

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

(ANATOMIC PATHOLOGY SECTION)

INTRODUCTION

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 with special expertise in the surgical pathology of tumors.

Thoroughly familiar with the gross and microscopic characteristics of mesothelioma and

The object of this review should be to classify the cases relative to the certainty of diagnosis using well defined criteria for the diagnosis of mesothelioma. In the present study this ^{morphologic} review is first being conducted with 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.

(Slide 1 Classification)

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. 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.

(Slide 2 Preliminary Results)

The preliminary results of the primary review of the first 106 cases are shown 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 ^dreview 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, there were 56.6% thought to be mesothelioma, 26.4% possibles and 10.3% not mesothelioma or excluded from the study. There were 6.6% that are still considered unknown.

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It should be pointed out that as further studies of this material are carried out, cases may be moving from one to another classification and this report should be considered only a preliminary report at this time. It also should be mentioned that less than half of the total number of cases in this study have been subjected to anatomic pathology review as of this time.

Discussion: 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 this portion of the study progresses, the ~~mesotheliomas~~ mesotheliomas will be categorized as to pleural, peritoneal or other, and an attempt will be made to categorize the histologic structure based on its predominant pattern, into (1) epithelial (tubulo-papillary and undifferentiated polygonal), (2) sarcomatous or mesenchymal and (3) mixed.

As has been emphasized by others two problems become apparent on review of this material. The first is the separation of localized or nodular (and sometimes benign mesothelial reactions) from diffuse or malignant mesothelioma. In the present study this is a minor problem because of the selection of the material being reviewed, having been obtained from the Tumor Registry where the vast majority of these cases would have been reasonably carefully reviewed in their own institution and they would have had benefit of the ~~course or~~ ^{different} progression of the disease. As is the practice in Connecticut, cases are occasionally reclassified or removed from the Tumor Registry by the local hospital when it is determined that they do not represent the malignancy originally reported.

A00547

The second and more important problem in the present study is the separation of mesothelioma from metastatic carcinoma. The findings at autopsy in the cases so evaluated are extremely ^{in the past} valuable in this regard and 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 in this regard. It can be pointed out that as one gains experience in looking at large numbers of mesotheliomas, one begins to recognize a characteristic pattern which has been well described by many workers in this field. This coupled with experience in surgical pathology of tumors enables one to categorize ^{most} ~~many~~ of these cases in the proper class. ~~As pointed out earlier, however, on further review, this was not possible in some of the cases, however.~~ ^{also} It is ~~possible~~ ^{probable} that with additional studies and special stains this classification should become more accurate.

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There is 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 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.

RAV 10/28/80

A00543

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 ^{compare} ~~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, 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 ~~(example from listing~~ (Fig. 1).

ADDEND

III. Results

Descriptive Epidemiology

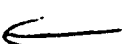
The following descriptive results are based upon ~~the information~~^{information} available ~~from~~^{from} the CTR and will require adjustment following the completion of ~~our~~^{the} slide review. Using the 1950 US population as a standard, the age-adjusted incidence rate for mesothelioma in Connecticut 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~~⁵⁷ years. Average survival time from date of diagnosis to date of death is ten months.

¹⁰ New London Labor Market Area (LMA)
~~Ten~~ cases were reported in ~~an~~^{as} ~~LMA~~ (New London) where shipyards are located, and ~~five~~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} ~~also~~ centers ^{for LMA's.} ~~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).

A00554

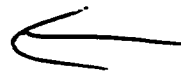
SLIDE REVIEW

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 pleural 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). ^{here 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 on 8/30/84 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} slide 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

A00556

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 (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% ^{were} thought to be mesothelioma, 26.4% ^{were} possible ^{mesothelioma} 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.

A00557

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 has pointed out several ^{reasons} ~~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 (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., Dept. of Health, 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 diagnosed were~~ ^(reviewer) between 1955 and 1977. A recently passed ~~Of.~~ Statute, whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

A00557

Insert (+)

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 ^{metastatic melanoma} 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.

RAV 10/28/80

A00552

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)

paragraph
insert ⑥
paragraph 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, no~~ (lifestyle, habits, hobbies, part-time activities, ^ede^etailed 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.

A00560

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

A00561

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

A00562

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

<u>Diagnosis^a</u>	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	<u>Autopsy^b %</u>
	<u>Autopsy, Microscopic Evidence of Cancer</u>	<u>Autopsy, Gross Evidence of Cancer</u>	<u>Autopsy Gross Evidence, Unknown Whether Cancer</u>	<u>Autopsy, but only Indirect Evidence of Cancer</u>	<u>Autopsy, no Report</u>	<u>No Autopsy</u>	<u>Unknown</u>	<u>Number Dead</u>	
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%

^aWHO (1976)

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

A00563

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

RAV 8/1/80

A00564

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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A00565

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

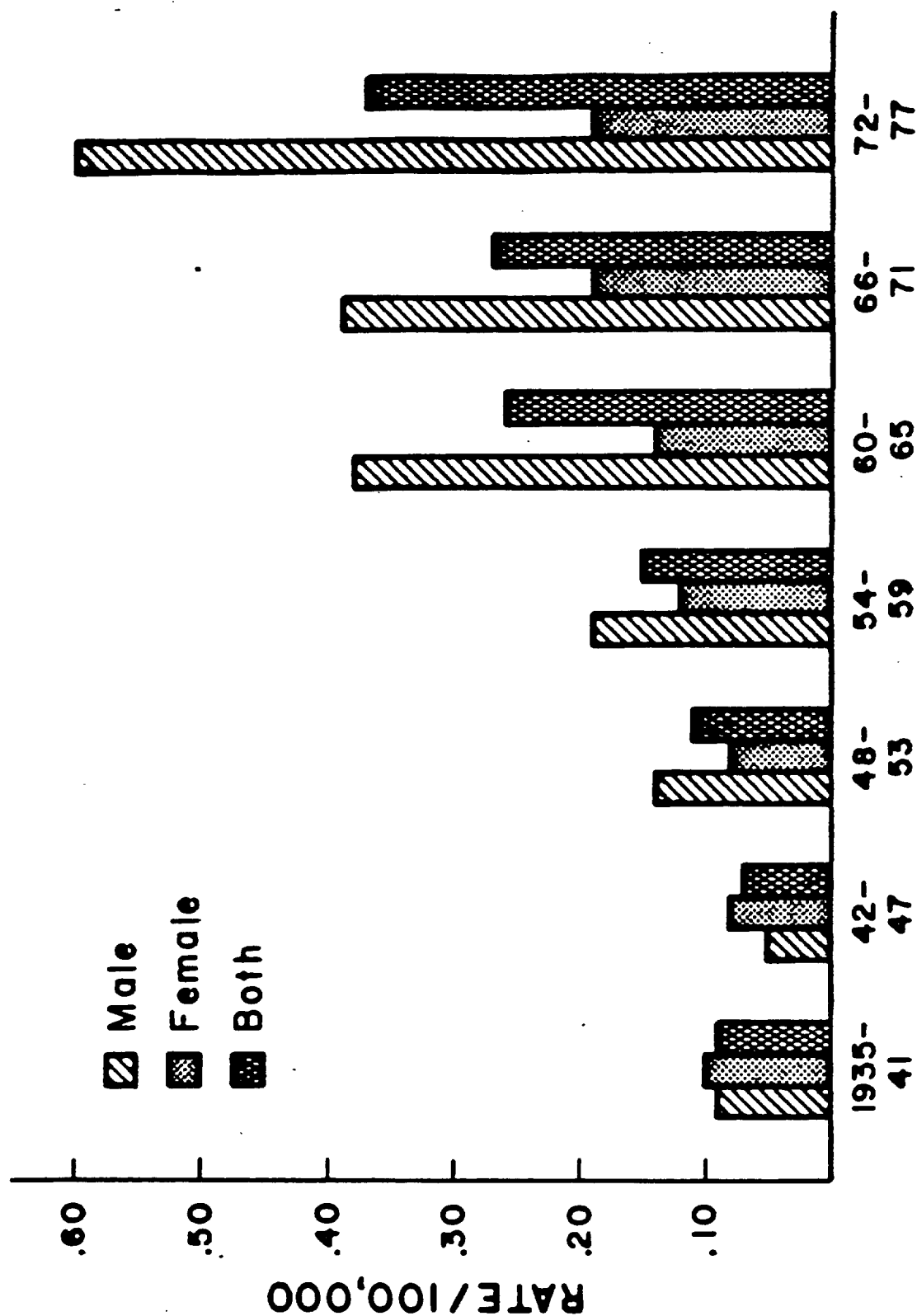


Figure 2

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A00568

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

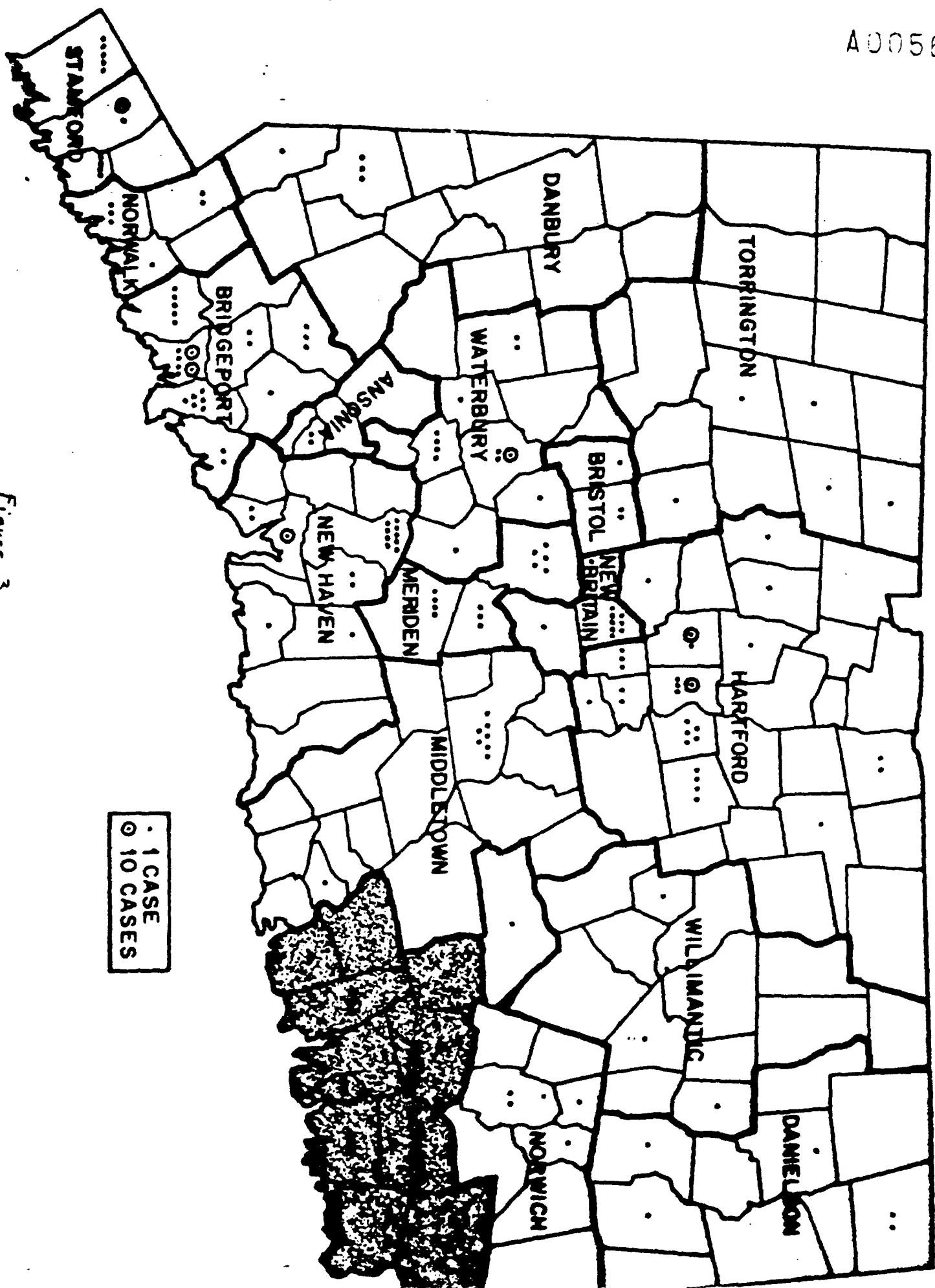


Figure 3

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

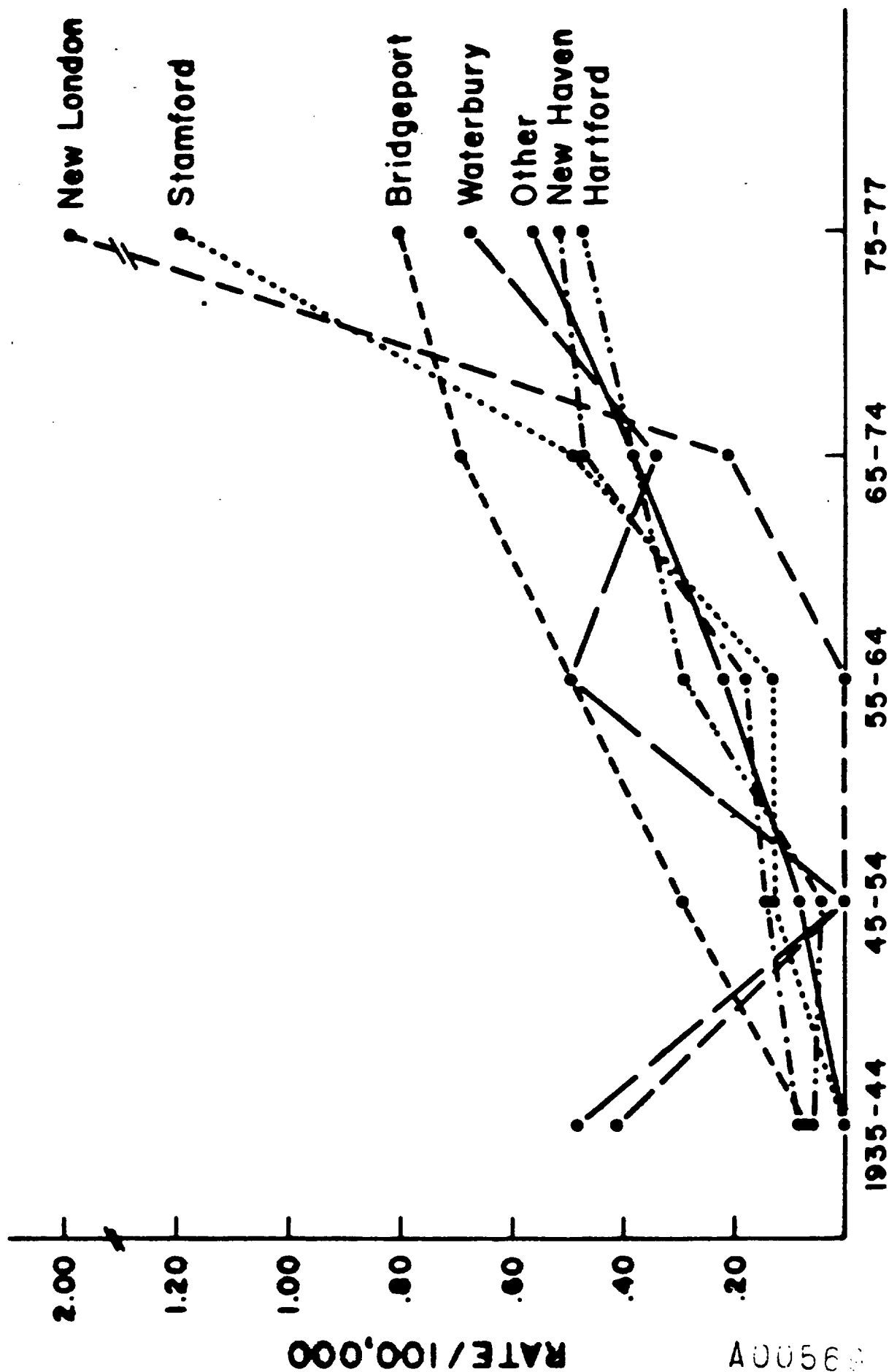


Figure 4

~~28.~~
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A00570

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Felton, J.S. (1980) Letter to the Editor. JAMA, 244, 1675

Kannerstein, M., McCaughey^{hey}, W.T.E., Churg, J. (1977) A Critique of the Criteria for the Diagnosis of Diffuse Malignant Mesothelioma. Mt. Sinai J. Med, N.Y. 44, 485-494

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A00571

DISCUSSION

Although this study was undertaken initially in an attempt to discover whether it would be feasible to determine the environmental factors responsible for the increase of malignant mesothelioma in the State of Connecticut, it has suffered from the lack of detail in available records. ~~Table II and III illustrate one of the~~

ies
major deficiencies in the data available for study, ~~namely~~ *is are* the low autopsy rate *pathological material* ~~of (22%)~~ for the pleural mesotheliomata and the inadequacy of the ~~types of tissue~~ available and used for diagnostic purposes.

→ It has been our experience that occupational histories are not routinely obtained and included in hospital records. Smoking habits are not routinely recorded and no inquiries are made of patients admitted with suspected malignant disease regarding their hobbies or part-time activities.

In our search through the C. T. R. paper files (i.e. hospital records), we found job titles for only 17% of the mesothelioma cases. If we exclude from this group those merely designated as "retired", "housewife" or "student", the figure is reduced to 12%. We were only able to ascertain the type of industry in 7% of these cases. This data is applicable to 220 cases consisting of:

195 mesotheliomas in the Connecticut Registry, 1955 - 1977,

5 mesotheliomas from the Veterans Administration files, 1955 - 1977, and

20 pleural tumors, not mesothelioma, recorded 1955 - 1977.

It is apparent from our study of these files that the awareness of this disease increased in the late 1950's and early 1960's and that this appeared to introduce a diagnostic bias which might partly account for apparent increase after 1955.

A00606

Comment on the significance of the findings on the slide review.

It is evident that until the physicians or hospitals investigating cases of malignancy appreciate the importance of ^{occupational &} environmental facts ^{or on} of the etiology of these diseases, no attempt can be made to apportion the blame to any particular factor unless adequate histories are available containing complete information on lifestyle, habits, hobbies, part-time activities and details of occupation and industry. It is also essential, particularly in the case of a rare tumor which may present diagnostic difficulties, to obtain sufficient tissue for study before the final diagnosis is made. Whenever a tumor is found where ^{an} ^{is suspected} ~~no~~ association ~~exists~~ between it and a particular occupational or environmental factor, every attempt should be made to fully document all the ~~medical~~ facts and to subsequently verify the diagnosis by means of a full autopsy.

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...was admitted to the hospital for investigation of weight loss and an upper abdominal mass. She had been treated for chronic recurring synovitis of the knees with dexamethasone in dosages from 0.5 to 1.5 mg daily intermittently for ten years. During this period, the skin of her forearms became extremely thin, and she experienced several episodes of subcutaneous extravasation of blood.

On the fourth hospital day, she was transported to the x-ray department, where it was noted that she had two superficial tears in the skin of the left forearm with gaping margins. Attempts were made to suture the skin edges together, but the sutures tore through the skin. The edges were held together with strips of sterile tape.

On one other occasion during her hospital stay, similar lesions developed during the course of transport to and from her bed for other diagnostic procedures. These lesions failed to heal during her hospital stay, and gross evidence of infection was not noted.

Comment.—Transport by handling of the forearms, even though carefully done, resulted in serious, poorly healing tears of the skin in this overweight, weak woman. Even though extra care was taken after the initial episode, there was recurrence. In this case there was no complaint or dissatisfaction expressed by the patient or the family, but such episodes have the potential for risk of compensable injury. Certainly there have been allegations of hospital-based injury with lesser justification.

It would be prudent for physicians hospitalizing patients who have been receiving steroid therapy to place a warning note on the chart advising hospital personnel to use extreme care when bathing, assisting, or transporting such patients.

LOUIS T. C. WONG, MD
Downey, Calif.

Carcinoma at the Site of Herpes Simplex Infection

To the Editor.—THE JOURNAL recently published a letter entitled "Carcinoma at the Site of Herpes Simplex Infection" (243:2296, 1980). My letter is to note further the occurrence of such a situation. I personally had basosquamous carcinoma develop on two occasions. The first occurrence was approximately five or six years ago at the site of a vaccination for small pox that I had received for traveling. After the vaccination site did not heal for one year, I became suspicious and had it excised at the local university hospital. I was approximately 55 years old at that time.

During the past year, a similar situation developed at the site of a localized herpes simplex infection that had occurred on my upper lip and had not healed for approximately one year. It was removed by a Mohs surgical procedure at a local university center, and a diagnosis of basosquamous cell carcinoma was made again. At that time, the dermatologist performing the chemosurgery mentioned how unusual the lesion was, inasmuch as there were not supposed to be such things as basosquamous carcinomas. Both wounds healed without any unusual event.

After the first occurrence, I contacted Dr. Herman Pinkus in Detroit, and he stated that there were about a dozen cases in the literature at that time. I saw him at a meeting shortly after the chemotherapy, and he commented on the unusual nature of this condition occurring more than once, though he was more aware of its occurrence than he had been before.

There is an embarrassing situation about this personally, and that is that I am a dermatologist.

There were no other forms of therapy used on these lesions with either surgery, antibiotics, or photodynamic inactivation; nor am I a smoker. I have had an occasional localized herpes simplex infection during the past 20 years.

MARTIN L. GORD, MD
Allport Medical Group, SC
Chicago

The Autopsy and Asbestos Exposure

To the Editor.—In the article entitled "The Autopsy: Past, Present, and Future" by Anderson and co-workers (242:1036, 1979), the fall in the rate of autopsies is decried, and several cogent reasons are presented for a return to the previous high number of such examinations, a goal formerly pursued by dedicated house officers.

One additional need for postmortem reviews has been given emphasis in recent years by the epidemiologic and clinical information gathered in connection with the asbestos-related disease. Because workers are now beginning to present radiological and altered physiological evidence of the effects of the inhalation of free asbestos fiber, years to decades after initial work exposure, a problem in worker's compensation adjudication has arisen. The changes elicited through clinical study, although present, most often do not have accompanying symptoms, *as yet*, nor have they caused any disability, *as yet*. There

will be disability, however, with the passing of time.

In those instances where death has resulted from pulmonary cancer or a thoracic or peritoneal mesothelioma, it is important to identify the tissue alterations directly attributable to occupational contact with the respirable asbestos fiber.

As we have counseled family survivors of such persons dying of asbestosis or its related disease states, or both, to request a necropsy to lend substance to a worker's compensation claim, it is strongly suggested that all physicians or house staff caring for such patients urge relatives to permit the examination. These procedures will not only aid the beneficiaries but will also prove of worth to physicians in familiarizing them with the findings characterizing a greatly underdiagnosed job-generated disease.

Furthermore, such postmortem data will aid in our knowing what actually happens to a worker under certain conditions of exposure and will help to rectify the inaccurate conclusions drawn from the current underreporting of occupationally associated disease.

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Safety of Ipecac Syrup

To the Editor.—On behalf of the American Association of Poison Control Centers, I am concerned about the titling of a recent JAMA article, "Death Resulting From Ipecac Syrup Poisoning" (243:1927, 1980). I am worried that the index skimmer or scanner—particularly if he is of the older school reared in an era of gastric lavage for management of poisonings—may inadvertently conclude that the typical emetic dose of syrup of ipecac was responsible. In reality, the dose was three to four bottles per day for three months—thus representing a long-term poisoning.

As noted by the authors, syrup of ipecac as an emetic agent has a remarkable safety record; its current availability over-the-counter and in the home permits an enormous saving of needless visits to emergency rooms for the treatment of accidental ingestions. I think that it would be unfortunate indeed were the inference drawn that single emetic doses were risky.

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Seattle

DRAFT 10/17/80

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935-1977

by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

Presentation to the Connecticut Thoracic Society, November 4, 1980

A00572

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'.^(2,3) 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.

A00573

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-control comparisons will ~~include~~ ^{comprise} ~~include~~ 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

A00574

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)^(c)

^bNumbers in brackets refer to the period 1955-1977

A00575

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).

A00576

III. Results

Descriptive Epidemiology

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

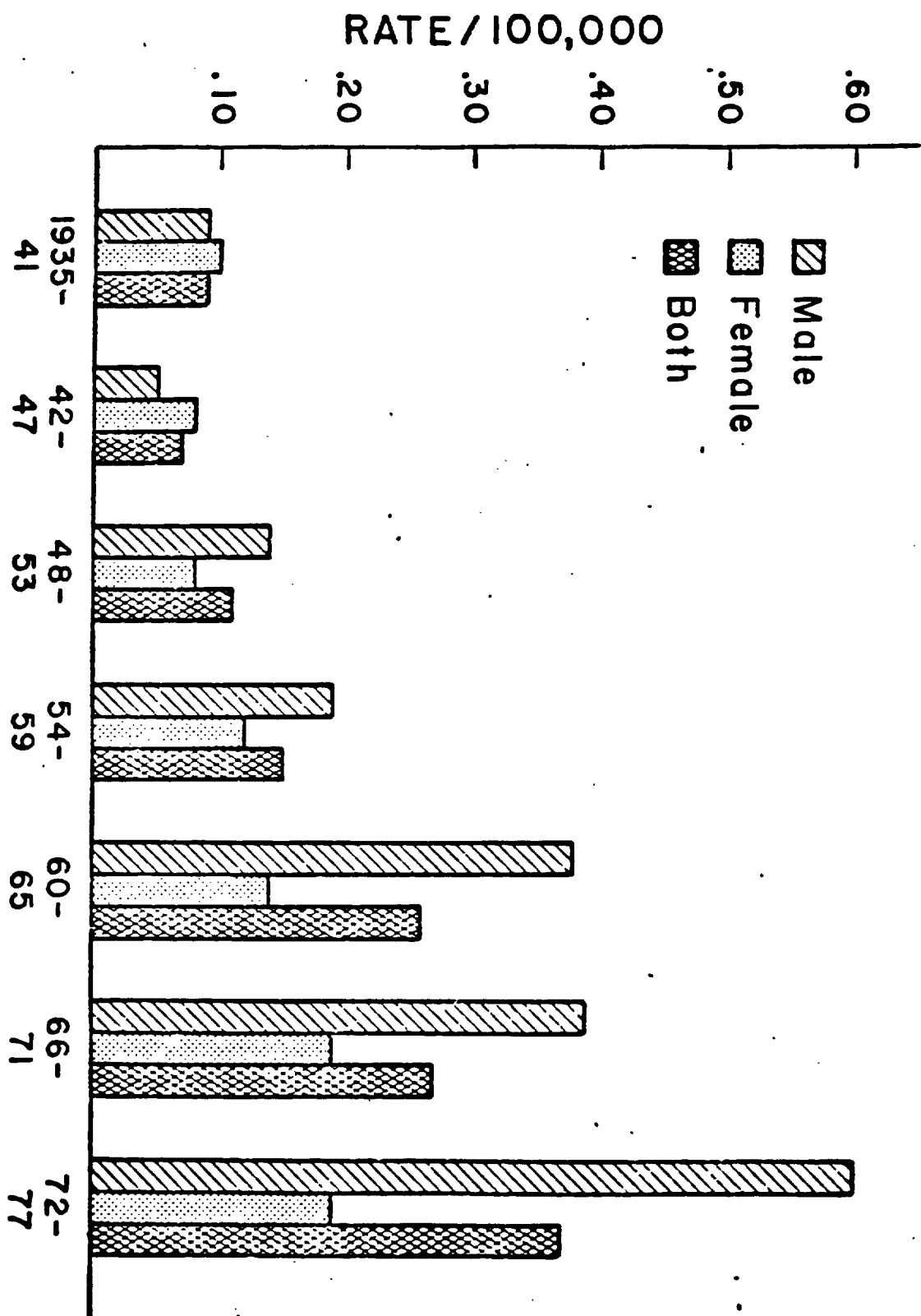
~~Five~~ ^{Ten (10)} cases were reported in ~~of the~~ ^{New London Labor Market Area (LMA)} ~~(New London)~~ where shipyards are located, and ~~five~~ ^{5 (5%)} of these were identified between 1975 and 1977 (Fig. 3).

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} ~~also~~ ^{LMA's.} centers for Labor Market Areas (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).

A00577

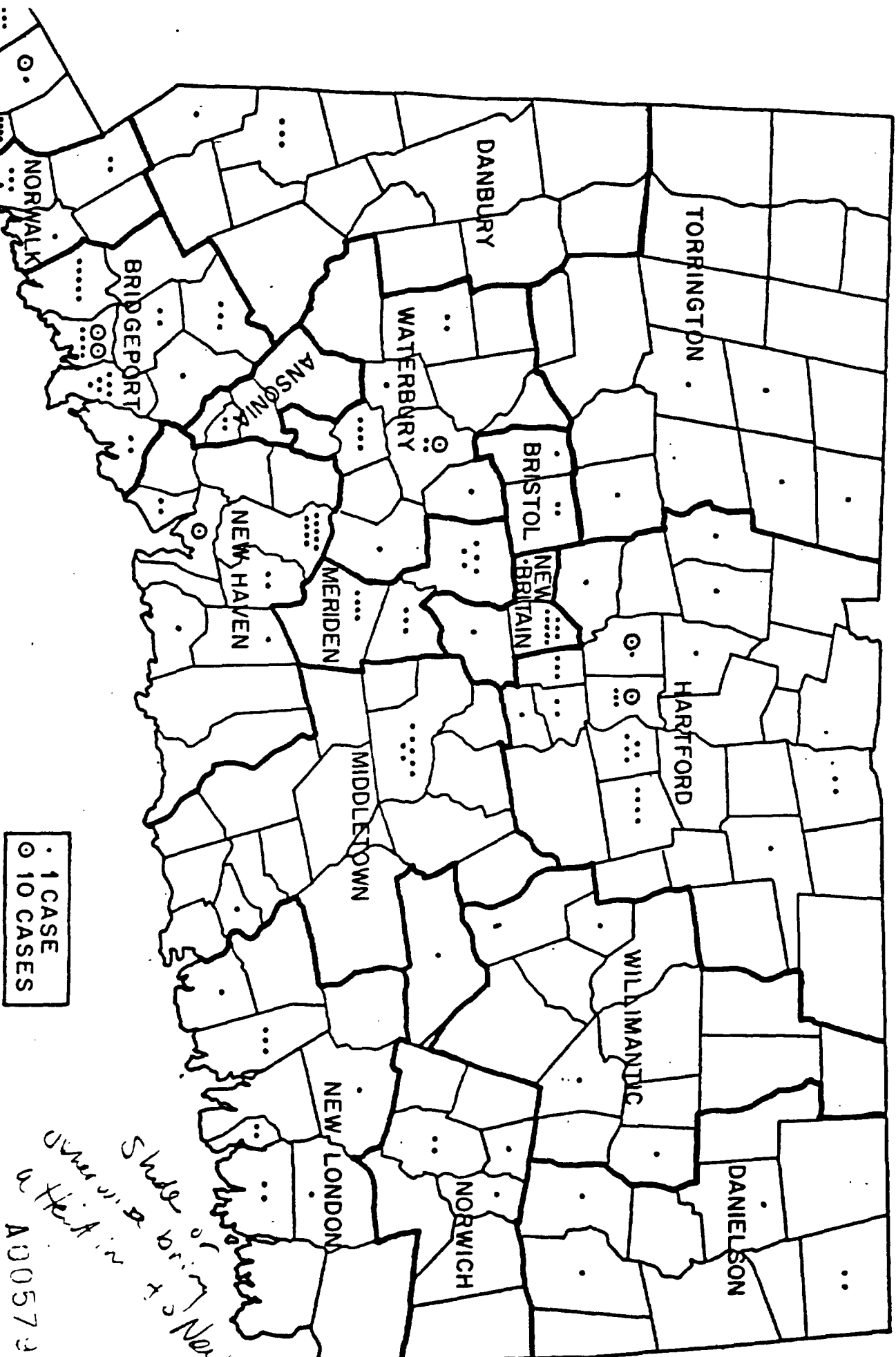
Fig 2

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



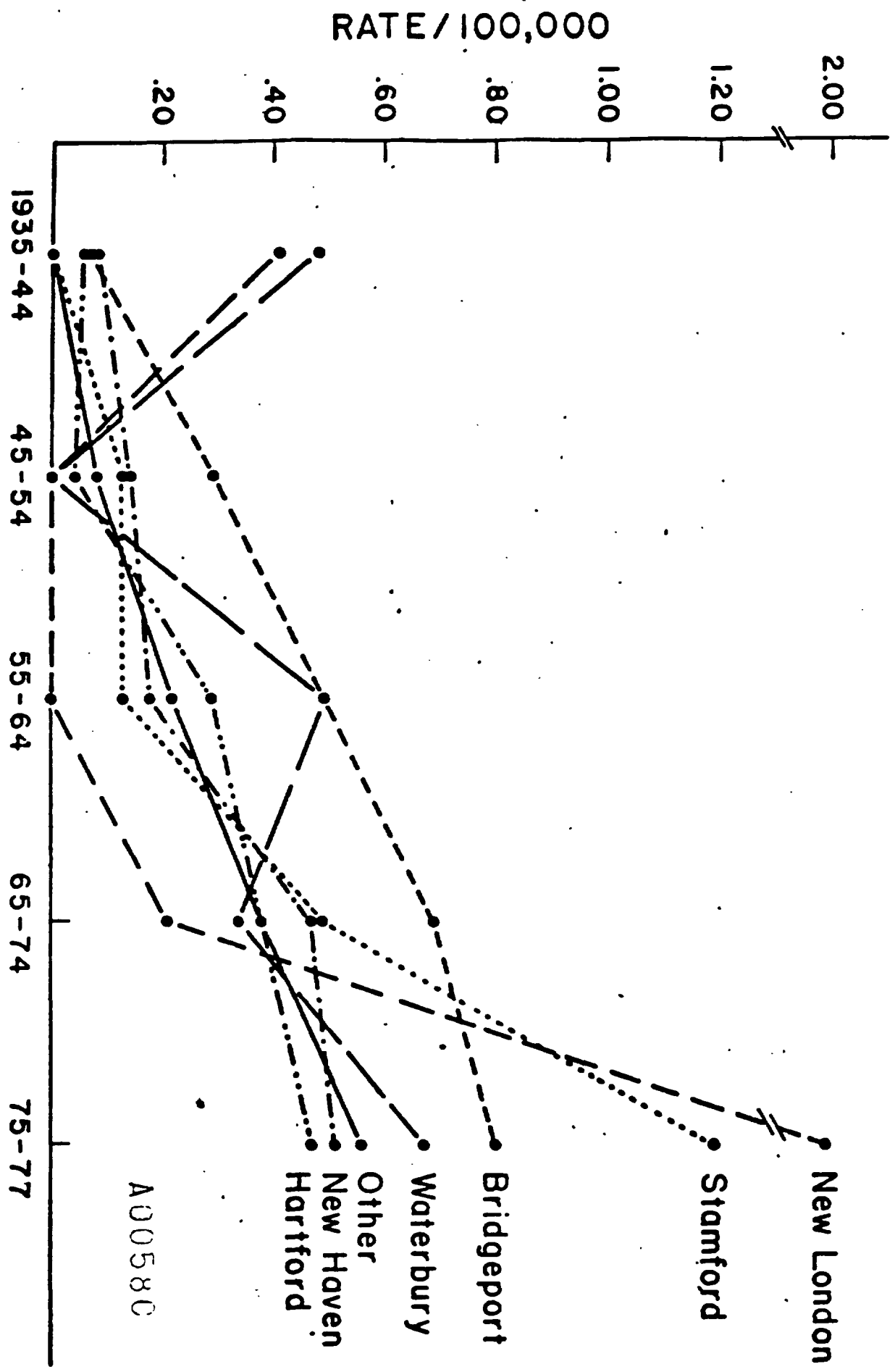
A00578

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



*Shade in bright
 in New Haven
 A00573*

Fig 1
 AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA
 FOR CONNECTICUT MALES BY YEAR OF DIAGNOSIS
 AND LABOR MARKET AREA



SLIDE REVIEW

Malignant mesothelioma is a very rare disease, ^{with} only 2 cases per million population expected annually. ⁷ 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. ⁽⁷⁾

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 105 (44% ~~105~~) of the 238 deceased cases are known by the CTR to have been autopsied, but on 82 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} ~~slide~~ 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.

^{preliminary}
(Summary of Dr. Vidone's Findings)
^

A00581

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

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

A00582

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

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	
<u>Diagnosis^a</u>	<u>Autopsy, Microscopic Evidence of Cancer</u>	<u>Autopsy, Gross Evidence of Cancer</u>	<u>Autopsy Gross Evidence, Unknown Whether of Cancer</u>	<u>Autopsy, but only Indirect Evidence of Cancer</u>	<u>Autopsy, no Report</u>	<u>No Autopsy</u>	<u>Unknown</u>	<u>Number Dead</u>	<u>Autopsy^b %</u>
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%

^aWHO (1976)

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

A00583

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.

⁽¹²⁾ Felton 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 appearances 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.

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^e, detailed job histories^a) , 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.

A00585

26.

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Feltm —

A00586

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A00507

~~The Influence of Occupational~~
~~and Environmental Asbestos~~
~~Exposure on the Incidence of~~
Malignant Mesothelioma in
Connecticut, 1935-1977

by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

Presentation to the Connecticut Thoracic Society, November 4, 1980

A00583

~~The Influence of Occupational and Environmental Asbestos Exposure on
the Incidence of Malignant Mesothelioma in Connecticut, 1935-1977~~

by H. C. Lewinsohn, J. W. Meigs, and M. J. Teta

I. Introduction and Aims

Bruckman et al. (1977a) reported that "the combined sex age-adjusted mesothelioma incidence rate (AAR) per 100,000 Connecticut population has exhibited a possible ten-fold increase since 1935..." They acknowledge that the available statistics might be subject to diagnostic error but, nevertheless, postulate that the rapid increase in the State's mesothelioma incidence rate is closely related to the increase in the State's "cumulative asbestos consumption", which includes asbestos emissions from industrial sources, motor vehicles, and building demolition.

One criticism of their study is the failure to make available complete occupational exposure histories for the 133 diagnosed (1935-1972) cases of mesothelioma drawn from the Connecticut Tumor Registry (CTR). The Air Compliance Unit of the Connecticut Department of Environmental Protection has monitored asbestos concentrations in Connecticut (Bruckman, 1977b; Bruckman, 1978) and proposed an ambient air standard for Connecticut of 30ng/m^3 , measured over a thirty-day interval. The rapid increase in the State's mesothelioma incidence reported in 1977 is referred to as justification for this proposal. A second criticism is the failure to investigate the degree of certainty in these diagnoses and to institute a pathological review, if it is warranted. The present study has been designed to re-examine the identified cases of malignant mesothelioma recorded in the

A00500

CTR and attempt to determine the role of various etiological factors, such as occupational and environmental asbestos exposures. In view of the ~~the~~ ^{Suggest} ~~knowledge~~ possible diagnostic errors, which our results ~~verify~~, a thorough review of available histological material is being undertaken.

A00501

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). ~~Disease topology and morphology are coded according to the ICD-9 (World Health Organization, 1976) classification.~~ 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 case-control comparisons will include 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 ~~increasing~~ ^{lack of} awareness of ^{this earlier} mesothelioma associated with the ~~later~~ time period (1935-1977). 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, 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.

~~The three-digit~~ 1970 U. S. Census industrial and occupational codes (U. S. Dept. of Commerce, 1971) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. A machine readable listing of job and industry titles has been developed for all cases, spouses, ^{1955-1977.} and controls, This will form the basis for classification of study subjects

TABLE 1

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' ^b histology	Percent autopsied ^c
Pleural mesothelioma	102 (94) ^b	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 WHO (1976)

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

^c (No. autopsied/no. deceased) x 100

Numbers in brackets refer to the period 1955-1977

A00563

into asbestos exposure categories for future case-control comparisons (sample from listing Fig. 1).

A00534

III. Results

Descriptive Epidemiology

age-adjusted
The ~~crude~~ incidence rate for mesothelioma in Connecticut is 2.1/million for the years 1935-1977. ~~Age-adjusted incidence rates~~ ^R 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. 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 approximately ten months.

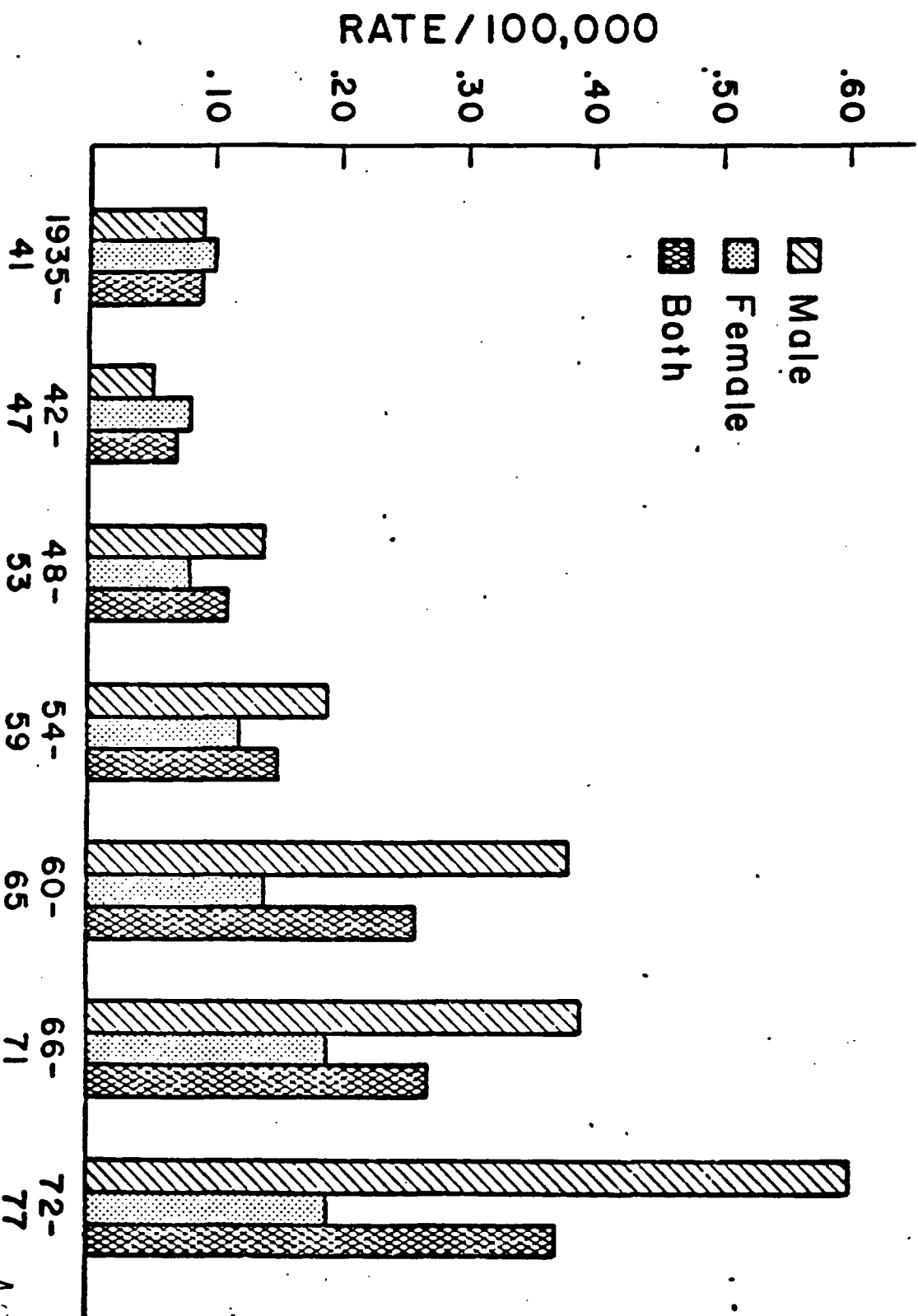
Ten cases were reported in an area (New London) where shipyards are located, and five of these were identified between 1975 and 1977 (Fig. 3). The geographical distribution of mesothelioma shows evidence of urban clusters in the 5 largest cities (Bridgeport, Hartford, Waterbury, Stamford, New Haven) 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 also centers of Labor Market Areas (LMA). All 6 areas exhibit a similarly increasing ^{age-adjusted} incidence ^{rate for males} ~~with the Bridgeport LMA the highest overall~~. The Stamford LMA's mesothelioma rate shows an *unexplained* sharp increase since 1965 (Fig. 4).

A00505

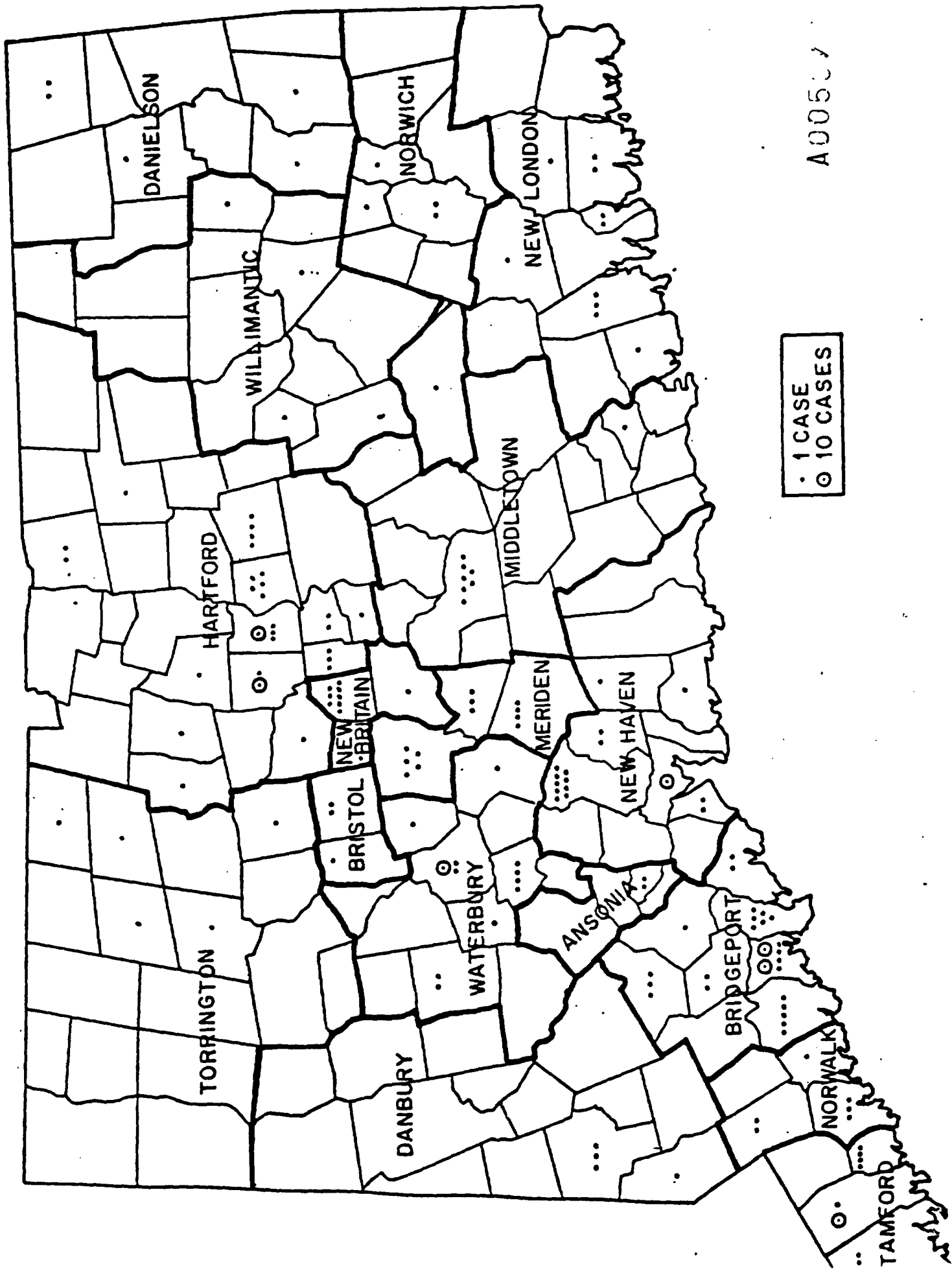
Fig 2

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



A00596

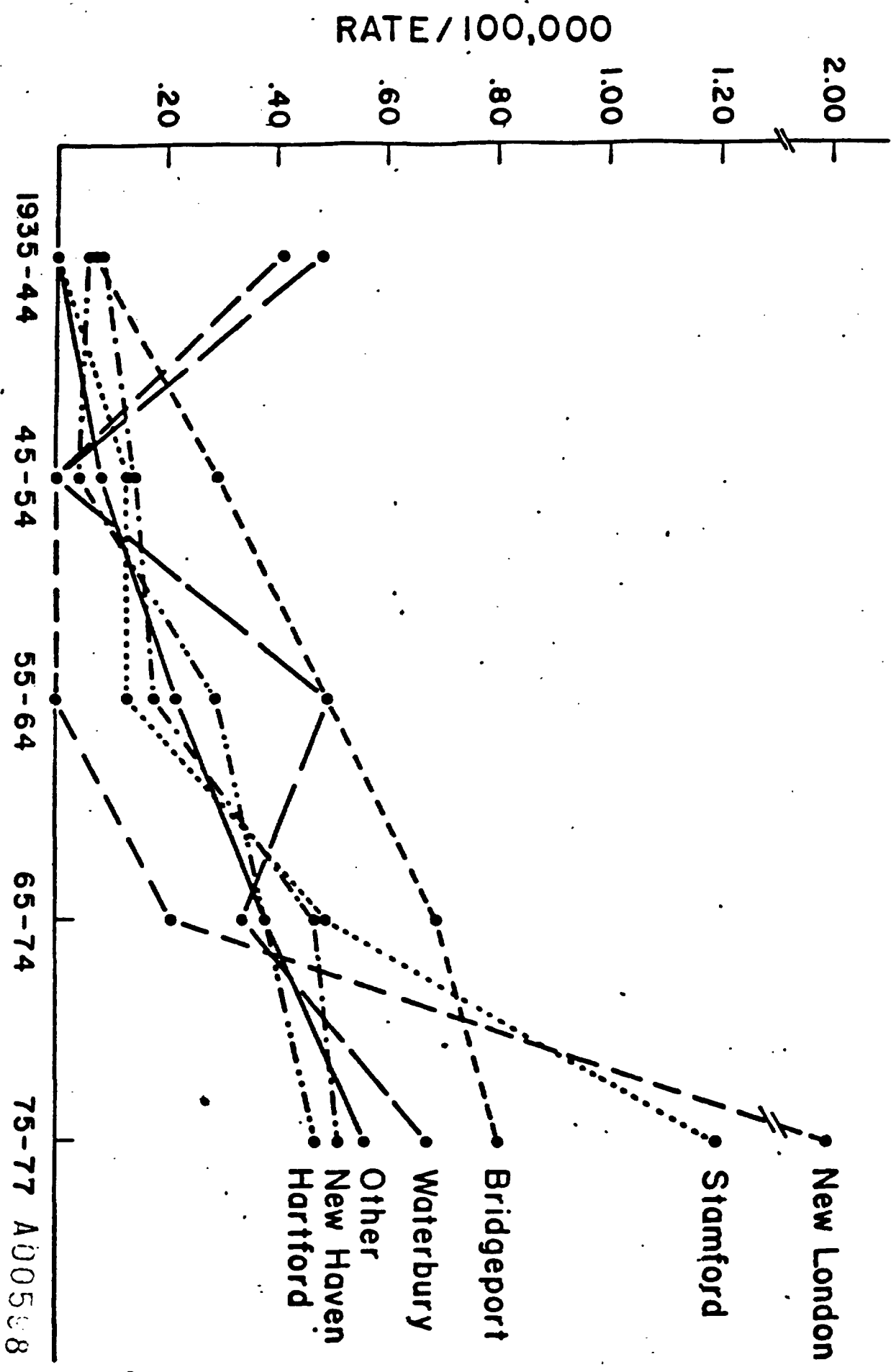
GEOGRAPHICAL MAPPING OF CASES OF MESOTHELIOMA (1935 - 1977) BY TOWN OF RESIDENCE AND 1960 LABOR MARKET AREA



A00507

Fig 1

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



SLIDE REVIEW

~~These descriptive results assume~~
~~identify completeness and accuracy of case~~
~~identification which is limited by factors relating to the quality of diag-~~
~~nosis.~~ Malignant mesothelioma is a very rare disease, expected in only 2
persons for every million at risk. Resistance to acceptance of mesothelioma
as a disease entity persisted until the late 1960's, despite Wagner's 1960
report of 33 histologically proven cases of pleural mesothelioma associated
with Cape crocidolite asbestos fields in So. Africa. This widely published publicized
association of mesothelioma with asbestos exposure, however, created the
potential for diagnostic bias.

~~In addition to its rarity and the subsequent lack of awareness,~~ positive
diagnosis of mesothelioma is often complicated by its confusion with other forms
of cancer. (Dr. Vidone's discussion of simulators.) The controversy over
criteria for positive diagnosis is well-documented in the literature. Most
experts agree, however, that without an autopsy it is difficult to distin-
guish mesothelioma from a metastasis from another primary site.

~~In the light of these difficulties~~ 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
of the cases, no known pathological material existed at time of diagnosis,
the origin of material varied.
while available specimens vary from biopsy to D & C tissue.
(1935-1977)

Overall only 44% (105) of the 238 deceased cases are known by the CTR
to have been autopsied. The percentages for all categories, except peritoneal
mesothelioma, are low, ranging from 33% to 40%.

These results suggested the advisability of a case review, which was
made feasible by the large proportion of patients with available histological
material at time of diagnosis. Dr. Romeo Vidone, chief pathologist at St.

A00599

Raphael's Hospital, is presently ^{studying} ~~reviewing~~ the medical records (except occupational data) and slides we have obtained for cases diagnosed after 1954. Cooperation was ^{sought} ~~elicited~~ from 37 hospitals, of which 30 have ^{thus far} provided us with the materials requested.

(Dr. Vidone-Summary of Findings)

A00600

TABLE 2: BASIS FOR DIAGNOSTIC EVALUATION
for Cases of Malignant Mesothelioma and Pleural
Tumors other than Meso. Diagnosed in Connecticut, 1935-1977.

Diagnosis ^a	Tissue ^b Available	Exfoliative Cytology	X-RAY	Direct Visualization	(unk) NOT MIC	UNKNOWN	TOTAL
benign Mesothelioma	136	3	3	-	1	4	14
benign Tumor (teratoma mesothelioma)	27	2	-	1	-	8	38
benign mesothelioma	31	-	-	1	1	-	33
mesothelioma at other sites & unknown sites	41	-	-	-	-	8	49
total	235	5	3	2	2	20	267

^a WHO (1976)

^b Specimen from biopsy, frozen section, surgery,
autopsy, or D+C

A00601

Primary and Pleural Tumors other than mesothelioma Diagnosed
Connecticut, 1935-1977

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	
Diagnosis ^a	Microscopic Evidence of Ca.	Gross Evid. of Cancer	Gross, Evid. UAK		Autopsy Type UAK	No Autopsy	UAK	No Autopsy	UAK	No Autopsy
Pleural mesothelioma	43	3	—	1	7	62	18	134		
Pleural Tumor other than mesothelioma	8	1	1	—	3	13	11	37		3
Peritoneal mesothelioma	21	4	—	—	—	2	1	28		8
Mesothelioma at other sites and unknown sites	11	—	—	—	2	21	5	39		3
Total	83	8	1	1	12	98	35	238		4

A00602

IV Discussion

Major areas for improvement in medical practice

importance of autopsy

" " " " Complete occupational histories
 smoking histories
 hobbies & part-time activities
 being alert to diagnostic bias

note: From CTR paperfiles (ie hospital records) we obtained - job titles for only 17.1% of cases. If we exclude retired, housewife, a student the figure is 12.4%. The percentage for industry information is 6.9%.

Above data is relative to 220 cases:

(195 meso. from CTR 1955-77 /
 5 " " V.A. " " / 2
 20 pleural tumors, not meso., 1955-77)

A00603

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A00605

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

by

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Malignant Mesothelioma in Connecticut 1935-1977

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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 (Table 1).

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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.

*Connecticut Tumor Registry

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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 (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). 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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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 Mucicarmin 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.

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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

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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 continued. 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.

SLIDE 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

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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 microscopic 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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- (1) Ship of Landing
- (2) X-Ray 9/5/79
- (3) X-Ray 3/30/80
- (4) X-Ray 7/23/80
- (5) Local X-Ray 7/23/80
- (6) Lung
- (7) Lung - cross up
- (8) Lung + pencil beam
- (9) Pencil beam - cross up
- (10) Pencil beam - cross up
- (11) Histology
- (12) Histology
- (13) Electron photo-micrographs
- (14) Asthma exposure summary

- (15) X-Ray report 9/5/79
- (16) Asthma exposure 9/7/79
- (17) " " 7/22/80
- (18) Memo to Henry
- (19) Table 1
- (20) Figure 1
- (21) Figure 2
- (22) Figure 3
- (23) Figure 4
- (24) Table 2
- (25) Table 3
- (26) Table 4
- (27) Table 5

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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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New London Labor Market Area

<u>Town</u>	<u>I.D.</u>	<u>Occupation</u>	<u>Dx</u>	<u>Sex</u>	<u>Site & Histology</u>
Old Lyme	675092	At home spouse-atty	(1966)	F	Pleural mesothelioma
East Lyme	711723	Clothing merchant	(1971)	M	Peritoneal mesothelioma
	781723	E.B. Safety Nuclear Eng.	(1976)	M	Pleural mesothelioma
	792536	Architect, retired eng. Past exposure to some asbestos long ago	(1977)	M	Pleural mesothelioma
Montville	793335	Housewife spouse-truck driver paper & board co.	(1977)	F	Pleural mesothelioma
Ledyard	761292	Painter-glazer sub-base	(1975)	M	Pleural mesothelioma
Groton	200401	Landscaper-Gardiner	(1939)	M	Pleural mesothelioma
	501121	At home	(1950)	F	Pleural mesothelioma
New London	693627	Supt.-E.B. machinest	(1968) (3 time periods)	M	Pleural mesothelioma
	779762	Rigger-E.B. erector-E.B. stevedore- railway	(1976) (2 time periods) (1 time period)	M	Pleural mesothelioma
	10 Cases	9 Pleural 1 Peritoneal			

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DISCUSSION

Although this study was undertaken initially in an attempt to discover whether it would be feasible to determine the environmental factors responsible for the increase of malignant mesothelioma in the State of Connecticut, it has suffered from the lack of detail in available records. ~~Table II and III illustrate one of the~~

major deficiencies ^{ies} in the data available for study, ^{is are} namely the low autopsy rate ^{pathological material} ~~of (1/2) for the pleural mesotheliomata and the inadequacy of the types of tissue~~ available and used for diagnostic purposes.

It has been our experience that occupational histories are not routinely obtained and included in hospital records. Smoking habits are not routinely recorded and no inquiries are made of patients admitted with suspected malignant disease regarding their hobbies or part-time activities.

In our search through the C. T. R. paper files (i.e. hospital records), we found job titles for only 17% of the mesothelioma cases. If we exclude from this group those merely designated as "retired", "housewife" or "student", the figure is reduced to 12%. We were only able to ascertain the type of industry in 7% of these cases. This data is applicable to 220 cases consisting of:

195 mesotheliomas in the Connecticut Registry, 1955 - 1977,

5 mesotheliomas from the Veterans Administration files, 1955 - 1977, and

20 pleural tumors, not mesothelioma, recorded 1955 - 1977.

It is apparent from our study of these files that the awareness of this disease increased in the late 1950's and early 1960's and that this appeared to introduce a diagnostic bias which might partly account for apparent increase after 1955.

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Comment on the significance of the findings on the slide review.

It is evident that until the physicians or hospitals investigating cases of malignancy appreciate the importance of ^{occupational +} environmental facts ^{or on} of the etiology of these diseases, no attempt can be made to apportion the blame to any particular factor unless adequate histories are available containing complete information on lifestyle, habits, hobbies, part-time activities and details of occupation and industry. It is also essential, particularly in the case of a rare tumor which may present diagnostic difficulties, to obtain sufficient tissue for study before the final diagnosis is made. Whenever a tumor is found where ^{an} association ^{is suspected} ~~exists~~ between it and a particular occupational or environmental factor, every attempt should be made to fully document all the ~~medical~~ facts and to subsequently verify the diagnosis by means of a full autopsy.

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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 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^a</u>	<u>Tissue^b Available</u>	<u>z</u>	<u>No Tissue Available</u>	<u>z</u>	<u>Total</u>	<u>z</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, b 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 Σ
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	30	33
Total	83	8	1	1	12	98	35	238	442

^aWHO (1976)

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

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Table 5

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

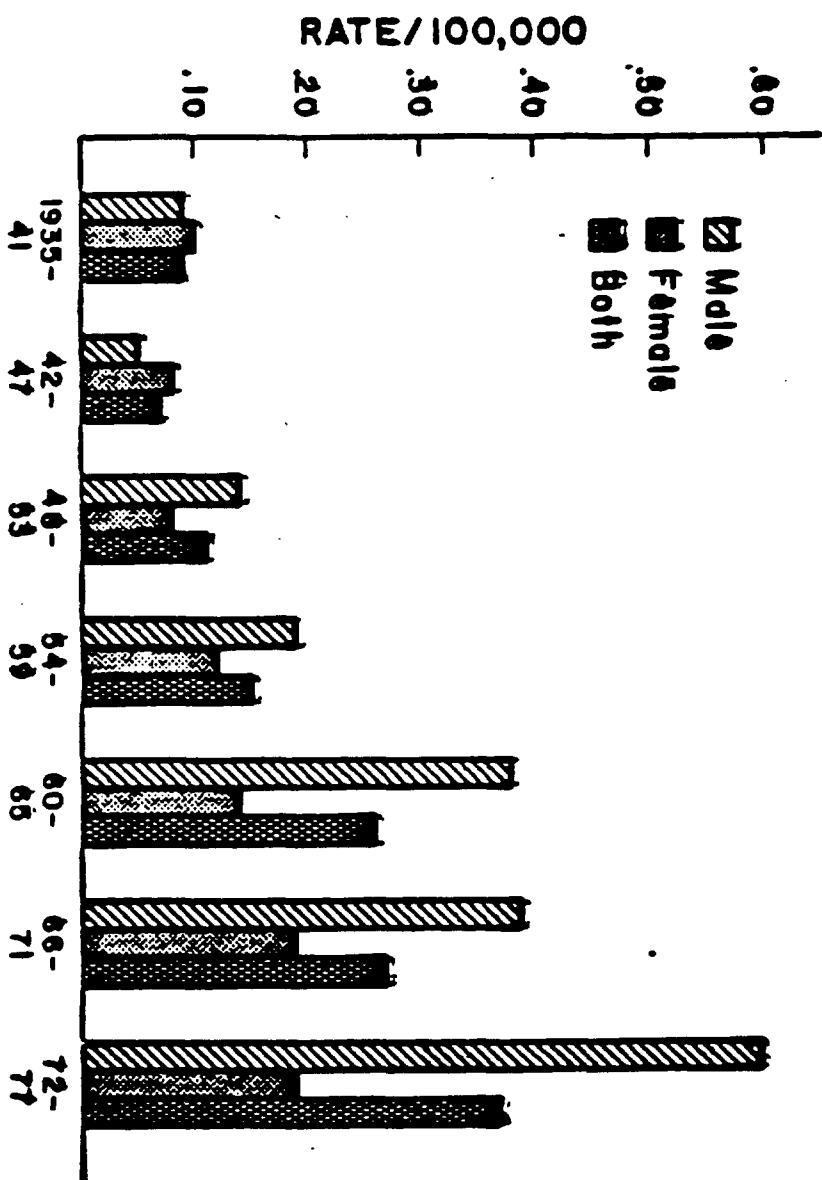


Figure 2

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Draft

~~I must apologize to you right at the outset of this talk. Being a foreigner I have been involved in something called FLEX - the Federal of Licensing Examinations Board or something and I just finished the exams last week. This is the second time I have taken it which indicates to you how much I know about basic sciences and biochemistry and all the things that have appeared on this scene since I graduated. The time I have had to prepare this talk has not been very great and I apologize to you because ~~what~~ I am going to ~~do~~ ^{read} ~~is take~~ a paper that was published this year in the British Journal of Industrial Medicine of which I was a co-author. I was only a co-author by virtue of the fact that I was ^{employed} ~~able to be~~ in a factory in the United Kingdom which has preserved its personnel records since the turn of the ~~from~~ the last century ~~onwards~~ ^{late} and which has good medical records going back to the 1940's-early 1950's. ^{These} ~~and which~~ had previously been studied by my predecessor, John Knox in association with Richard Doll who is ^{now known} ~~the~~ Professor of Medicine at Oxford University ^{and} whom I am sure you ^{Sir} know of as a leading epidemiologist ~~in the field~~. It was Richard Doll who, in 1955 (based upon studies of the population I am about to describe to you) ~~it was Richard Doll who~~ proved that there was indeed an association between lung cancer and exposure to asbestos. ^{would be} ~~Before we start~~, I think it is ~~always~~ worthwhile to ~~go through~~ ^{describe} the old pot boiling mechanisms of telling you ~~exactly~~ what asbestos is ^{and} ~~well not exactly~~ but just ^{give} you some idea of ^{the material} ~~what~~ we are talking about. ~~Unlike the Chairman of Turner & Newall, the company which I worked for which was a large company with 30,000 employees in the United Kingdom and many subsidiaries throughout the world including mines in Canada, and Southern Rhodesia and factories in many countries.~~ ^{Your background data will then be better than that of the son of}~~

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of an international asbestos company;

Chairman, who went out to Rhodesia to see for himself where the asbestos came from and after breakfast said "Let's go and look at the plantation." ^{1"} ~~If we could just have the first slide and the lights~~

~~off then I could illustrate to you just briefly that~~ Asbestos is a fibrous mineral silicate and ~~that~~ there are a number of varieties that are of commercial importance. I am not going to go into ~~all~~ the arguments ~~and the details~~ about the differences in biological effects which exist between the various forms of asbestos. Chrysotile asbestos which comes from Canada, Southern Rhodesia, the Soviet Union, Swaziland ^{and the} is Cyprus, ~~South Africa~~, United States, the type of fiber which composes about 95% of the world's usage of this material. It is a hydrated ^{fibrous} magnesium silicate. Crocidolite, which is a blue ~~pale~~ fiber, ^{is mined in} comes from South Africa at the present time ⁱⁿ from the Northwest Cape Province and ~~from~~ the Northeast ~~and~~ Transvaal. It ~~used~~ to be mined in Australia but that ~~mining~~ no longer takes place and there was a disastrous experience there with regard to ^{the incidence} ~~accounts~~ of mesothelioma among the miners. Amosite is not ^{really} ~~an~~ acceptable mineralogical term because it ^{is} ~~merely~~ ^{an abbreviation} stands for "Asbestos Mines of South Africa" ^I ~~and that~~ ^a is ^a unique ^{fiber} in that it only comes from ^{this} one part of the world i.e. ~~and that's from~~ the Northeast Transvaal. The amosite and crocidolite from the Northeast Transvaal ~~often~~ ^{rock} occurred in the same seam in the ~~rock~~ and therefore it is ~~not always~~ possible ^{and vice versa.} to say that amosite ~~is~~ may be ~~not~~ contaminated with ~~some~~ crocidolite. ~~That is possible.~~ There are deposits of amosite in India but I don't think they have been commercially exploited yet, ~~but there are some there of that type of fiber.~~ ^{belongs to} ~~Its~~ ^{cummingtonite-grunerite} ~~Amosite~~ really ~~is part of~~ the cummingtonite-grunerite (2) series and just to digress for a moment the importance of the CG series (or the fact that amosite is part of that series) became apparent when ^{the} Reserve Mining Company ~~found~~ ^{itself} ~~enbattled~~ with EPA, the State of ^{Connecticut}

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Minnesota and various other people regarding the dumping of ^{early} tailings from its ^{taronite} mines in Silver Bay into Lake Superior, and ~~Dr. Selikoff~~ ^{early} waltzed into Minnesota and waltzed out again and really upset the whole apricot there and that battle is still going on with Reserve Mining. I am sure you are familiar with that story. ~~That was CG~~ ^{The fiber in the tailings} and the later ^{apparently} which is similar to commercially used amosite. Apart from the fact that a lot of the fibers initially discovered were Diatomite skeletons (Anthrophyllite isn't very widely used in industry. It's one of the oldest ^{known} asbestos fibers particularly ⁱⁿ Finland where for thousands of years it's been incorporated in the building of Sauna baths. If you like to go into that sort of occupation. However, it isn't terribly important. Biologically it is ^a very ~~very~~ interesting because no cases of mesothelioma have as yet been described ⁱⁿ with the association ^{with} of anthrophyllite exposure, and we can forget about the other two except the bottom one Tremolite which is ^{a fiber which is} often found in commercial talc or industrial talc. Just to give you some idea of the fact that chrysotile crocidolite ^{really} is blue amosite is sort of an in-between color. Those are both iron containing fibers this is magnesium and various anthrophyllite which is also an _____.

Slide 3 That's (a mine up in Canada) showing what has happened to the country side. This is a composite slide ^{which shows} and this is what we did with asbestos in Rochdale in England. ^{The} ^{is crushed and graded} That's a rock, ~~it was opened~~ at the mine and the ^{is} to some extent, It ~~was~~ further opened at the factory in the process of what we called fiberizing. ^{After} ^{is formed into} and carding it ~~was used as~~ a sliver and then spun into a yarn, and that is the process and then ~~The yarn would be~~ ^{can} woven or sold to customers. Cloth ~~would~~ ^{can} be used for various purposes such as wrapping around insulation sections, laminating with resin, for friction materials, solvent containers etc. Another thing I think you should appreciate if you will read in the paper if you have it or wish to read it is the fact that in the United Kingdom, Regulations were made in 1931 which took affect

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in 1933, ~~which~~ and prior to the making of those regulations, which were called the Asbestos Industry Regulations, ~~and which therefore only apply to the asbestos industry and that also is important from the point of view of what happens subsequently however those regulations resulted after~~ a study which was conducted by ^{Meriwether} Morrywhether and Price in 1929 and published in 1930 ^{and it became} which is one of the most famous study in this field ~~and is~~ a milestone in/~~xxxxxx~~ British asbestos industry. What they found was that in people who had been employed for 20 or more years, ~~81%~~ - 81% had pulmonary fibrosis. We are talking about asbestosis, ~~and it's important to remember that asbestosis was it is~~ a 20th Century disease. The first case of asbestosis was not described until the beginning of the Century in London by Montague Murray. ~~and therefore this is a 20th Century occupational disease.~~ The first evidence that exposure to asbestos was going to cause a problem to the health of ~~the~~ workers was the finding of asbestosis and the regulations that were made in 1931 and that took affect in 1933 were designed to reduce the incidence of pulmonary fibrosis. Lung cancer was not ^{then} associated with asbestos exposure apart from speculative case histories that first began appearing in 1935. No epidemiological study was done to confirm this suspected ~~xxxxxx~~ association until the work of Richard Doll in 1955, ^a Although the same ^{Meriwether} Morrywhether in 1947 had shown that 13% of asbestosis cases diagnosed in the United Kingdom were dying of lung cancer or had died of lung cancer. That leads to another speculation, ~~again which I don't intend to dwell upon and that~~ ^{the development of} ~~is where~~ asbestosis ~~is~~ a prerequisite for the development of lung cancer or ^{can} ~~that~~ lung cancer occur in an asbestos worker without asbestosis, ~~is nevertheless an occupational disease and we would only enter in many arguments especially in view of the known~~ multiplicative effect which cigarettes ~~xx~~ smoking has on lung cancer in asbestos workers.

However, I ~~show that simply to point out what the situation was~~
~~in 1930 with regard to asbestosis.~~ ^{In 1929} ~~Thx Pulmonary fibrosis was of~~ ^{world.}
~~crippling and killing people and~~ 81% of those ^{with} more than 20
 years exposure, ~~were suffering from this condition.~~ By comparison
 in 1975 only 0.77 or 0.8% of the ^{entire} group ~~were~~ compared with 26.2% ^{in 1929} were
 found to have asbestosis and the 20 year and over ^{group} ~~the~~ incidence ~~were~~
 down to 5%. ^{This} which obviously is still ~~an~~ unacceptable but ~~what you~~
~~have to remember is that~~ some of these cases ^{he} were in fact exposed ^{in this population}
^{he 1931} before regulations. They were still ^{employed} ~~working~~ and ^{as} this ~~xxx~~ is a
 table of prevalence not incidence ~~and consequently~~ they were there
^{were included} and counted. It does indicate quite dramatically that those regulations
~~in industry~~ had reduced the incidence of asbestosis. ~~If we go to the~~
~~paper know we will see that~~ ^{whose mortality exposure} This co-hort ~~that~~ we are describing in the
~~paper~~ has been the subject of 3 previous reports and the last of
 these ~~reports~~ was published in 1968. ~~the one prior to this and~~ They
^{from} dealt particularly with mortality ~~of~~ lung cancer and respiratory
 disease in workers exposed to the high dust levels which preceded the
 1931 asbestos industry regulations. They attempted to examine the
 dependence of lung cancer incidence on ~~the~~ age and duration of ^{asbestos} exposure.
~~The last one~~ ^{the paper} In 1968 the cohort was divided into 6 groups. ~~with the~~
 Group 1 had more than 10 years of exposure ^{before 1933 but} ~~xxx~~ groups 1, 2, 3 and 4 had
^{total exposure} all had more than 20 years ~~but group 1 had greater than 10 years~~
~~exposure before 1933.~~ Group 2 had between 5 and 10 years exposure
 before 1933 when the regulations took affect. Group ³ ~~2~~ had less than
 5 years exposure and Group 4 had had no exposure before 1933. Group
 5 was all males and had had more than 10 years exposure but less
 than 20 with no exposure prior to 1933 and group 6 was all females and
 they ~~xxx~~ had all been exposed after 1933 for more than 10 years.
~~When you look at~~ ^{For} Cancer of the lung and pleura, ^{15 cases were observed where} you see that the
~~observed was 15 and the expected 1.6~~ ^{were expected was} so there is about an 11 times

A00907

excess incidence of lung cancer in ^{the} ~~that~~ group which ~~has~~ had the longest exposure prior to the improvements which came with regulations.

~~As you go down you see that that diminishes. When you get to this~~

In ^{the} ~~group here~~ ^{with} no exposure before 1933 ^{but} with more than 20 years ^{since} the

difference is not statistically significant. That was ^a very

^{Satisfying observation}

interesting but the authors were wise ~~and they pointed~~ out that no

~~further~~ firm conclusions could be drawn because little carcinogenic

effect ~~was~~ would be expected for 20 years after first exposure and

some of the follow-up had not been for long enough. ~~If we just go~~

~~through two more slides dealing with that cohort or with these figures.~~

~~here we have~~ ^{In} the men and women all exposed ~~to~~ since 1933 and ~~you~~

~~can see that~~ ^{for} cancer of the lung and pleura ~~was~~ there was no statistically

significance difference ^{between observed and expected} and ~~in~~ the women there ~~was this difference~~

~~and that was only~~ ^{were} 2 cases ^{but} and it was not possible to state what the

meaning of that was ^{because of small numbers}. What we are dealing with here is men and

women employed 10 years or longer since 1933. This is the ~~same~~ group

~~with less than 20 years or 10 to 19 years and you see no difference~~

~~in the observed to the expected ~~rate~~ incidence of lung cancer.~~

In men employed 20 years ^{or more} those who worked before 1933 ~~as we have~~

~~said before~~ ^{there were lung cancer observed} 11 to 0.8 ^{for} (11 to 1) and ^{observed} all neoplasms 15 to 3 ^{expected} and since

1933 ^{there were observed} 3 to 2.9 ^{expected} and ~~so~~ Therefore, it appeared from this information,

that people who had worked since 1933 were ~~now~~ no longer at risk and,

if you accepted this, ^{because} that the dust levels ~~that~~ had been brought

down, had been achieved a disappearance of the lung cancer. Further-

more this was against a diminishing background of incidence of

asbestosis and as ~~you saw~~ in 1975 the prevalence of asbestosis

was only ~~0.8%~~ ^{compared with 26% in 1929.} in the factory population studied. The report published

in 1977 is concerned with the ~~post-1933 population~~ the post-1932

population mainly, which, ~~as I said~~ although exposed ^{to} dust levels ~~which~~

were higher than the present ~~present~~ permitted levels, ~~this~~
~~population~~ was employed during the time of improving dust controls
 and plant modernization. The study is based on 1,106 men and women
 only (284 women) and the cohorts ^{have} ~~has~~ been roughly sub-divided in the
 same way except that you will see there are only 5 groups instead
 of 6. ~~and ^{from} the previous group 3 and 4 have been combined. If I~~
~~think that's what happened. I don't want to go into it too carefully.~~

Again we got years in asbestos areas 20 or more, 10 or more before
 1933 and than 20 or more less than 10 we have taken out the less than
 5 group from that and then we have ~~gone~~ gone on so that will be from
 _____ to 10 instead of just 5 to 10 and then we go on to 20 or more
 with no exposure after 1933 and that's the group we are particularly
~~interested~~ interested in 10 to 19 and then females with 10 or more. Well
 there may be some ~~females~~ females who have done 20 years. We get
 1,106 with a total of 16,000 person years of observations.

Re-examination of our personnel records since the ~~last~~ last report
 in 1968 showed that a further 23 workers were eligible for inclusion
 in cohorts 1 and 2 and in addition 205 workers who ^{had} ~~have~~ completed
 10 years employment since June ~~16~~ 1966 were added to cohorts 3, 4
 and 5. So the study comprised 822 (men) and 284 women and the followup
 was until the 31st of December 1974 using the factory ~~personnel~~ personnel
 records and the National Health Service Central register. Only 2%
 of workers could not be traced and 13 ~~and that's~~ (1.2%) were
 recorded in the National Health Service Central registry as having
 immigrated or were not currently registered with ^a ~~the~~ GP. As you know
 everyone in the UK is registered with a GP, ~~you don't have to be, but~~
~~most people are. From this you can see that a very small percentage~~
~~are not. Especially among the working population who are not able~~
~~to afford private treatment.~~ The remaining 1,071 (96.8%) have been

A00909

followed-up to the end of 1974. The number of deaths in each group which have been attributed to lung cancer (and lung cancer includes deaths due to mesothelioma) ~~and the number of deaths in each group attributed to lung cancer~~ other cancers, respiratory disease and other causes are shown in the next slide and although it looks complicated it isn't really. If you simply look at ^{the} that column which ^{is} ~~is~~ the ~~xxx~~ ^{for} cause of death, which ^{is} ~~is~~ lung cancer and mesothelioma, other cancers, respiratory diseases and other causes, and if you will just look at the ones which ^{show} ~~is~~ statistically ~~significant~~ significant, ~~there~~ you will see that ~~again~~ in Group 1 (which ~~we knew before~~ ^{we knew before} ~~we~~ had the ^{15:0.8} ~~10 or 12~~ observed to expected ratio) ~~xxx~~ in ~~group~~ the respiratory diseases again there is a 3.6 observed to expected ratio and all causes the ratio is about 2 to 1 so there is an excess mortality in this population which is largely attributable to lung cancer but some of which is attributable to other respiratory diseases which might reflect a ~~xxx~~ residue of asbestosis in ~~the~~ this population. The expected numbers ~~for those of you who are interested~~ were calculated from National death rates by 5 year periods and 5 year age groups. To insure that the expected ^{numbers} ~~members~~ are not underestimated, immigrants and those lost to follow up were assumed to be alive on December 1, 1974. Deaths before the 1st of January 1931 or after the ~~xxx~~ age of 85 are ignored and expected members are calculated accordingly. In Rochdale itself lung cancer mortality was lower than the national average ^{for males} ~~among the men~~ which is interesting, ~~in that~~ This is the ~~xxx~~ largest asbestos textile factory in the world. Rochdale ^{with} ~~has~~ a population of about 80,000 people ~~and it~~ had a lower than average lung cancer mortality. It doesn't prove anything but ~~you~~ ~~we knew for those who say that~~ ^{if} asbestos is an environmental pollutant which is going to cause an excess incidence of lung cancer in the general population ~~*~~, this doesn't seem to make sense. The A00910

Table II

standardized mortality ratio ~~is~~ in Rochdale is 87^{for men} and ~~similar~~ for women ~~104 that's~~ (1959 to 1963 Register^{year} General 1971). Workers first exposed before 1933 ~~that's for~~ ^{i.e.} cohorts 1 and 2, suffered from ^{an} excess ^{incidence} of lung cancer and respiratory disease, ~~xxxx~~

Particularly those with 10 or more years exposure prior to ¹⁰33.

and there is also some excess mortality ^{from} lung cancer and mesothelioma (36 observed and 19.3 expected; ~~the P is less than~~ [<] 0.01) and respiratory disease (35 observed, 25 expected; ~~P equals~~ 0.03) in those who entered after the 1st of January 1933 ~~that's~~ (cohorts 3, ~~and~~ 4 and 5 combined). ~~You combine these 3 cohorts.~~ This excess is very much less than in the first two cohorts. ~~What it indicates is that in even~~ In those people ~~with longer follow up now these people~~ who were first exposed after 1933, the longer follow up indicates that there is still an excess mortality from lung cancer, mesothelioma and respiratory diseases. In the 1968 study there was a slight excess of circulatory disease in cohorts 3 and that hasn't increased (27 observed 20.6 were expected). In cohorts 4 and 5 there was a matching deficit (50 observed, 60.10 expected). The ^{inference} ~~incidence~~ that this was probably a chance observation seemed confirmed. There were 16 deaths attributable to gastro-intestinal cancer compared with 15.7 expected. This cohort, ever since it has been formed and ~~it has been~~ followed, has not yielded an excess incidence of ~~g~~ deaths from gastro-intestinal carcinoma. It is also interesting that in a paper published in the same issue of the British Journal of Industrial Medicine, Elmes in Belfast, following up his insulation workers finds the incidence of gastro-intestinal carcinoma is declining as the ~~xxxx~~ time goes by and ~~that he~~ thinks that this might be due to improvements in earlier years. ~~now that he is following the population further ahead in time.~~ However this excess incidence of gastro-intestinal carcinoma (in asbestos workers appears to be something that is related to the most heavily

^{worker}
 exposed ~~g~~ groups. ~~and~~ Although this group of textile workers
 in the earlier years was probably as heavily exposed as any, it has
 progressively been getting less and less exposure and ^{an} ~~this~~ excess
 of gastro-intestinal carcinoma has ~~never~~ been found ~~in Rochdale~~
~~I~~ think ~~it~~ ^{we} will ~~only~~ find that gastro-intestinal carcinoma
 is associated ^{only} ~~with it in some way with~~ very severe exposures.
 That is just my personal opinion. No excess, ^{incidence} ~~for any of those that is~~
 gastro-intestinal carcinoma approached/significant ^{statistical} in any cohorts
 and no peritone^{al} mesothelioma was reported. To distinguish exposure
 immediately after 1933 from that under present conditions cohorts
 3, 4 and 5 were divided into those first entering or first ~~being~~
 exposed from 1933 to 1950 and those starting later. The reason
 we took 1950 was because ~~in 1951~~ we regarded ¹⁹⁵¹ ~~it~~ as the start of the
 modern period in that factory. ~~because~~ It was the year in which
~~the~~ routine dust sampling was initiated. Although ^{Memorandum} ~~Merryweather~~ had,
 way back in the 1930's, ~~had~~ tried to give some indication as to what
 he considered to be an unacceptable ^{dust level,} ~~dusty~~ the instrumentation and
 the techniques were not available to assess dustiness ~~numerically~~
~~and to assess~~ accurately. It was only in 1951 when the thermal
^{precipitation}
 percipitator came into use in that factory, ~~and~~ ~~xxx~~ then subsequently
 was followed by the long-running thermal ^{le} percipitator and then, in
 1961, by the membrane filter method, that it was possible to attempt
 to measure ~~what~~ the exposure ~~was~~ of these people and to control the
 environment ^{using} ~~according to~~ measurable ^{measurable} dust levels rather than ~~according to~~
 best achievable ^{visible} results, ~~visibly~~. Observed and ~~expected~~ deaths for
 those first exposed between 1933 and 1950 are shown in Table ~~1A~~ but
 I think before we get there, no we got there, ^{men} ~~Men and women first~~
~~exposed 1933 to 1950 there were 616 Men and women first exposed~~
~~1951 or later lung cancer 33 to 50 ~~if~~ observed 30 expected 16~~
~~with a 2 to 1 ratio.~~ Here we find that the 1968 authors were

wise to add a word of caution about the length of follow up. It had only been 20 years and 20 years may not be long enough because here we ^{have} ~~had~~ emerging ~~now~~ something they didn't find ^{and} that is a slight excess ~~fits by no means the significant excess of 11 to 1 that we have had previously~~ but there is still a slight excess of lung cancer in those persons exposed between 1933 and 1950. What ^{have had after} about 1951? Well we have it again. We ~~have~~ have a ratio of 1.9, ^{observed to expected lung cancer deaths is} That is only 6 cases ^{are} observed to 3.2 ~~expected~~. The numbers might at this stage ^{be} small and therefore this has to be followed up ~~and we~~ have to increase the numbers and ~~the length of we have to~~ lengthen the follow-up, ^{but in the process of} ~~but even~~ people who first entered since 1951 ~~up to 1974~~ ^{follow-up} which gives you (24 years) still show this slight excess. Again the statistical significance is not as great as for the ^{remainder} other half of the cohorts ~~not exactly the half other 2/3 approximately of the cohorts~~, but here we have evidence that the lung cancer has not been totally eliminated in this population. There have been very few deaths among those first exposed in 1951 ~~or~~ subsequently and if we look at table 4, one of the things that is going to crop ~~up~~ about those 6 cases after 1951 is whether they smoked or not. ~~It is as important for the others but we~~ don't have the information available in ^{all HC} ~~their~~ medical records but we do ~~for~~ for cases who died after a certain period of time ^{since} ~~when~~ smoking histories were added. In fact, the lack of information on cigarette smoking in the earlier studies was a serious omission, but there were no smoking ^{data recorded} records kept in the medical records of ~~a~~ cigarette smoking until I went there in 1966. I then started meticulous ~~smoking~~ recording smoking habits. From that one could see that In 1976 if you ^{divided} ~~broke~~ the population into age groups smokers, ex-smokers and non-smokers I ~~went go into how these are defined just suffice to say~~ (0.913) that that's the way they were at the time. There were 22% who were ~~non~~ non-smokers, 13% who had given up smoking and ~~they~~ ~~there~~ were

65% who still smoked, ~~and these~~ ^{therefore} were comparable to the national figures, ~~in a way~~. This population was ^{therefore} no different ~~xxx~~ in its smoking habits from the general population. ~~What do you do about smoking? I don't know.~~ Table ^{IV} shows deaths ^{from} of lung cancer (including ~~peritineo~~ mesothelioma) in the men and ^{from} women first exposed 1933 to 1950 and men and women first exposed 1951 or later. They are distributed according to ^{date of} ~~the day by day first~~ ^{exposure} and time since first exposure. If you look at that 10 to 14 years since first exposure 15 to 19, 20 years or more ^{group} In the the 20 years or more ~~xxx~~ the ~~ratio~~ ^{ratio} is 2 to 1. ~~In these two groups it probably is not significant.~~

In Men and women first exposed 1951 or later 20 years or more if you take ~~xxxxxxx~~ that group 15 to 19 because one of them was just about 19 years which is close enough to 20 makes it 5 instead of 3 and 2 ^{there are} you get 5 observed, 1.8 expected (2.7 as ^{the} ~~your~~ ratio of observed to expected.) The 6 employees who were first exposed after 1950 who died of lung cancer were all men and they were all smokers. 5 worked in areas where dust levels were high in 1951 and one of them may have been exposed to asbestos dust from 1925 to 1930 in a previous occupation. He was a welder in a shipyard. No case of mesothelioma has occurred in the population first exposed after 1950 but that may not be long enough for follow up, ^a although in view of the long latent ^{none} period, ~~not~~ would yet be expected. ~~An approximately~~

A multiplicative effect of asbestos exposure and cigarette smoking ^{incidence} on lung cancer has been suggested. As you know, Selikoff has suggested that an asbestos worker who smokes has a 92 times greater chance of dying from lung cancer than a non-smoking non-asbestos worker. ~~or to put it another way, that an asbestos worker who smokes has~~ an 8 times greater chance of dying from lung cancer than ^{a nonexposed person} ~~an asbestos worker who does not smoke~~. But without detailed smoking histories which have been collected for the future, we can't quantify what the effect of smoking were in this particular study. Asbestosis was

A00914

~~I think these are average levels and in those are particles per cc and after 61 you got the membrane filter technique and you are getting down to fiber per cc.~~ ^{The} That operation, I'll show you in a moment, is totally closed.

Of course that is the way to deal with ~~it anything~~ ^{anything dusty} If you ^{ever} close it you ^{will} get no dust. ~~But these gradually went down 6 fiber in 1961 to 3 in 74.~~ ~~xxx~~

This factory population was used and studied by the British Occupational Hygiene & Society in 1966 ~~xxx~~ and on the morbidity study which was done at that time ~~not a xxx mortality but a morbidity study~~ ^{hygiene} the present standard

for asbestos ~~xxxx~~ fiber was developed, and ~~to~~ ^{the dismay} ~~horror~~ of the people who developed it ^{it} became widely accepted throughout the world and ^{is} now the current ^{US} standard ^{for} (or threshold limit values) in asbestos of ~~xx~~ 2 fiber/cc.

Originally it was a cumulative standard of 100 fibers ~~xxx~~ years/cc. ~~so~~ ^{if}

a man worked for 50 year in 2 fiber/cc he stood a 1% risk of ~~x~~ getting asbestosis. The standard was not designed for lung cancer. Although there

^{is} ~~was~~ some indication, ^{as} that I have shown you, ^{that the incidence of} if ~~you reduce~~ asbestosis ^{is reduced} you ~~also reduce~~ the incidence of lung cancer ^{is also reduced} ~~but~~ ^{you} may have to reduce the

exposure levels further still below 2 fiber/cc if we are going to eliminate the lung cancer. However no population in the world has been followed for

long enough which has been purely ~~exposed~~ ^{for longer} exposed to 2 fiber/cc or less.

No population has been followed ^{for longer} to say that 2 fiber/cc is or is not a

no effect level for lung cancer, ~~and as you know~~ There is a lot of

controversy about whether there is or isn't either a safe or no effect

level for any carcinogen. As you can see, in certain operations dust

levels came down dramatically ^{and} by 1974 in the whole weaving operation

there were less than 1. ~~There have been less than 1 for a long time.~~ ^{There}

(In) that weaving ^{shed} there has never been a case of lung cancer associated with exposure that ^I know of and asbestosis doesn't occur in that weaving shed.

~~and that's why~~ The old timers, people who were involved in reporting the

data to the British Occupational Hygiene Society in 1966 (and some of them

had been at the factory for a long time) ^{using} ~~using~~ their "gut feeling" felt

that 2 fibers/cc was a reasonable level because of the health experience

A50916

of that weaving shed. No single population in the world has been followed-up for long enough at a 2 fiber/cc or ~~any~~ less level to ~~say~~ ^{enable us to say what}, based upon human experience ~~whether~~ this is ^{an} adequate level or not. ~~Let's look~~ ^{at Table 11 which shows} ~~which is~~ the mean dust ^{levels} ~~table~~ and the number of men exposed to them ^{over the period of observation}. From 1936 to ~~1967~~ ¹⁹⁶⁷ obviously I told you we ~~didn't~~ ^{did not} have dust counts. ~~In 1936 they didn't start having dust counts until 51. that is~~ ^{was not routine, d.c.s} ~~but it is~~ Based on calculations made by the committee of the British Occupational Hygiene Society ~~(and the~~ ^{statistician} ~~status~~ ^{station} involved was Geoffrey Berry of the Medical Research Council's Pneumonociosis Unit in Penarth) ~~and they arrived at a~~ ^{means} ~~monas of calculating~~ ^{based upon present} ~~levels~~ ^{that} what would be a reasonable estimate of exposure in those years when dust counts were not available. ~~So you can see as the years go by the dust counts come down not much until 1952. Again, 1952 was also~~ ^{period of} ~~the beginning of a modernization of the factory which was~~ ^{and was} completed in about 1954, ~~and a lot of work was done, a lot of jobs were changed, a lot of many processes were~~ ^{altered} ~~latered~~ ^{it all} and ~~that~~ ^{working} resulted in a better environment. ^{In} 1969 new Regulations were made. Those ~~x~~ new regulations were ~~called~~ ^{called} ~~the~~ no longer ^{the} "Asbestos Industry Regulations" but the "Asbestos Regulations" and they applied not only to the asbestos industry, but to anybody using asbestos where ~~xxxx~~ ^{was} asbestos dust was ^{giving} off in ~~excess~~ ^{such} concentrations as ~~is~~ ^{is} liable to be harmful to the health of the exposed person. As opposed to the American method of doing it, the British ~~xxx~~ have not put a figure in the asbestos ~~standard in the regulations~~ ^{to} there is no legally enforceable figure. The way it has been done is ~~by publishing~~ ^{to} as an addendum to the standard ~~if you like~~ guidelines for the benefit of those people ~~xxx~~ ^{who} ~~to whom~~ ^{have to apply the standard}. The guidelines ~~the standard applies which~~ indicate what the current thinking of the factory inspectorate is ~~at the present time~~ ^{dust} with regard to the levels ~~to be achieved~~ ^{to be achieved}. ~~they are going to enforce. That means that~~ ^{vary} ~~If they want to change those~~ ^{this} levels ~~to modify tomorrow~~ (and they have already changed them once since 1969), all they have to do is ~~pull that piece of paper out of circulation~~ ^{amend the published guidelines} and publish another. It ~~xxx~~ doesn't require an act of Parliament or any

A00917

formal consultative
~~sort of consultative~~ mechanisms to do this, although ~~ex~~ obviously they would
consult before^{with all agreed}. It really makes it very much simpler to operate the
regulations when you haven't got a number which you could be punished for
if you go .1 below or .1 above ^{this} which is the difference ~~the~~ between the
OSHA standard ~~the~~ and the British standard. However, that ~~ex~~ just shows
you the changes that took place. ^{In Table VI} You will see that the number of men
goes on increasing and then it starts declining and so this is obviously
because ~~the cohort~~ we are going to begin to ~~lose~~ people out of the cohort
now and there are obviously fewer ^{people} in 1972 who have been exposed for ^a long
period of time than there were in 1960 because we are losing them. As you
can see that ^{we} In 1972, 32% are exposed at less than 2 fiber/cc. In ~~1972~~ 1936
100% were exposed to ~~greater~~ greater than 5 fiber/cc and only 3% now remain
in it ~~1972~~ in 1972 who are exposed ~~the~~ ~~the~~ ~~exposed~~ to greater than 5
fiber/cc. What this is ^{demonstrates} really showing you is that with time the number
of people ~~being~~ exposed to high concentrations is declining. It is just
interesting to present it that way. There are a number of ~~ways~~
always in this type of thing. World War took place and ^{Second World War} During the ~~war~~
the regulations were relaxed. Factory inspector's didn't care too much
about what the levels were. The government wanted production, asbestos
was essential ^{and} it had to be ^{produced} made. Overtime ^{was} worked, ~~the~~ women were brought
in to work instead of men and long hours ^{of} blackout restrictions made
it impossible to ^{systematic anticipation} operate ventilations and all sorts of things. You have
this period in World War which I don't know what effect ^{this} that is going
to ^{have} on the follow up ^{in years to come}. // It is difficult to interpret the relevance of
the results which I have reported to you to ^{present day} modern conditions. What
we are looking at ^{the result} is a ~~hypothesis~~ of bad conditions in the past and
a continued exposure of the same population to changing conditions. What
we need is a long term follow up of people exposed ~~eventually at this~~
^{to} level ~~here~~ less than 2 fiber/cc for 20 or 30 years. // Dust levels don't come
down in a day. It takes a long time to get down to less than 2 fibers/cc
^{The next slide} and that is just a plot ^{graph showing} of in the way in which the levels in the factory

have been coming down. Even people exposed after 1950 ^{were} ~~are~~ having substantially higher levels of exposure than are at the present time permitted by law.

The thing to remember is that what we are interested in is diseases with an ^{incidence and} excess mortality. ~~That your factory may be build here and start producing~~

~~here and that is when you start fire the shot.~~ You ~~didn't~~ ^{usually} begin to

see any difference in mortality experience, ~~you may see a slight~~ ^{until a latent period of} difference after 20 years but you may have to ~~go~~ ^{follow up people for} 30, 40 or 50 years ^{from occupational cancer} with occupational cancers before ~~that~~ ^{an} excess mortality becomes apparent.

This is why it is important ~~that you~~ ^{to} keep records of medical findings,

~~you~~ ^{to} keep personnel records which are accurate with regard to ~~date~~

of employment and types of employment and if possible the type of

materials ~~to~~ ^{used} to which people ~~are~~ exposed, ~~which are hazardous or which~~

~~may be considered hazardous in the future and that you~~ Maintain a strict

control of your environmental monitoring and dust sampling and ~~that you~~

record these meticulously ^{bearing} ~~varying~~ in mind that some time they will have

to be related to the health experience of a group of people. It is only

if you are meticulous about all that, that in the future we will clear up

a lot of the arguments and lot of the mess which we are in at the present

time, simply because our ~~predecessors~~ predecessors had no concept of this type

of approach ~~to~~ occupational medicine. Occupational medicine ~~in the past~~

for many years was the transfer of general practice into the factory ~~at~~ with

a captive population ~~and you could treat them.~~ What it is ^{In} my opinion

~~is~~ that ~~part of it~~ ^{is} ~~that's~~ a fringe benefit, ~~what is~~ ^{more} important to me

is to establish a system of keeping records, ^{to enable me to} abstract from these records

~~contain~~ ^{and} information ^{to} analyze it statistically ~~and~~ obtain an idea as to how

~~this~~ ^{this} population compares with another population or ^{with} the general population.

^{can do all this} ^{will find out} If you ~~so that~~ you ~~have an idea~~ whether you are ^{your industry is} ~~in~~ in any way ~~in~~

~~impeding~~ ^{impairing} or ~~impairing~~ the health of ^{persons} the employed ^{by it.} person ~~and~~ I promised

that I ^{would} show you that improvement had taken place ^{at Rockdale} ~~and~~ ^{but} that doesn't show up

very well, ^{holding is} that's a man and those are his legs and what he ~~has~~ ^{is} is a pitchfork.

There is a hole in the ^{floor}~~ground~~ and he is standing on a big wooden drum.

This is asbestos and he is ~~xxx~~ using his pitchfork to blend it on a open floor throwing it up in the air and letting it settle. ^{It's blowing} ~~and xxxxxx~~ ^{about} all over the place. That was ^{taking} ~~taken~~ place in ^{the} factory that I ~~xxx~~ just ~~showxxx~~ talked about until 1954 and in some American factories that I visited in 1970 I saw that ~~still~~ ^{then} taking place and in some American factories that I visited in 1976 something very similar ~~xx~~ was still taking place. And therefore that is another caveat. Youx have got to be very careful when you read the world literature because working conditions in different countries vary and ~~xxxx~~ ^{when} some ~~xx~~ people ~~xxx~~ ~~describing~~ ~~xx~~ describe the horror and the disease associated with asbestos, ~~and their findings~~ ~~theyx~~ conditions under which those people worked have to be taken into account. I could show you lots of horror slides. I have been around the world and ~~xx~~ seen conditions and I ^{have} got slides to demonstrate the differences between the U.S., somewhere like South Africa, ^{Ham} ~~Monbasa~~, India, Britain, ~~and it~~ depends upon the degree of sophistication of ^{Government} Regulation and of dust control as to what is going to happen to those people but authors of papers describing the effects seldom pay attention to that, and they ~~xxx~~ will talk about asbestos or asbestos textiles or asbestos cement and never show the pictures of the factory or tell you what the conditions ~~xx~~ were like. ~~and that was 1954~~ and ^{for} So, ^{for} OSHA or NIOSH to say that the Rochdale population was always exposed to 2 fiber/cc and hence the 2 fiber/cc standard is no good because they are still getting lung cancer is a lot of ^{well} there are ladies present. ^{That's} That's what happened to ^{this} ~~the~~ job-it was totally enclosed. The drum is now ^{enclosed} ~~in there~~ and ^{and mixes the fibre} It revolves and ^{There is a} bag opening procedure ^{whereby} the bags are fed on ^{to} a conveyor belt and ~~go~~ ^{fiber go} into the drum, ^{After mixing it} and tips it into another bin down on the floor and ^{which} ~~that~~ is also all enclosed and there ~~is~~ no dust. ~~That's the way it was in 1954~~. When I walked into that factory in 1966 I was taken on a tour and ~~they~~ A00920

ME and asked I wanted
looked at ~~the~~ and ~~I~~ said where do you want to start. ¹⁹ and I said ~~I'll~~ start
at the beginning where the fiber comes in. ~~and I found can I~~
~~take my camera~~ and I took my camera and that's what I found. This of
course is very good fiber. ^{It} ~~that~~ is the best fiber in the world. ⁺ it comes
from Rhodesia. Turner & Newall owned the mines in ~~k~~Rhodesia and since
UDI they have not had any of that fiber. They have ^{not} had any of the profits
and they have been cut off from their mines because of ~~the British~~ sanctions.
~~I~~ ~~fact~~ I ~~wasn't~~ wasn't allowed to visit Rhodesia while I worked for Turner
& Newall. However in ^{American} ~~in Raybestos~~' factories there is plenty of this stuff.
The United States hasn't bothered about sanctions. Anyway this was 1966
these were ^{burlap} ~~rolled up~~ bags. Every now and then you could see holes
in them. Shippers used to love this stuff because it ^{made} ~~was~~ ~~very~~ beautiful
^{ballast.} ~~balanced.~~ They could put a few bags in a corner here and a few bags ~~and~~
~~a corner~~ in a hole there and they could trim their ships ^{with it} ~~and~~ That's the
way it ~~just~~ used to arrive in loose bags. The dockers had no respect
for these bags. ^{They} had big hooks and the way they lifted ~~that it~~ ^{it was} is to
plunge a hook into the bags swinging over their shoulders ~~the~~ ^{them} ~~chuck~~ ^{it} over
the side to someone else. ~~and have~~ ^{used to result} a horrible mess and these ^{bags} things used
to arrive at the factory ^{where} ~~and~~ the chaps in the warehouse ~~they~~ did not have
quite as big hooks ^{theirs} so the little holes are there ~~and they used to pull~~
~~these things off and what you found was a stack like that and that~~
~~represented about~~ You can't imagine the size of this warehouse. ^{It was a} huge warehouse
full of ~~of~~ fiber stacked to the ceiling. It ^{held} ~~was~~ 18 months supply because
they knew ^{UDI} ~~it~~ was coming and so they brought ~~as~~ as much as they could
and as much as they could stuff into the warehouse. There were bags
bursting, there was fiber all over the place, ~~that's~~ that's what you
found. ^{It} was an impossible situation and it was very very bad. That's the
^{way it is} ~~what you find today.~~ The bags are now ^{made of} polypropylene or polyethylene
they are pressure-packed at the mines. ^{They} ~~These~~ are all ^{solid} ~~hard~~ they are like
bricks, they are palletized and very often they are covered with an
^{is an example of fiber}

A00921

There are

~~in the~~ 2 mines; there is one in North British Columbia and one in ~~the Yukon~~
Territory ^{at} ~~Clinton Creek~~ ^{Creek.} and It's a nice part of the world to go to
in January. // What we have ^{here} is a story that is unfolding, and This is ^a rather
~~an~~ old slide ~~xx~~ it tells you about asbestosis beginning at the beginning
of the century. The incidence declining ^{is} in textile workers from 1930
onwards. I haven't mentioned insulation workers at all but the lung
cancer incidence noted to be increasing in the late 50's early 60's ~~affected~~
~~insulation workers to a large extent~~ Asbestosis and lung cancer ~~overall~~ increasing ^{as in occupation} this ~~is~~ in the U.K. while it was
~~declining among textile workers.~~ Mesothelial tumors ~~being~~ ^{were} recognized in association with asbestos in the
late 1950's-early 1960's, ~~and work production taken off like that~~ ^{Asbestos use increased markedly}
the War and ~~accelerating~~ ^{accelerated} afterwards so that asbestos became a ~~universally~~
~~widely used~~ ^{utilised} material. It was cheap, ~~xx~~ easy to find and not expensive
to mine and it was used in just about everything you could think of.
With regard to mesothelioma in case you think we haven't had any in that
factory, we have, and I don't want to get into a long argument about it
but that factory did also process crocidolite fiber and in my opinion
crocidolite fiber is the most hazardous type of fiber and the one mostly
associated with mesothelioma, and while I was there I collected ~~30~~ 27
cases of mesothelioma, and I hadn't seen any in ~~anybody~~ ^{people} exposed after 1950.
The average lapsed interval was long. At the present time Prof. Doll is
~~initiating a study of mesothelioma incidence at TBN.~~
Just before I left we completed going through our personnel record cards
back to ~~19~~ 18 and collected something like ~~nearly~~ ^{records of} 30,000 people who had
ever been employed. The group in Oxford are now going to check through
those. They will probably take a random sample to start with and ~~face~~ trace
them to see what they can find with regard to mesothelioma. ~~whether we~~ Have we
underestimated our experience? ~~or whether just to try and see what they~~
~~can find, so~~ That is the next study which is going to emerge from this
particular ~~group in Oxford.~~ ^{Factory.} I have taken up a lot of your time. I think
it's over the hour and I must apologize. That is all I have to say.

A00922

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

(ANATOMIC PATHOLOGY SECTION)

INTRODUCTION

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 with special expertise in the surgical pathology of tumors.

thoroughly familiar with the gross and microscopic characteristics of mesothelioma and

The object of this review should be to classify the cases relative to the certainty of diagnosis using well defined criteria for the diagnosis of mesothelioma. In the present study this ^{morphologic} review is first being conducted with 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.

(Slide 1 Classification)

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. 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

A00545

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.

(Slide 2 Preliminary Results)

The preliminary results of the primary review of the first 106 cases are shown 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, there were 56.6% thought to be mesothelioma, 26.4% possibles and 10.3% not mesothelioma or excluded from the study. There were 6.6% that are still considered unknown.

A00546

It should be pointed out that as further studies of this material are carried out, cases may be moving from one to another classification and this report should be considered only a preliminary report at this time. It also should be mentioned that less than half of the total number of cases in this study have been subjected to anatomic pathology review as of this time.

Discussion: " 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 this portion of the study progresses, the ~~mesotheliomas~~ mesotheliomas will be categorized as to pleural, peritoneal or other, and an attempt will be made to categorize the histologic structure based on its predominant pattern, into (1) epithelial (tubulo-papillary and undifferentiated polygonal), (2) sarcomatous or mesenchymal and (3) mixed.

As has been emphasized by others two problems become apparent on review of this material. The first is the separation of localized or nodular (and sometimes benign mesothelial reactions) from diffuse or malignant mesothelioma. In the present study this is a minor problem because of the selection of the material being reviewed, having been obtained from the Tumor Registry where the vast majority of these cases would have been reasonably carefully reviewed in their own institution and they would have had benefit of the ~~course or~~ ^{of the disease} progression of the disease. As is the practice in Connecticut, cases are occasionally reclassified or removed from the Tumor Registry by the local hospital when it is determined that they do not represent the malignancy originally reported.

A00547

The second and more important problem in the present study is the separation of mesothelioma from metastatic carcinoma. The findings at autopsy in the cases so evaluated are extremely ^{in valuable}valuable in this regard and 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 in this regard. It can be pointed out that as one gains ^{also}experience in looking at large numbers of mesotheliomas, one begins to recognize a characteristic pattern which has been well described by many workers in this field. This coupled with experience in surgical pathology of tumors enables one to categorize ^{most}many of these cases in the proper class. ~~As pointed out earlier, however, on further review, this was not possible in some of the cases, however,~~ ^{probable}It is ^{probable}possible that with additional studies and special stains this classification should become more accurate.

AU0548

There is 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 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.

RAV 10/28/80

A00549

10/24/80
DRAFT 10/17/80

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935-1977

by

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Presentation to the Connecticut Thoracic Society, November 4, 1980

A00050

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.

A00551