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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.

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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. ^{The} ~~Future~~ ^{cases} ~~cases~~-control comparisons will ^{comprise} ~~in-~~clude 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~~ 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, 1950-1977). 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 ~~(sample from listing)~~ (Fig. 1).

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III. Results

Descriptive Epidemiology

The following descriptive results are based upon ~~the information~~^{information} available ~~from the~~ CTR and will require adjustment following the completion of ~~our~~^{the} 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~~⁵⁹ years. Average survival time from date of diagnosis to date of death is ten months.

¹⁰ New London Labour Market Area (LMA)
~~Ten~~ cases were reported in ⁵ ~~an~~ ~~LMA~~ (New London) where shipyards are located, and ~~five~~ 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} ~~also~~ centers ^{for LMAs.} ~~for Labor Market Areas~~ (LMA). 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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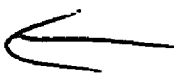
SLIDE REVIEW

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.. (Vidone discussion of simulators).  insert ①
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 pleural tumors other than mesothelioma (1935-77), the histological basis for diagnosis (Tables 2,3). ^{head ②} 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 83/105 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} ~~medical~~ 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.

(Summary of Dr. Vidone's Findings) 

~~Insert~~ ③, ④, ⑤

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Insert ① 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 connective tissue stains on surgical materials are valuable as well in this regard.

Insert ② 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. ~~As the case review progresses an attempt will be made to classify tumors according to the predominant histologic pattern.~~

Insert ③ 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 ~~present~~ 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.

Insert ④ On first review the cases in this study are being placed in one of six categories (see slide) which represent the relative certainty of the diagnosis of mesothelioma using anatomic criteria. (Table)
This is being carried out on all available materials, including cytologic preparations, surgical pathology and autopsy reports and slides. ~~As might be expected in a study of this type, the material available is quite variable.~~ In all cases the diagnostic classification is based on autopsy materials, or ~~in some cases~~ 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.

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Insert (5)

The preliminary results of the primary review of the first 106 cases are shown ^{in Table} ~~on this slide~~. ~~As you can see~~ 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 ~~to be~~ 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.

~~For purposes of this review~~ 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. ~~As broken down by percentage,~~ ^{These were} there ~~were~~ 56.6% ^{thought to be mesothelioma,} 26.4% ^{possibly} and 10.3% not mesothelioma or excluded from the study. ~~There were~~ 6.6% ^{classified as} that are still ~~considered~~ unknown.

Insert (6)

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 ^{thoroughly familiar with the gross and microscopic characteristics of mesothelioma and} conducted by an experienced pathologist ^{with} special expertise in the surgical pathology of tumors.

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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 ^{sample} pathological material available and used for diagnostic purposes.

Felton has pointed out several ~~needs~~ ^{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, 1970).

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 appearances and histological changes in the lung. Such information will help to eliminate present diagnostic uncertainties and ^{autopsy material is needed for these investigations}

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 Dir., Dr. Part, CTR), our search through records stored at the CTR (i.e. hospital records) produced job titles for only 17% of the mesothelioma cases.} ~~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, ^(Connecticut) ~~whose~~ ^(reference) ~~diagnosed~~ ^{between} 1955 and 1977. A recently passed ~~Statute~~ ^{Connecticut Statute}, whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

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Insert (7)

There is ^{been recognized which should be} another problem ~~that~~ [^] has arisen and hopefully will be addressed. ~~in the later anatomic pathology studies.~~ 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 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} ~~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.

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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)

paraphrase
insert (6)
paraphrase insert (7)

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,-ne~~ (lifestyle, habits, hobbies, part-time activities, ^edistilled^a job histories) , ~~any~~ attempt^s 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)

^aWHO (1976)

^bNumbers in brackets refer to the period 1955-1977

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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

<u>Diagnosis</u> ^a	<u>Tissue</u> ^b <u>Available</u>	<u>%</u>	<u>No Tissue</u> <u>Available</u>	<u>%</u>	<u>Total</u>	<u>%</u>
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)

^aWHO (1976)

^bspecimen 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

(1) Diagnosis ^a	(2) Autopsy, Microscopic 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	12	98	35	238	44%

^aWHO (1976)

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

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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

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MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION BASED ON ANATOMIC PATHOLOGY REVIEW

PRELIMINARY RESULTS (106 Cases)

<u>Classification</u>	<u>No.</u>	<u>No.</u>	<u>%</u>
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. %

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

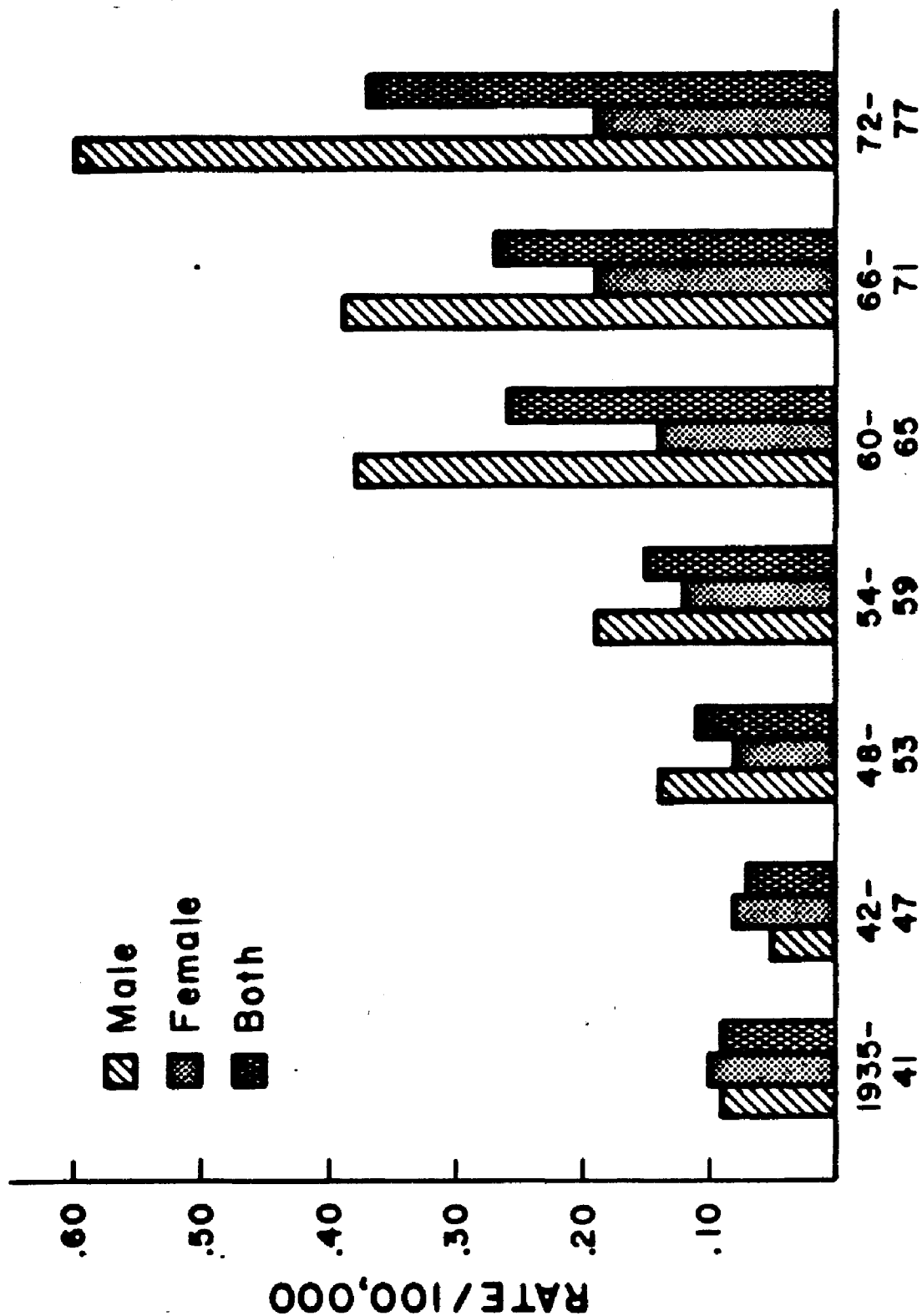


Figure 2

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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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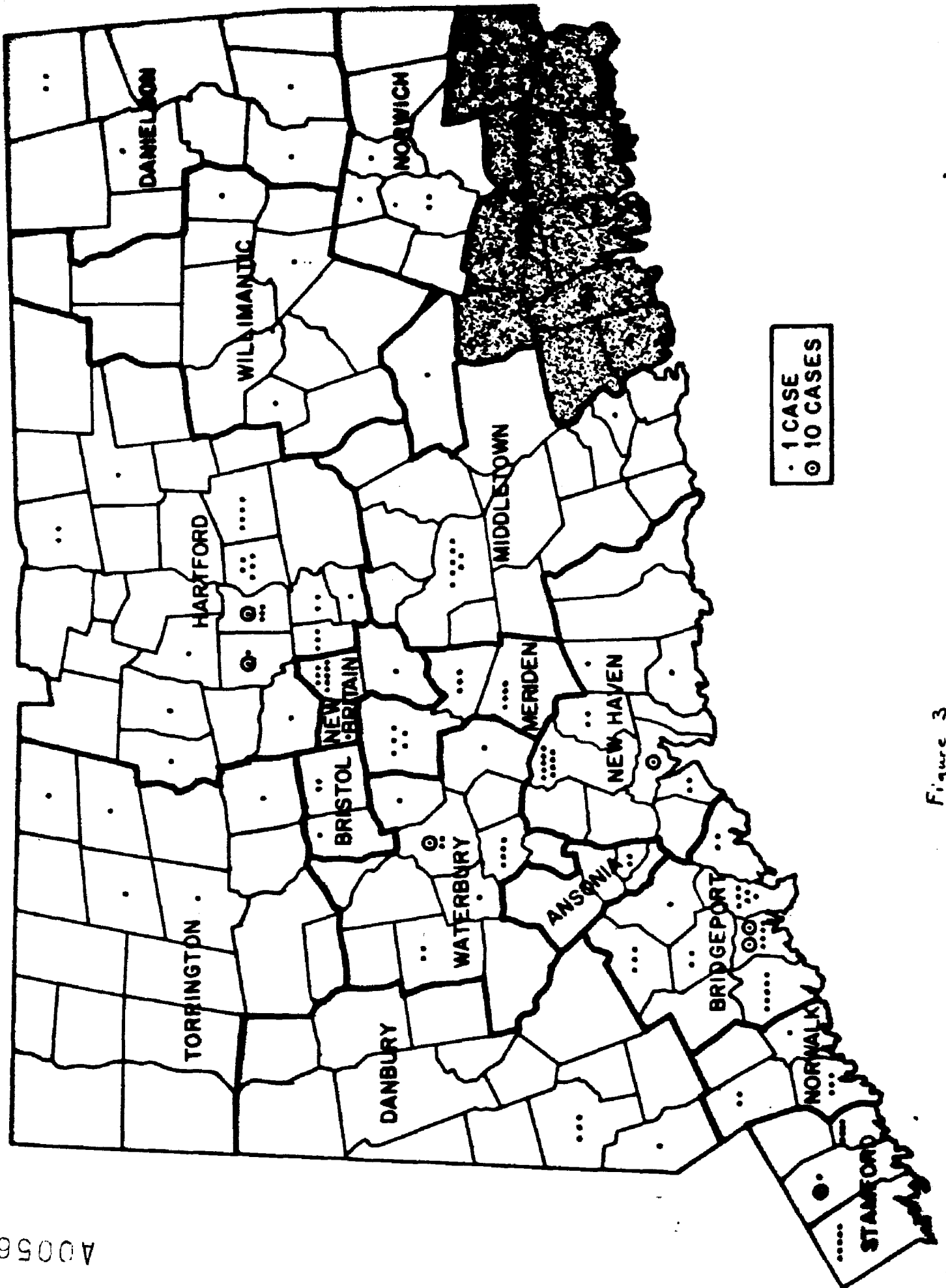


Figure 3

AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA FOR CONNECTICUT MALES BY YEAR OF DIAGNOSIS AND LABOR MARKET AREA

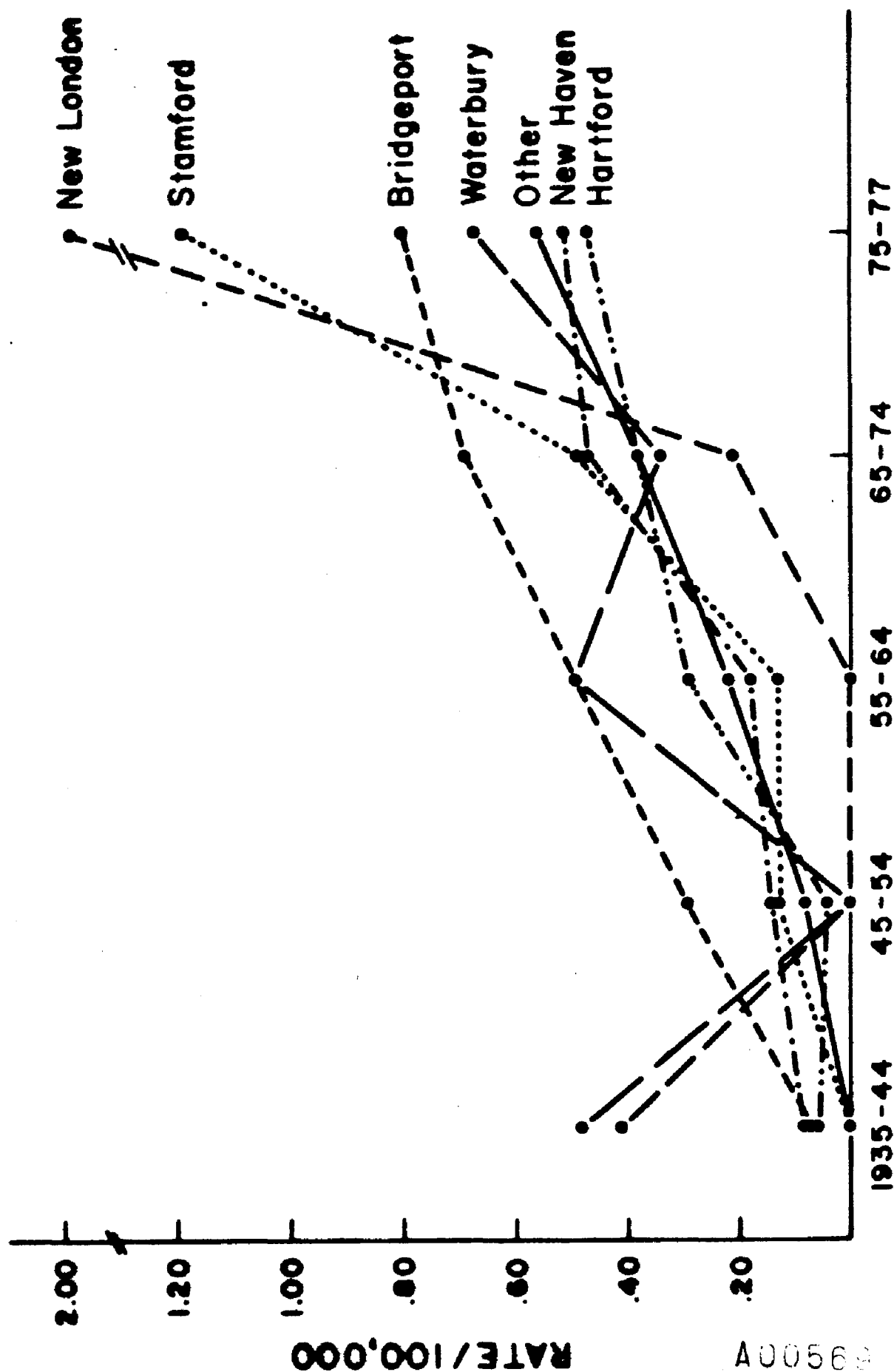


Figure 4

20.
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