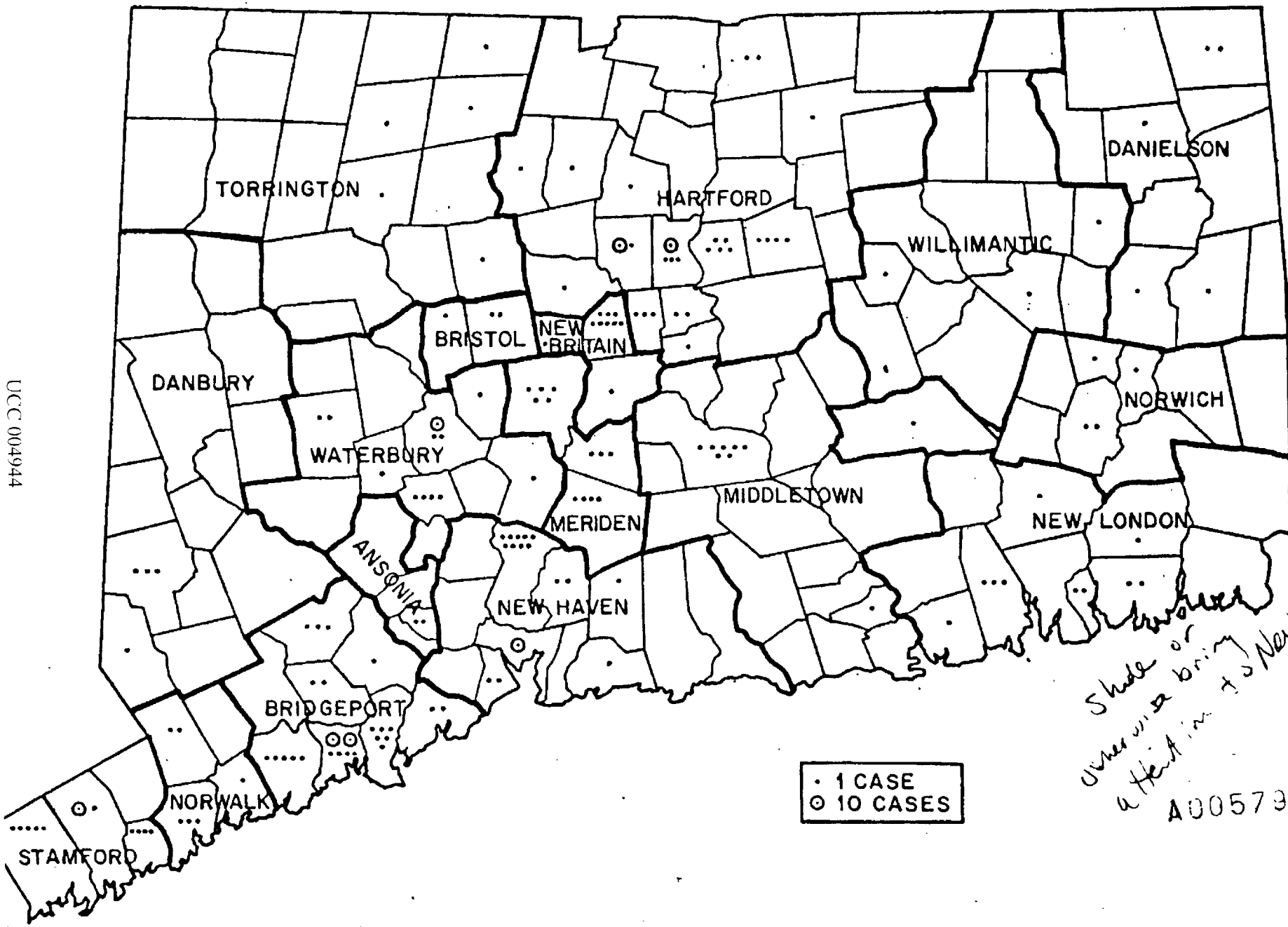
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GEOGRAPHICAL MAPPING OF CASES OF MESOTHELIOMA (1935 - 1977) BY TOWN OF RESIDENCE AND 1960 LABOR MARKET AREA

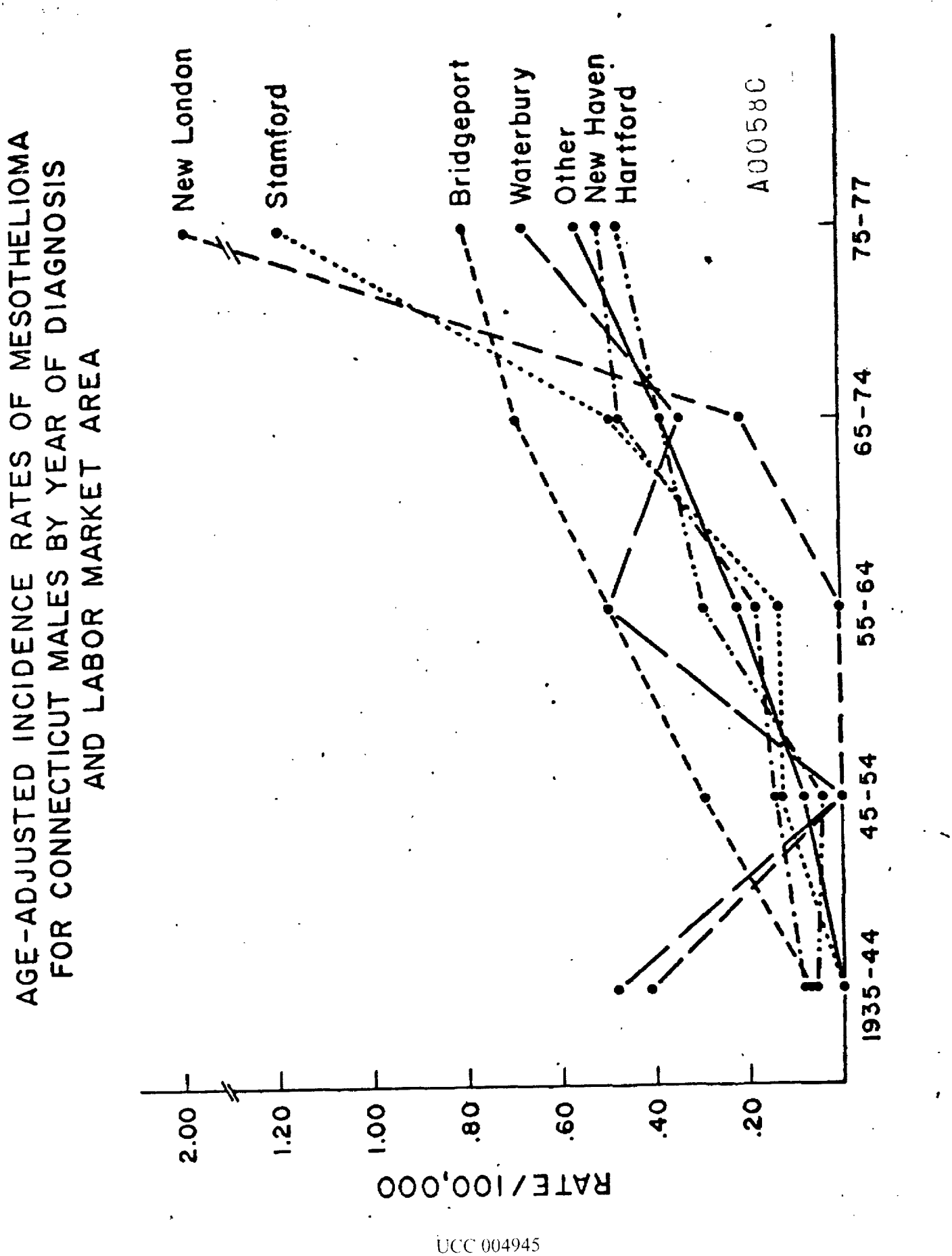


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AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA
FOR CONNECTICUT MALES BY YEAR OF DIAGNOSIS
AND LABOR MARKET AREA
New London
Stamford
Bridgeport
Waterbury
Other
New Haven
Hartford
A00580
RATE/100,000
2.00
1.20
1.00
.80
.60
.40
.20
1935-44
45-54
55-64
65-74
75-77

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SLIDE REVIEW

Malignant mesothelioma is a very rare disease with only 2 cases per million population expected annually.[5] Resistance to the acceptance of mesothelioma as a disease entity persisted until the late 1960's.[8] Wagner's widely publicized association of mesothelioma with Cape Crocidolite asbestos exposure created the potential for the introduction of diagnostic bias.[9]

Positive diagnosis of mesothelioma is often complicated by its confusion with other forms of cancer..(Vidone discussion of simulators).
The controversy over criteria for positive diagnosis is well documented in the literature.[10] Most experts agree, however, that a full autopsy is required to positively distinguish diffuse mesothelioma of the pleural or peritoneum from other primary or secondary neoplasms.[11]

We examined, for all CTR reported cases of mesothelioma and for all pleural tumors other than mesothelioma (1935-77), the histological basis for diagnosis (Tables 2,3). 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 (44%) of the 238 deceased cases are known by the CTR to have been autopsied, but only 83 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 medical records (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.

(Summary of Dr. Vidone's preliminary Findings)

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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

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

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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 the pathological material available and used for diagnostic purposes.

Felton (12) has pointed out several needs 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.

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.

Valuable information can be gained from a comparison between radiographic apperances and histological changes in the lung. Such information will help to eliminate present diagnostic uncertainties.

It has been our experience that occupational histories are not routinely obtained and included in hospital records. In our search through records stored at the CTR (i.e. hospital records), we found 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, whose diagnoses were between 1955 and 1977. A recently passed Ct. statute, whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

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

(Comment on the significance of the Slide Review)

It is evident that until the physicians investigating cases of malignancy appreciate the importance of occupational ~~factors on~~ and environmental factors ~~on the etiology of these diseases, no~~ (lifestyle, habits, hobbies, part-time activities, detailed job histories) , any attempt 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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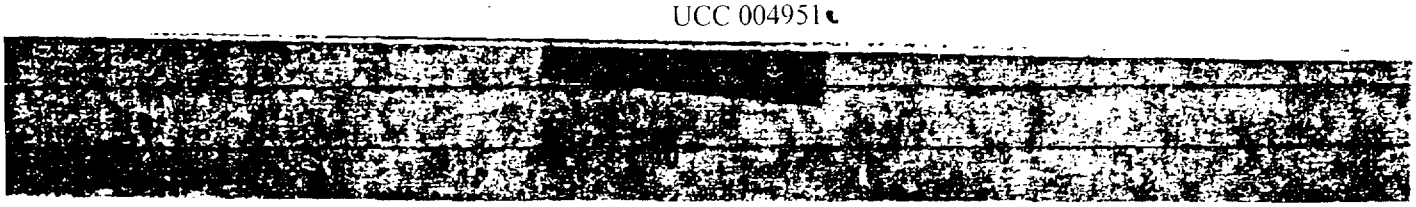
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