PLAINTIFF'S
EXHIBIT
UC-1271

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

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

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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.

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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, these 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.

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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 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 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,~~ It is 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 ~~unfirom~~ 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

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II. Methodology

The CTR has identified 229 cases of malignant mesothelioma as well as 38 other pleural tumors, not mesothelioma, which were diagnosed in the state between 1935 and 1977 (Table 1).

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

Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. ~~Future~~ The case-control comparisions will ~~include~~ comprise cases (215) diagnosed after 1954 (Table 1), and controls (604) whose deaths occurred during this same time period. This procedure yields a case-control ratio of approximately 1:3, while reducing sources of error resulting from the limited occupational and medical data prior to 1955 and the lack of awareness of mesothelioma associated with this earlier time period (1935-1954). ~~The Price and Lee~~ City Directories 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

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list of job and industry titles has been developed for all cases, spouses, and controls (1955-1977). This will form the basis for classification of study subjects into asbestos exposure categories for future case-control comparisons ~~(sample from listing~~ (Fig. 1).

ADDED

III. Results

Descriptive Epidemiology

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

New London Labour Market Area (LMA)

~~Ten~~ 10 cases were reported in ~~an 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 ~~also~~ all centers ~~for Labor Market Areas (LMA)~~ for LMA's. All 6 areas exhibit a similarly increasing age-adjusted incidence rate for males. The Stamford LMA's mesothelioma rate shows an unexplained sharp increase since 1965 (Fig. 4).

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SLIDE REVIEW

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

Positive diagnosis of mesothelioma is often complicated by its confusion with other forms of cancer. (Vidone discussion of simulators). ← insert (1)
The controversy over criteria for positive diagnosis is well documented in the literature (Kannerstein, 1977). Most experts agree, however, that a full autopsy is required to positively distinguish diffuse mesothelioma of the 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). insert (2) For 12% (32) of the cases, no tissue was examined at time of diagnosis, while the origin of available material varied. Overall (1935-77) only 44% (105) of the 238 deceased cases are known by the CTR to have been autopsied, but only 83% 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 ~~slide~~ case review. Dr. Romeo Vidone, chief pathologist of St. Raphael's Hospital, is presently studying the ~~medical~~ 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.

~~(Summary of Dr. Vidone's Findings)~~ ←

insert (3), (4) (5)

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Insert ① It is important to differentiate between mesothelioma and metastatic carcinoma. Autopsy findings in such cases are extremely helpful in this regard. The use of special stains such as Alcian Blue with and without hyaluronidase, PAS with and without Diastase and to a lesser extent Mucicarmine and connective tissue stains on surgical materials are valuable as well in this regard.

Insert ② Whitwell has pointed out that the most striking histologic character of diffuse mesotheliomas 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.

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Insert (5) The preliminary results of the primary review of the first 106 cases are shown in Table ~~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,~~ Thus ~~there were~~ 56.6% thought to be mesothelioma, 26.4% ~~were~~ are mesothelioma possible, and 10.3% not mesothelioma or excluded from the study. ~~There were~~ 6.6% ~~that~~ are still ~~considered~~ classified as " " 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 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.

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IV. Discussion

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

Felton has pointed out several ~~needs~~ reasons for post-mortem review. A problem may arise in workers' compensation adjudication where a decision has to be made, years to decades after initial work exposure, in those instances where death has resulted from pulmonary cancer or a thoracic or peritoneal mesothelioma. It is therefore important, in such cases, to be able to confirm by the presence of asbestos related effects that there has been exposure to respirable asbestos fibers (Felton, 1978).

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. ~~In our search through records stored at the CTR (i.e. hospital records), we found job titles for only 17% of the mesothelioma cases.~~ Although job information was obtained for 99% of the cases from all three sources (Coroner's, Dr. reports, CTR), our search through records stored at the CTR (i.e. hospital records) produced job titles for only 17% of the mesothelioma cases. If we exclude from this group those designated as "retired", "housewife", or "student", the figure is reduced to 12%. We were only able to ascertain type of industry in 7% of these cases. The sample size for these statistics was 220 cases, ~~whose~~ diagnosed ~~were~~ between 1955 and 1977. A recently passed Connecticut statute (retroactive), whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

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ACL Doc 16428 · Page 12 of 111 asbestosclaims.law/library/16428/12

Insert (+)

~~There is~~ Another problem ~~that~~ has been recognized which should be ~~arisen and hopefully~~ will ~~be~~ addressed ~~in the later anatomic pathology studies~~. There is variation in the literature on the classification of these tumors. The lines between localized and diffuse ~~mesothelioma~~ mesothelioma are not always clear cut and the separation of benign from malignant is not always as readily apparent as one would be lead to believe by review of the literature. In fact, there are discrepancies between some of the classic papers in this field regarding characteristics of these neoplasms, both gross and microscopic. This is not limited to growth patterns such as that in the pleura or peritoneum, but includes such important characteristics such as metastatic patterns and certainly applies to histologic descriptions which are not ~~unfirom~~ 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

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

paragraph Insert (6)

(Comment ~~on~~ the significance of the Slide Review)

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, detailed job histories) , ~~any~~ attempts to apportion blame to any particular factor for disease causation or promotion will be severely hampered. It is particularly essential in the case of a rare tumor, which may present diagnostic difficulties, to obtain sufficient tissue for study before a diagnosis is made. Whenever a tumor is found and an association is suspected with a particular occupational or environmental factor, every attempt should be made to document all relevant facts and to subsequently verify the diagnosis by means of a full autopsy.

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

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

[a] WHO (1976)

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

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

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

[a] WHO (1976)

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

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ACL Doc 16428 · Page 17 of 111

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

Diagnosis[a]	(1) Autopsy, Microscopic Evidence of Cancer	(2) Autopsy, Gross Evidence of Cancer	(3) Autopsy Gross Evidence, Unknown Whether Cancer	(4) Autopsy, but only Indirect Evidence of Cancer	(5) Autopsy, no Report	(6) No Autopsy	(7) Unknown	(8) Number Dead	Autopsy[b] %
Pleural Mesothelioma	43	3		1	7	62	18	134	40
Pleural Tumor (other than mesothelioma)	8	1	1		3	13	11	37	35
Peritoneal Mesothelioma	21	4				2	1	28	89
Mesothelioma at other sites and unknown sites	11				2	21	5	39	33
Total	83	8	1	1	12	98	35	238	44%

[a] WHO (1976)

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

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ACL Doc 16428 · Page 18 of 111

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION OF CASES

(Based on Review of Anatomic Pathology Material)

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

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ACL Doc 16428 · Page 19 of 111

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION BASED ON ANATOMIC PATHOLOGY REVIEW

PRELIMINARY RESULTS (106 Cases)

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

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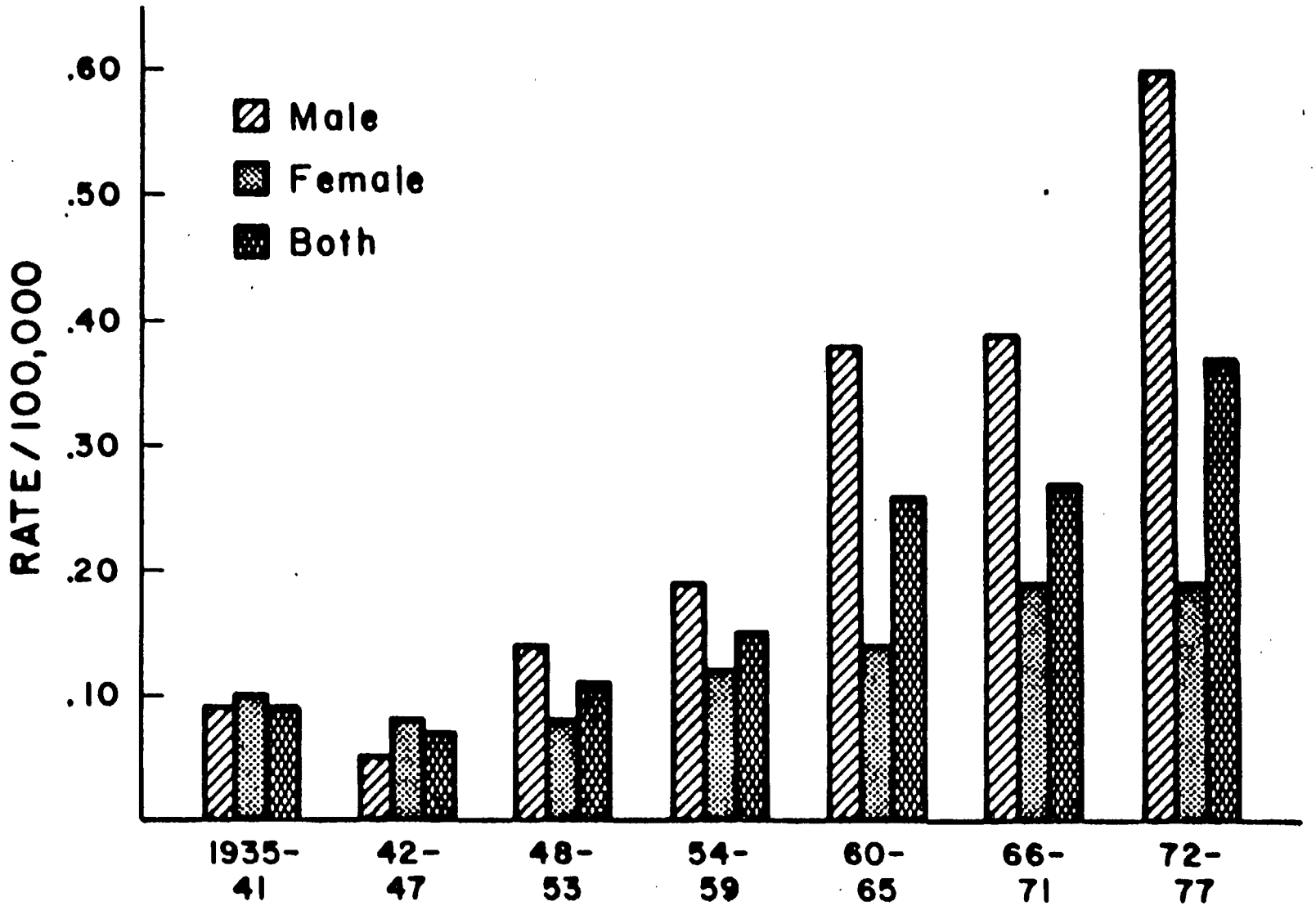
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12261741  255MLDLRS HELPER                                  503359012105 8DRDNANCE
12261751  256LMPLLYLD                                       999304012106 8DRDNANCE
12261760  255GLN ASSLMBLER                                  602304012107 8DRDNANCE
14795  62 398LXECUTIVE RETIRED                             245999996580 1NOT SPECIFIED M
15995  61 017CHICKEN FARMER                                801999995510 1AGRICULTURAL PR
16337  61 999MACHINIST                                     461993994130 1
16337  31 13E                                              999345014103 1MISC. NONMETALL
16337  41 147MACHINIST                                     461187014105 1OTHER PRIMARY I
16337  51 147MACHINIST                                     461187014106 1OTHER PRIMARY I
16337  60 147MACHINIST                                     461187014107 1OTHER PRIMARY I
16535  60 777CHEF                                          912645014100 1HOTELS AND MOTE
16535  59 999CHEF                                          512999994107 1
00061  62 999APPLIANCE SERVICE MECHANIC                    482999992110 1
00061  32 999SALESMAN                                      280999992113 1
00061  37 779ROUTE SALESMAN                                266097012114 1LAUNDERING, CLE
01161     569FOOTWEAR DEALER RETIRED                       280999992100 8DRY GOODS & APP
01161 12  658SHOE DEALER                                   280999992101 8SHOE STORES
01161 22  655SHOE DEALER                                   280999992102 8SHOE STORES
01156  62 367SECRETARY                                     372425014100 1MISC. PLASTIC PI
01156  37 165STENOGRAPHER                                  376288014104 1OFFICE & ACCOUN
01156  42 168STENOGRAPHER                                  376288014105 1OFFICE & ACCOUN
01156  52 166STENOGRAPHER                                  376288014106 1OFFICE & ACCOUN
01156  61 168STENOGRAPHER                                  376288014107 1OFFICE & ACCOUN
03109     31ELACE WORKER                                   673012012220 8MISC. TEXTILE M
05146     008HIGHWAY WORKER                                715999997200 8GENERAL CONTRACT
05146 12  317EMPLOYED                                      999335017201 8YARN, THREAD, &
05146 22  999FARMER                                        801599997202 8
05146 32  937EMPLOYED                                      999999997203 8LOCAL PUBLIC ADM
05146 37  937EMPLOYED                                      999999997204 8LOCAL PUBLIC ADM
07653     026WATCHMAN                                      562341014120 8FISHERIES
07653 42  025                                              999999994125 8FISHERIES
07653 52  025EMPLOYED                                      999583014126 8FISHERIES
07653 61  028NIGHT WATCHMAN                                962583014127 8FISHERIES
07711     527PIPE FITTER                                   522999993220 8STATE PUBLIC ADM
07716 37  317EMPLOYED                                      999251013224 8YARN, THREAD, &
07716 42  469                                              999999993225 8ELECTRIC-GAS UTI
07716 52  469FOREMAN                                       441560013226 8ELECTRIC-GAS UTI
07716 61  999PIPEFITTER                                    522372013227 8
06977     207BAKERY MANAGER                                402999991350 8BAKERY PRODUCTS
06977 42  267MANAGER                                       245725011355 8BAKERY PRODUCTS
06977 52  267CHAUFFEUR                                     714725011356 8BAKERY PRODUCTS
05519     917WARRANT OFFICER                               394999992310 8FEDERAL PUBLIC AI
05519 52  147WIRE TESTER                                   610040012316 8OTHER PRIMARY IRI
05519 62  927WARRENT OFFICER                               394999992317 8STATE PUBLIC ADM
09994     769                                              999754014110 8PRIVATE HOUSEHOLI
03337     017LABORER                                       822999995300 8AGRICULTURAL PRO
03093     937LABORER                                       765999991110 8LOCAL PUBLIC ADM
05934 42  157E                                             599999991115 6CUTLERY, HAND TOO
05934 52  157EMPLOYED                                      999014011116 8CUTLERY, HAND TOO
03944 61  857HIGH SCHOOL CAFETERIA COOK                    912999934120 1ELEMENTARY & SECO
03944 63  999TOOL & DIE MAKER                             561516314120 2
03944 41  999CHAUFFEUR                                    714999994125 2
03944 51  999MACHINIST                                    461999994126 2
03944 60  999MACHINIST                                    461999994127 2
03967     999ELECTRICAL ENGINEER                           012999993220 8SELF EMPLOYED
03237     645PRACTICAL NURSE RETIRED                       075999994100 6HEALTH SERVICES,
03776 61  953PRESS HELPER                                  690999994110 1PRINTING FACTORY
03776 36  359                                              999108014114 1PRINTING, PUBLISH
03776 41  359                                              999108014115 1PRINTING, PUBLISH
03776 51  359                                              999108014116 1PRINTING, PUBLISH
03812     407EMPLOYED                                      999999992101 8RAILROAD & RAILWA
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ACL Doc 16428 · Page 20 of 111
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ACL Doc 16428 · Page 21 of 111

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



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Figure 2

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

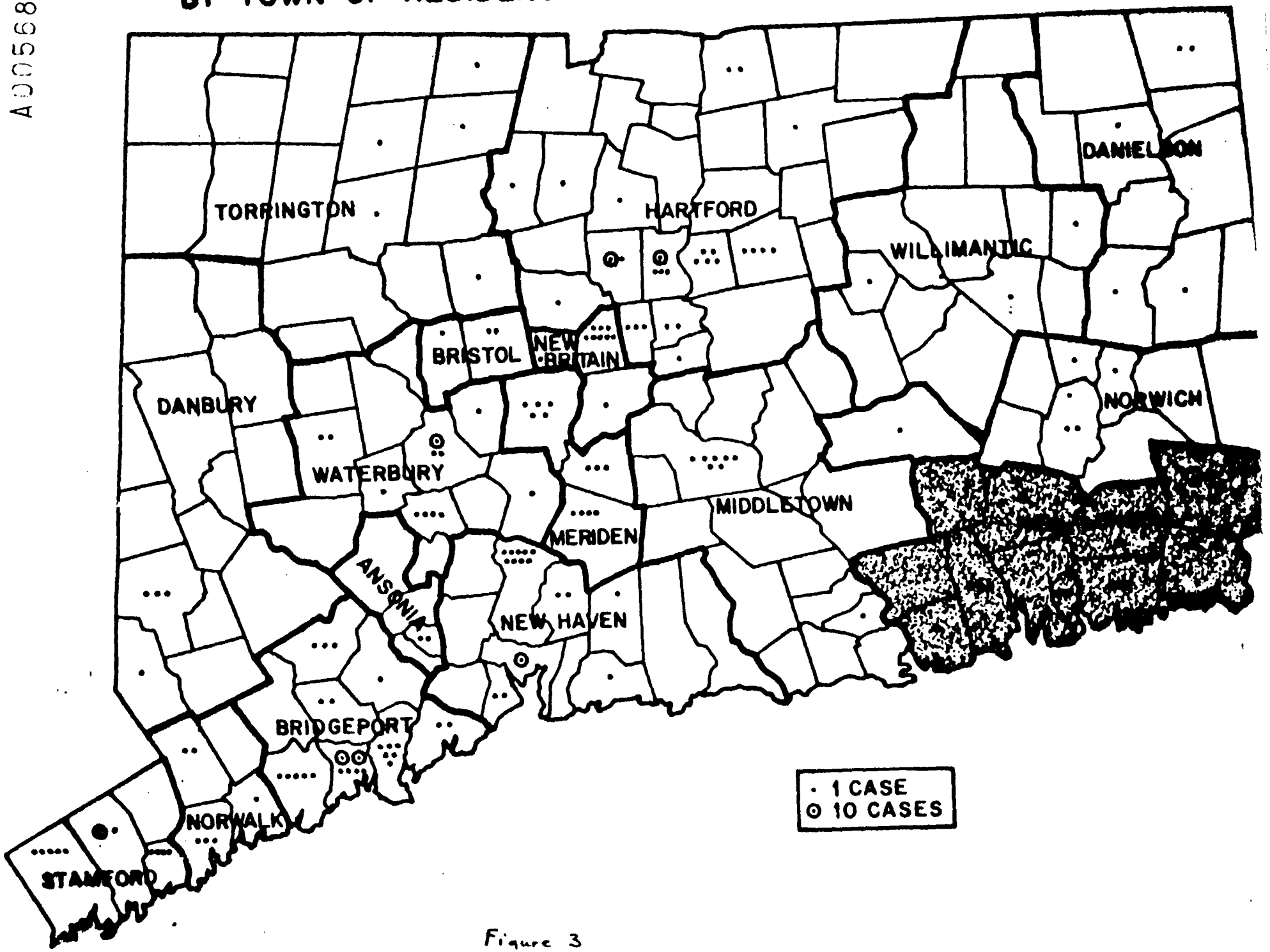


Figure 3

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ACL Doc 16428 · Page 22 of 111
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ACL Doc 16428 · Page 23 of 111

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

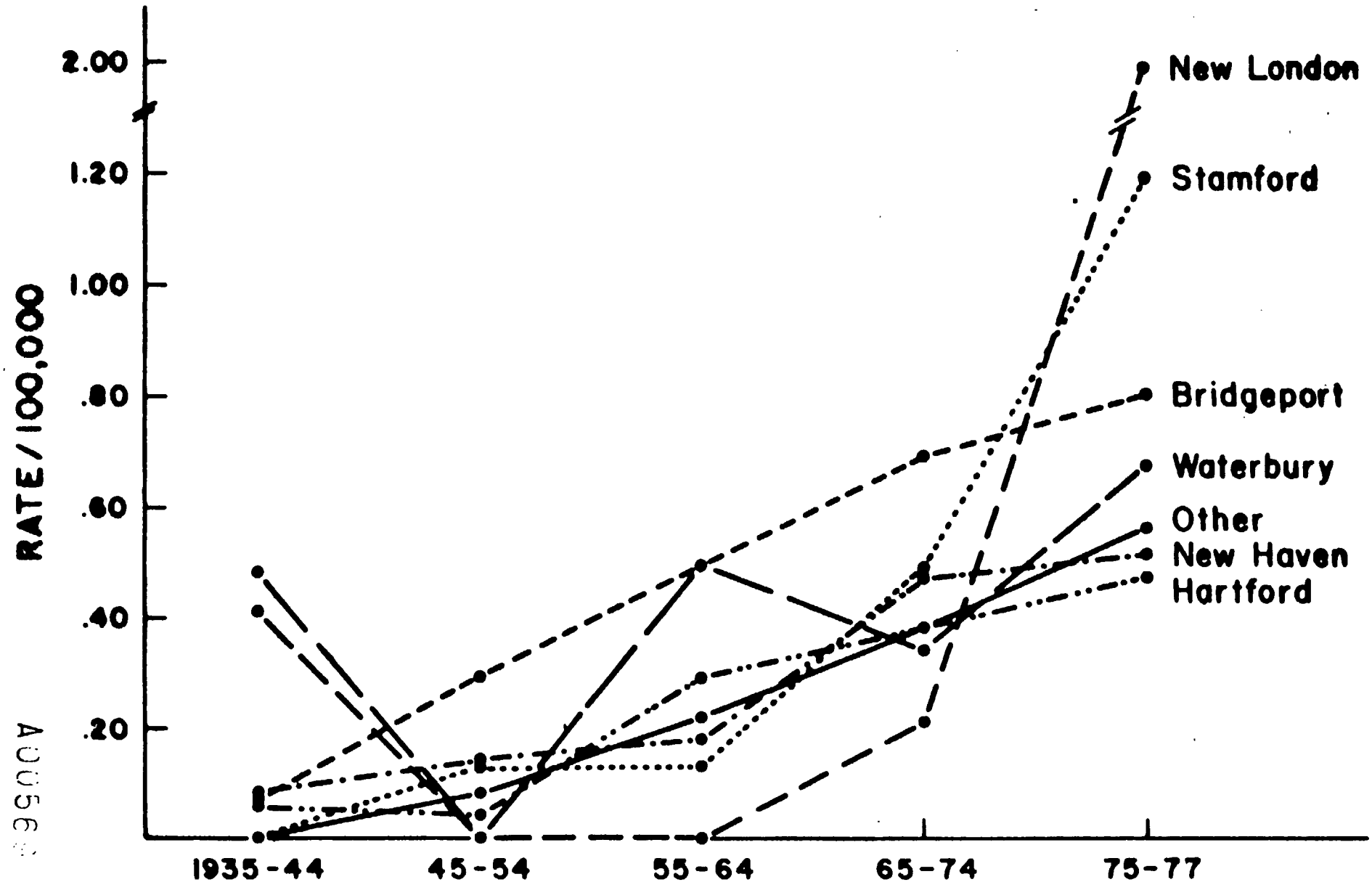


Figure 4

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A00570

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ACL Doc 16428 · Page 24 of 111 asbestosclaims.law/library/16428/24

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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~~ major deficiencies in the data available for study, ~~mainly~~ the low autopsy rate ~~of~~ for the pleural mesotheliomata and the inadequacy of the ~~types of tissue~~ pathological material 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 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 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.

A00607

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[illegible] A [illegible] 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.

[illegible] 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" (243:2396, 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. Gross, 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 (242:1056, 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.

[illegible] MD
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Los Angeles

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" (242:1927, 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.

William O. Robertson, MD
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and Medical Center
American Association
of Poison Control Centers
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A000608

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ACL Doc 16428 · Page 28 of 111 asbestosclaims.law/library/16428/28

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

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

I. Introduction and Aims

The combined sex age-adjusted mesothelioma incidence rate for Connecticut was reported in 1977 to have increased ten-fold since 1935.(1) Although available statistics might be subject to diagnostic error, the apparent rise was attributed to the increase in the State's 'cumulative asbestos consumption'.(1,3) Complete occupational histories for the cases of mesothelioma were not presented. A detailed review of the available pathological material by an independent pathologist to investigate the degree of diagnostic certainty was not undertaken. The present study attempts to determine the role of various etiological factors, such as occupational and environmental asbestos exposures, and includes a review of available pathological material.

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II. Methodology

The CTR has identified 229 cases of malignant mesothelioma as well as 38 other pleural tumors, not mesothelioma, which were diagnosed in the state between 1935 and 1977 (Table 1).

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

Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. ~~Future~~ The case-control comparisions will ~~include~~ comprise cases (215) diagnosed after 1954 (Table 1), and controls (604) whose deaths occurred during this same time period. This procedure yields a case-control ratio of approximately 1:3, while reducing sources of error resulting from the limited occupational and medical data prior to 1955 and the lack of awareness of mesothelioma associated with this earlier time period (1935-1954). The Price and Lee City Directories (4) were searched for job title and name of specific employer or industry for cases, controls and spouses at 1, 10, 20,25, 30, 40 and 50 years prior to date of diagnosis, death or until the subject was less than twenty years old. An occupational history search was attempted for spouses to coincide with these intervals for their corresponding cases.

1970 U.S. Census industrial and occupational codes (U.S. Dept. of Commerce, 1971) (5) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. A computerized

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ACL Doc 16428 · Page 31 of 111 asbestosclaims.law/library/16428/31

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

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

[a] WHO (1976) (c)

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

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

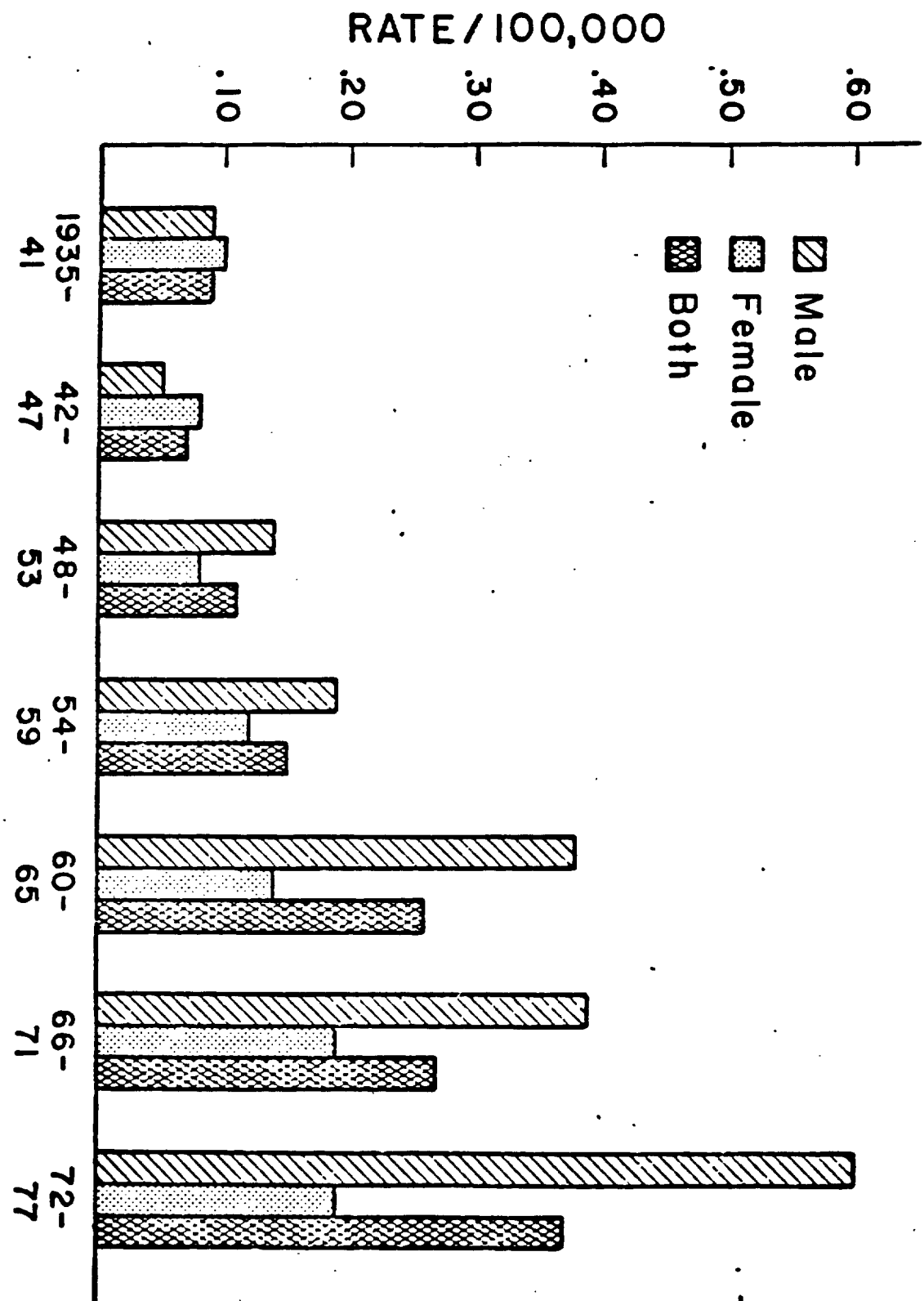
~~Ten~~ Ten (10) cases were reported in ~~a LMA (New London)~~ New London Labor Market Area (LMA) where shipyards are located, and ~~five~~ 5 (50%) of these were identified between 1975 and 1977 (Fig. 3). The geographical distribution of mesothelioma shows evidence of urban clusters in the 5 largest cities (Bridgeport, Hartford, Waterbury, Stamford , New Haven) where 30 % of the cases resided at time of diagnosis (Fig. 3). Since these locations have comprised 20-30% of Connecticut's population (1940-1977), the suggested urban effect may reduce to a factor of population density. These 5 large cities and New London are ~~also~~ all centers for ~~Labor Market Areas (LMA)~~ LMA's. All 6 areas exhibit a similarly increasing age-adjusted incidence rate for males. The Stamford LMA's mesothelioma rate shows an unexplained sharp increase since 1965 (Fig. 4).

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ACL Doc 16428 · Page 34 of 111 asbestosclaims.law/library/16428/34

Fig 2

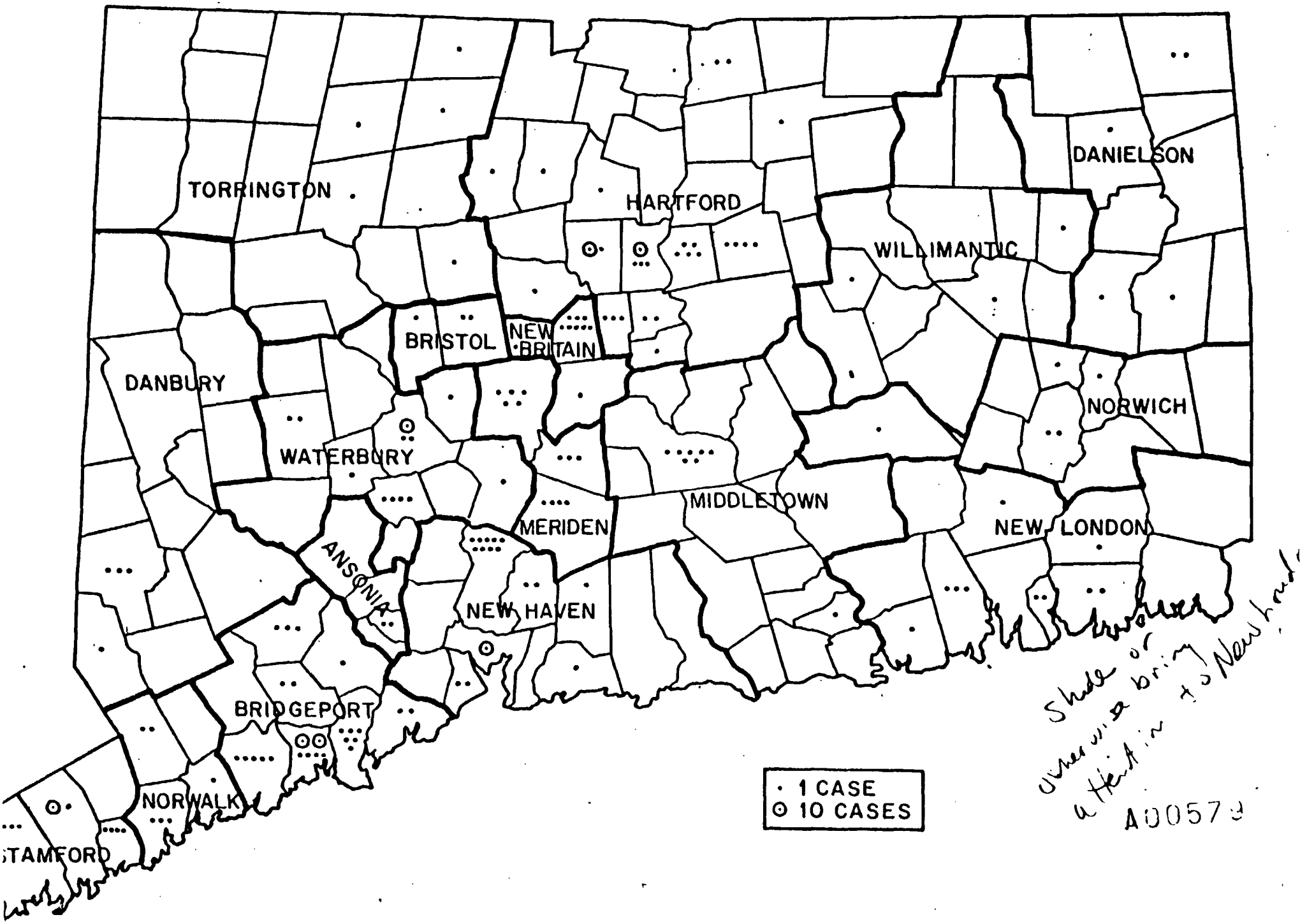
AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA
IN CONNECTICUT BY YEAR OF DIAGNOSIS AND SEX



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



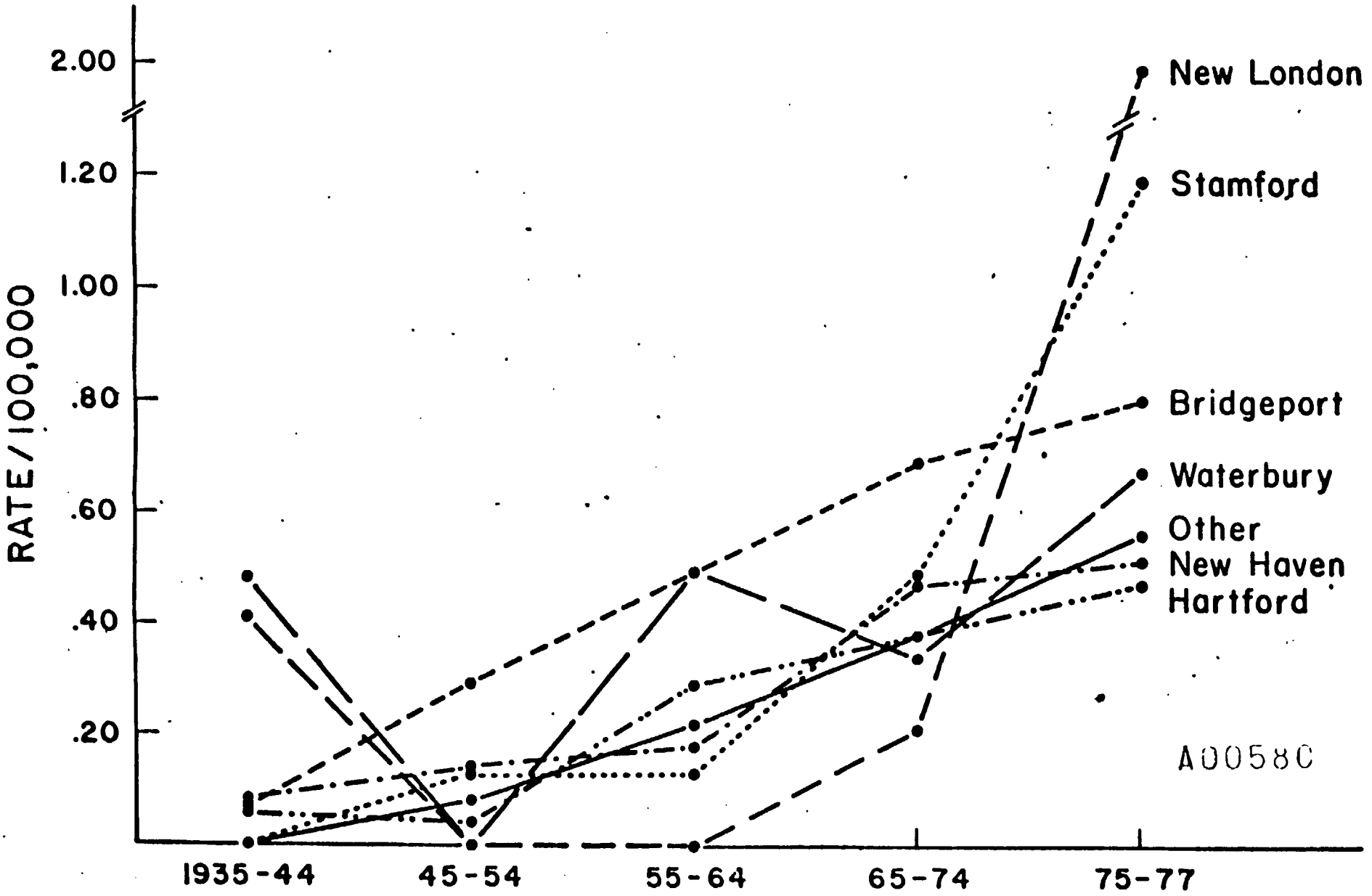
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ACL Doc 16428 · Page 36 of 111

Fig 1

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



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ACL Doc 16428 : Page 37 of 111

SLIDE REVIEW

Malignant mesothelioma is a very rare disease with only 2 cases per million population expected annually.[6] Resistance to the acceptance of mesothelioma as a disease entity persisted until the late 1960's.[8] Wagner's widely publicized association of mesothelioma with Cape Crocidolite asbestos exposure created the potential for the introduction of diagnostic bias.[9]

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

We examined, for all CTR reported cases of mesothelioma and for all pleural tumors other than mesothelioma (1935-77), the histological basis for diagnosis (Tables 2,3). For 12% (32) of the cases, no tissue was examined at time of diagnosis, while the origin of available material varied. Overall (1935-77) only ~~44%~~ 105 (44%) (~~105~~) of the 238 deceased cases are known by the CTR to have been autopsied, two-thirds 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 ~~office~~ case review. Dr. Romeo Vidone, chief pathologist of St. Raphael's Hospital, is presently studying the medical records (except occupational data) and slides we have obtained for cases diagnosed after 1954. Cooperation was sought from 37 hospitals, of which 30 have thus far provided us with the materials requested.

(Summary of Dr. Vidone's preliminary Findings)

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ACL Doc 16428 · Page 38 of 111 asbestosclaims.law/library/16428/38

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

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

[a] WHO (1976)

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

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

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	
Diagnosis[a]	Autopsy, Microscopic Evidence of Cancer	Autopsy, Gross Evidence of Cancer	Autopsy Gross Evidence, Unknown Whether Cancer	Autopsy, but only Indirect Evidence of Cancer	Autopsy, no Report	No Autopsy	Unknown	Number Dead	Autopsy[b] %
Pleural Mesothelioma	43	3		1	7	62	18	134	40
Pleural Tumor (other than mesothelioma)	8	1	1		3	13	11	37	35
Peritoneal Mesothelioma	21	4				2	1	28	89
Mesothelioma at other sites and unknown sites	11				2	21	5	39	33
Total	83	8	1	1	12	98	35	238	44%

[a] WHO (1976)

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

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ACL Doc 16428 · Page 40 of 111
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IV. Discussion

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

Felton (12) has pointed out several needs for post-mortem review. A problem may arise in workers' compensation adjudication where a decision has to be made, years to decades after initial work exposure, in those instances where death has resulted from pulmonary cancer or a thoracic or peritoneal mesothelioma. It is therefore important, in such cases, to be able to confirm by the presence of asbestos related effects that there has been exposure to respirable asbestos fibers.

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

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

It has been our experience that occupational histories are not routinely obtained and included in hospital records. In our search through records stored at the CTR (i.e. hospital records), we found job titles for only 17% of the mesothelioma cases. If we exclude from this group those designated as "retired", "housewife", or "student", the figure is reduced to 12%. We were only able to ascertain type of industry in 7% of these cases. The sample size for these statistics was 220 cases, whose diagnoses were between 1955 and 1977. A recently passed Ct. statute, whose method of implementation is under study, will hopefully alleviate the paucity of employment data from medical records.

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ACL Doc 16428 · Page 41 of 111 asbestosclaims.law/library/16428/41

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

(Comment on the significance of the Slide Review)

It is evident that until the physicians investigating cases of malignancy appreciate the importance of occupational ~~factors on~~ and environmental factors ~~on the etiology of these diseases, no~~ (lifestyle, habits, hobbies, part-time activities, detailed job histories) , any attempt to apportion blame to any particular factor for disease causation or promotion will be severely hampered. It is particularly essential in the case of a rare tumor, which may present diagnostic difficulties, to obtain sufficient tissue for study before a diagnosis is made. Whenever a tumor is found and an association is suspected with a particular occupational or environmental factor, every attempt should be made to document all relevant facts and to subsequently verify the diagnosis by means of a full autopsy.

A00585

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ACL Doc 16428 · Page 42 of 111
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Felton —

A0056

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ABC57

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~~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

A00589

~~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 ~~day~~ study has been designed to re-examine the identified cases of malignant mesothelioma recorded in the

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ACL Doc 16428 · Page 46 of 111 asbestosclaims.law/library/16428/46

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

A00591

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-O (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 lack of awareness of mesothelioma associated with ~~the later~~ this earlier time period (1935-1955). 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, and controls, 1955-1977. This will form the basis for classification of study subjects

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ACL Doc 16428 · Page 48 of 111 asbestosclaims.law/library/16428/48

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] Field Number 19 (US Department of Health, Education, and Welfare, National Cancer Institute (1976)

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

Numbers in brackets refer to the period 1955-1977

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

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III. Results

Descriptive Epidemiology

The ~~crude~~ age-adjusted incidence rate for mesothelioma in Connecticut is 2.1/million for the years 1935-1977. ~~Age-adjusted incidence~~ Rates per 100,000 population (using the 1950 US population as a standard) increased for both sexes, but there was a rapid rise from about 1960 for males (Fig. 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.

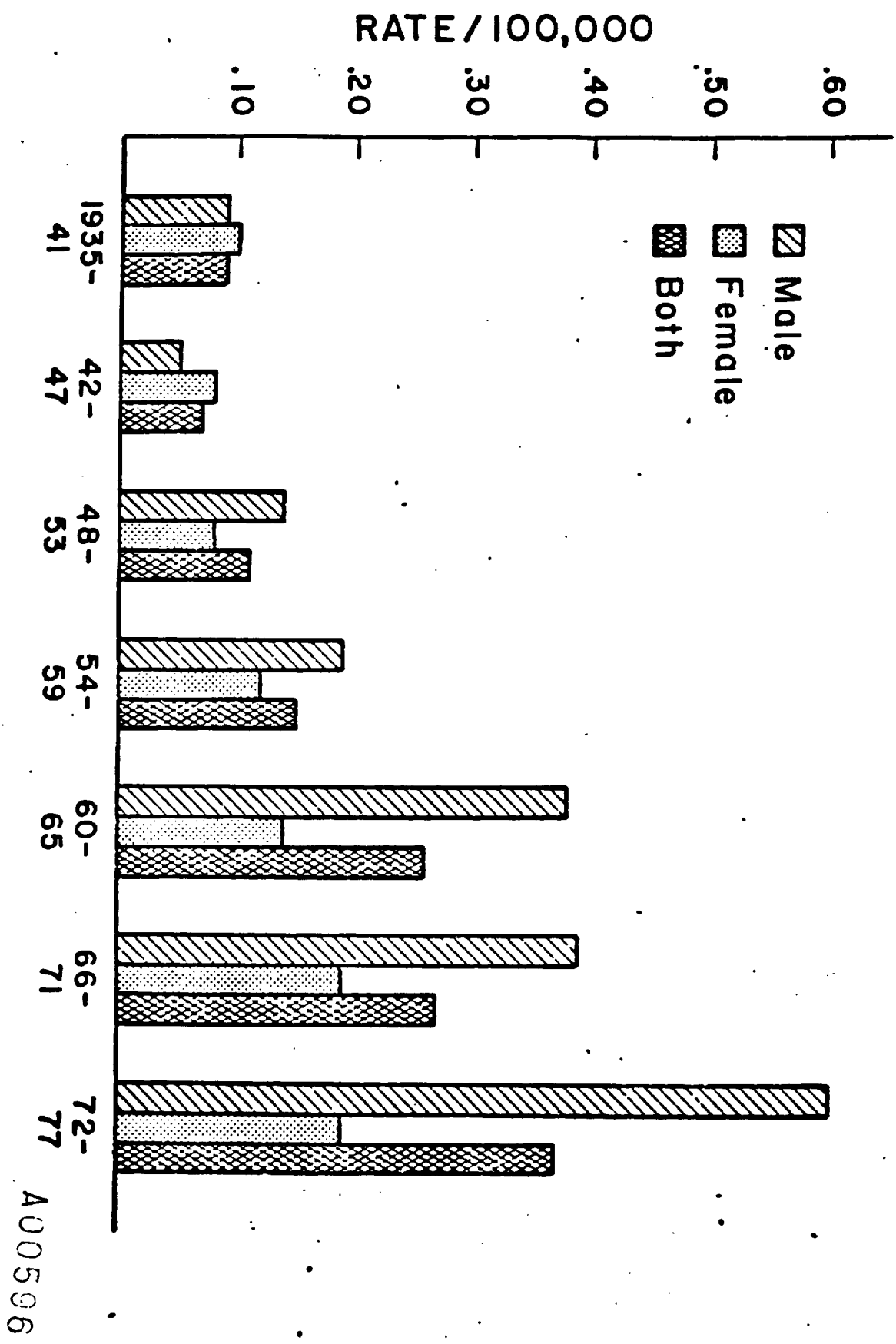
Ten cases were reported in an area (New London) where shipyards are located, and five of these were identified between 1975 and 1977 (Fig. 3). The geographical distribution of mesothelioma shows evidence of urban clusters in the 5 largest cities (Bridgeport, Hartford, Waterbury, Stamford, New Haven) 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 rate for males incidence ~~with the Bridgeport LMA the highest overall~~. The Stamford LMA's mesothelioma rate shows an unexplained sharp increase since 1965 (Fig. 4).

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Fig 2

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

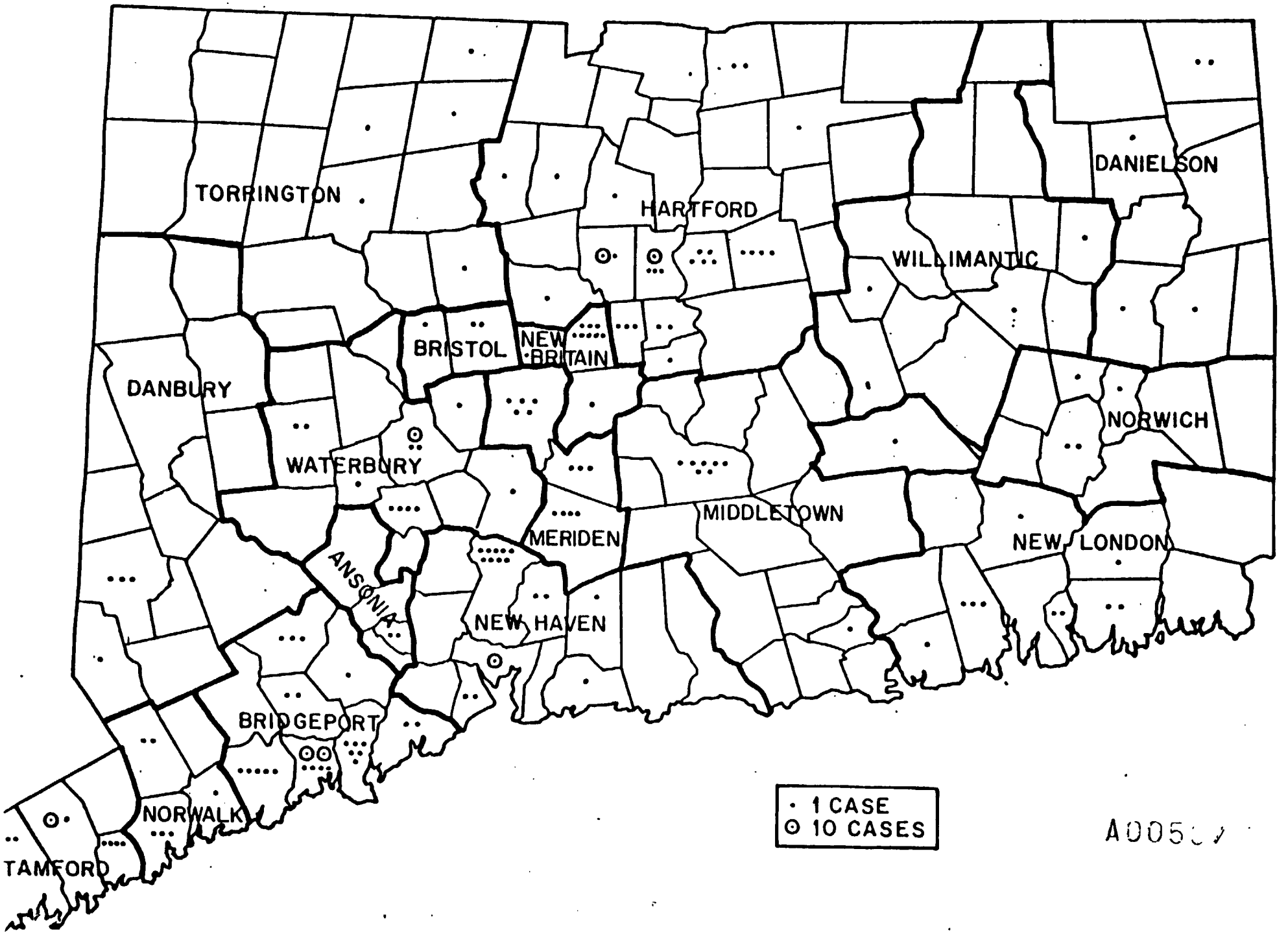


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ACL Doc 16428 · Page 52 of 111
Published by AsbestosClaims.Law
asbestosclaims.law/library/16428/52

Union Carbide trial exhibit UC-1271: Lewinsohn, Meigs and Teta, Malignant Mesothelioma in Connecticut 1935-19...
ACL Doc 16428 · Page 53 of 111

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

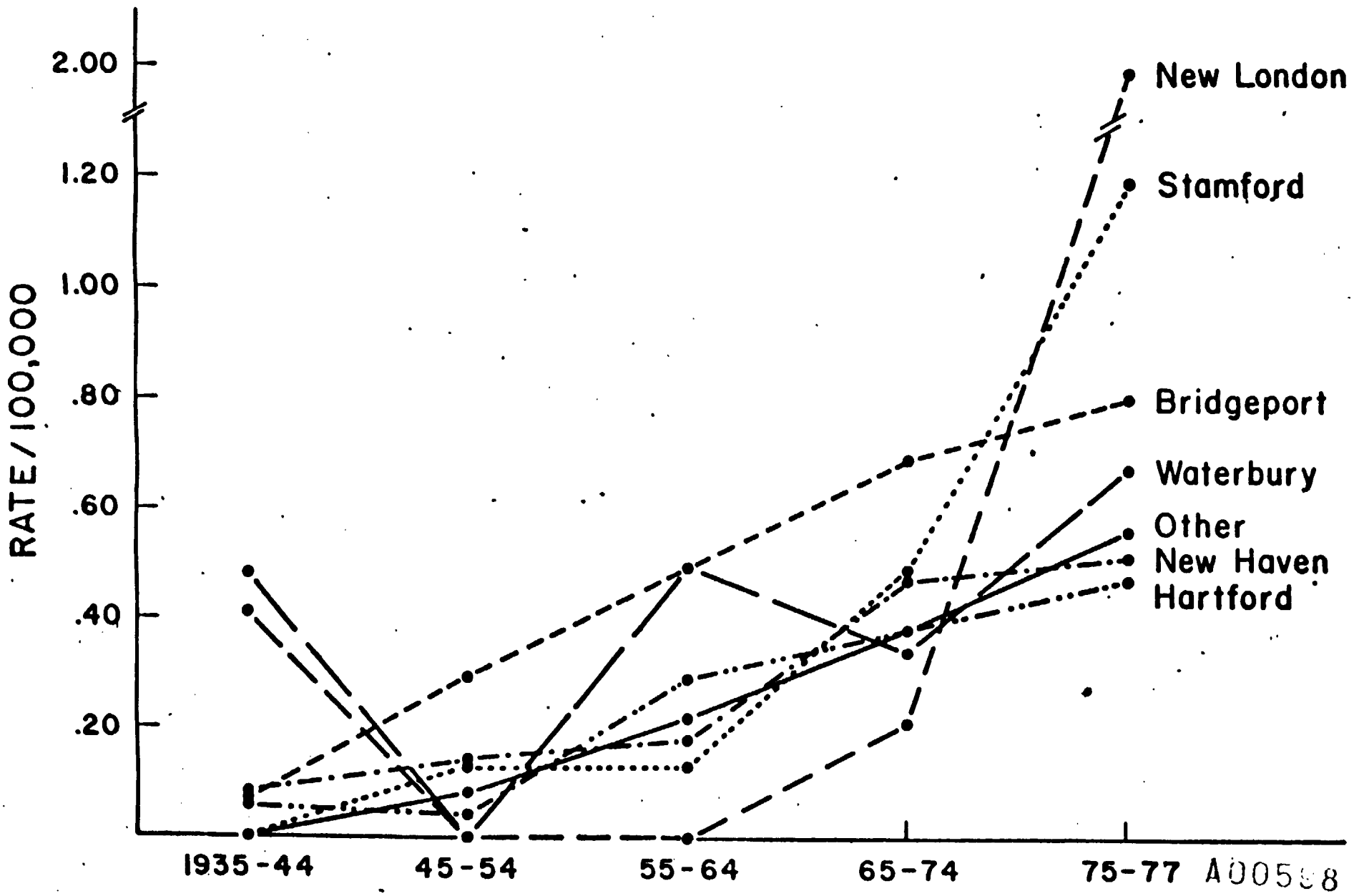


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Fig 1

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



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ACL Doc 16428 · Page 54 of 111

SLIDE REVIEW

~~These descriptive results examine completeness and accuracy of case identification which is limited by factors relating to the quality of diagnosis.~~ assume annually 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.~~ Wagner's ~~This~~ widely ~~published~~ publicized Cape ~~crocidolite~~ Cape crocidolite association of mesothelioma with asbestos exposure and, ~~however~~, created the ~~awareness~~ for the introduction of 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 distinquish 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 ~~known pathological material existed~~ tissue was examined at time of diagnosis, while available ~~specimens vary from biopsy to D & C tissue.~~ the origin of material varied. (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.

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ACL Doc 16428 · Page 55 of 111 asbestosclaims.law/library/16428/55

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

(Dr. Vidone-Summary of Findings)

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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	(clinical) Not Mic	Unknown	Total
Pleural Mesothelioma	136	3	3	—	1	4	147
Pleural Tumor (not Mesothelioma)	27	2	—	1	—	8	38
Peritoneal 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

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ACL Doc 16428 · Page 57 of 111 asbestosclaims.law/library/16428/57

Pleural 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 Unk		Autopsy Type Unk	No Autopsy	Unk	No Dead
Pleural mesothelioma	43	3	—	1	7	62	18	134
Pleural Tumor other than mesothelioma	8	1	1	—	3	13	11	37
Peritoneal mesothelioma	21	4	—	—	—	2	1	28
Mesothelioma at other sites & unknown sites	11	—	—	—	2	21	5	39
Total	83	8	1	1	12	98	35	238

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ACL Doc 16428 · Page 58 of 111
asbestosclaims.law/library/16428/58

R. Lewinsohn

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 paper files (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. + " // &
20 pleural tumors, not meso., 1955-77)

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— 11 —

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ACL Doc 16428 · Page 60 of 111 asbestosclaims.law/library/16428/60

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ACL Doc 16428 · Page 61 of 111 asbestosclaims.law/library/16428/61

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

A00629

~~Presentation to the Connecticut Thoracic Society, November 4, 1980~~

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ACL Doc 16428 · Page 62 of 111 asbestosclaims.law/library/16428/62

Malignant Mesothelioma in Connecticut 1935-1977

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

I. Introduction and Aims

The combined sex age-adjusted mesothelioma incidence rate for Connecticut was reported in 1977 to have increased ten-fold since 1935. 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 Mucicarmine and corrective tissue stains on surgical materials are valuable as well in this regard. The controversy over criteria for positive diagnosis is well documented in the literature (Kannerstein, 1977). Most experts agree, however, that a full autopsy is required to positively distinguish diffuse mesothelioma of the pleura or peritoneum from other primary or secondary neoplasms.

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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.

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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

A00634

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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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ACL Doc 16428 · Page 67 of 111 asbestosclaims.law/library/16428/67

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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ACL Doc 16428 · Page 68 of 111 asbestosclaims.law/library/16428/68

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

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

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

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

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ACL Doc 16428 · Page 69 of 111 asbestosclaims.law/library/16428/69

(1) Slide of histology

(2) X-Ray 9/5/79

(3) X-Ray 3/30/80

(4) X-Ray 7/23/80

(5) Lateral X-Ray 7/23/80

(6) Lung

(7) Lung - close up

(8) Lung + pleural tissue

(9) Pleural tissue - close up

(10) Pleural tissue - close up

(11) Histology

(12) Histology

(13) Electron photomicrographs

(14) Histo. exposure slide

(15) X-Ray report 9/5/79

(16) Histo exposure 9/5/79

(17) " " 7/22/80

(18) Memo to Hess

(20) Table 1

(21) Figure 1

(22) Figure 2

(23) Figure 3

(24) Figure 4

(25) Table 2

(26) Table 3

(27) Table 4

(28) 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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ACL Doc 16428 · Page 71 of 111 asbestosclaims.law/library/16428/71

New London Labor Market Area

Town	I.D.	Occupation	Dx	Sex	Site & Histology
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

A00640

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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 in the data available for study, ~~mainly~~ the low autopsy rate ~~of~~ for the pleural mesotheliomata and the inadequacy of the ~~types of tissue~~ pathological material 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 in 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 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.

A00607

[illegible] 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.

[illegible] 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" (243:2396, 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 personality, 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. Gabel, 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 (242:1056, 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.

[illegible] MD
University of Southern California
School of Medicine
Los Angeles

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.

William O. Robertson, MD
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and Medical Center
American Association
of Poison Control Centers
Seattle

A00608

Union Carbide trial exhibit UC-1271: Lewinsohn, Meigs and Teta, Malignant Mesothelioma in Connecticut 1935-19...
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ACL Doc 16428 · Page 77 of 111
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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

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ACL Doc 16428 · Page 78 of 111
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Union Carbide trial exhibit UC-1271: Lewinsohn, Meigs and Teta, Malignant Mesothelioma in Connecticut 1935-19...
ACL Doc 16428 · Page 79 of 111

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

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

[a] WHO (1976)

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

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ACL Doc 16428 · Page 80 of 111

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

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

[a] WHO (1976)

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

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

Diagnosis[a]	(1) Autopsy, Microscopic Evidence of Cancer	(2) Autopsy, Gross Evidence of Cancer	(3) Autopsy Gross Evidence, Unknown Whether Cancer	(4) Autopsy, but only Indirect Evidence of Cancer	(5) Autopsy, no Report	(6) No Autopsy	(7) Unknown	(8) Number Dead	Autopsy[b] %
Pleural Mesothelioma	43	3		1	7	82	18	154	40
Pleural Tumor (other than mesothelioma)	8	1	1		3	13	11	37	35
Peritoneal Mesothelioma	21	4				2	1	28	89
Mesothelioma at other sites and unknown sites	11				2	21	5	39	33
Total	83	8	1	1	12	98	35	238	44%

[a] WHO (1976)

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

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Table 5

MALIGNANT MESOTHELIOMA IN CONNECTICUT 1935 - 1977

CLASSIFICATION BASED ON ANATOMIC PATHOLOGY REVIEW

PRELIMINARY RESULTS (106 Cases)

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

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ACL Doc 16428 · Page 82 of 111
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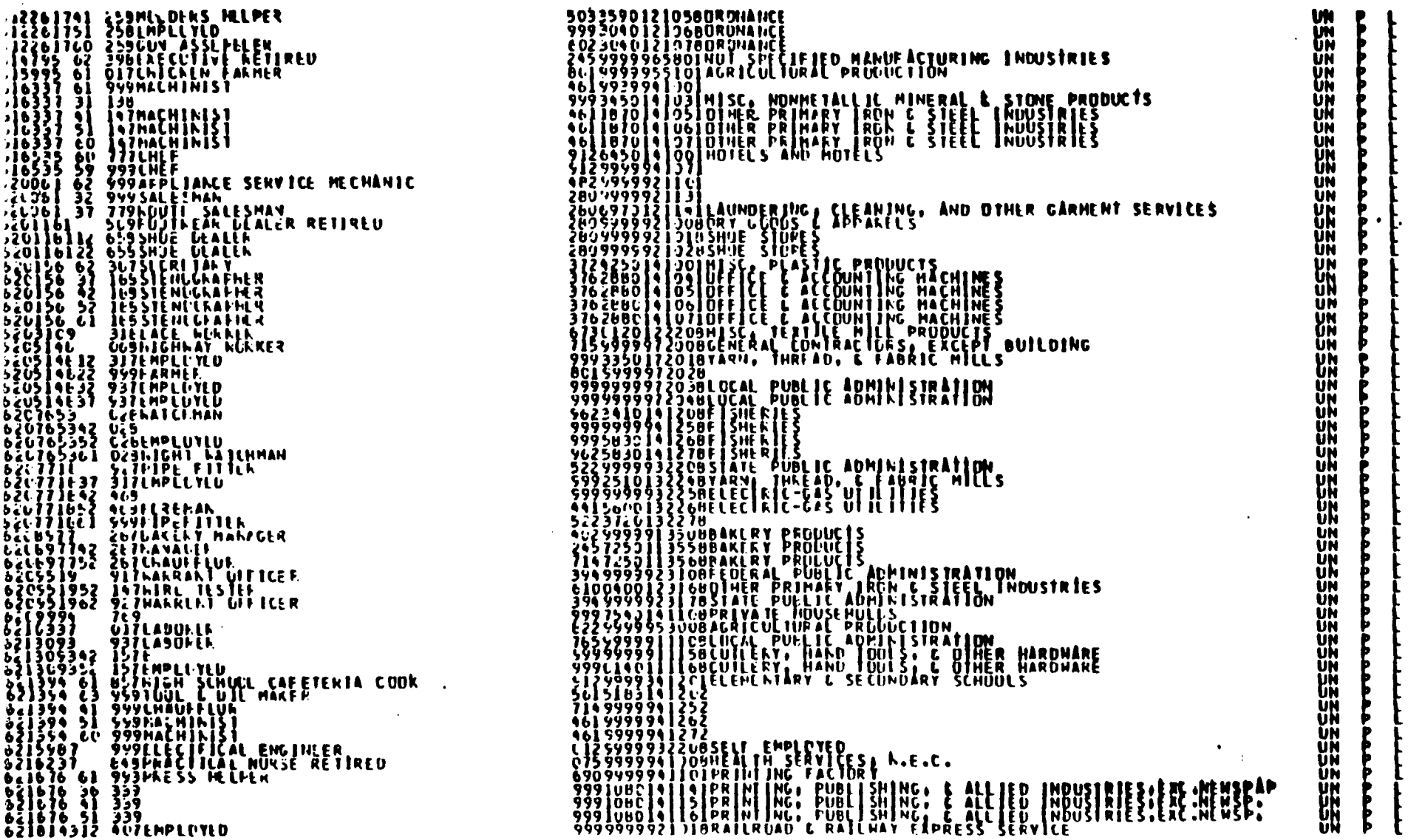


Figure 1

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ACL Doc 16428 · Page 83 of 111
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AGE-ADJUSTED INCIDENCE RATES OF MESOTHELIOMA IN CONNECTICUT BY YEAR OF DIAGNOSIS AND SEX

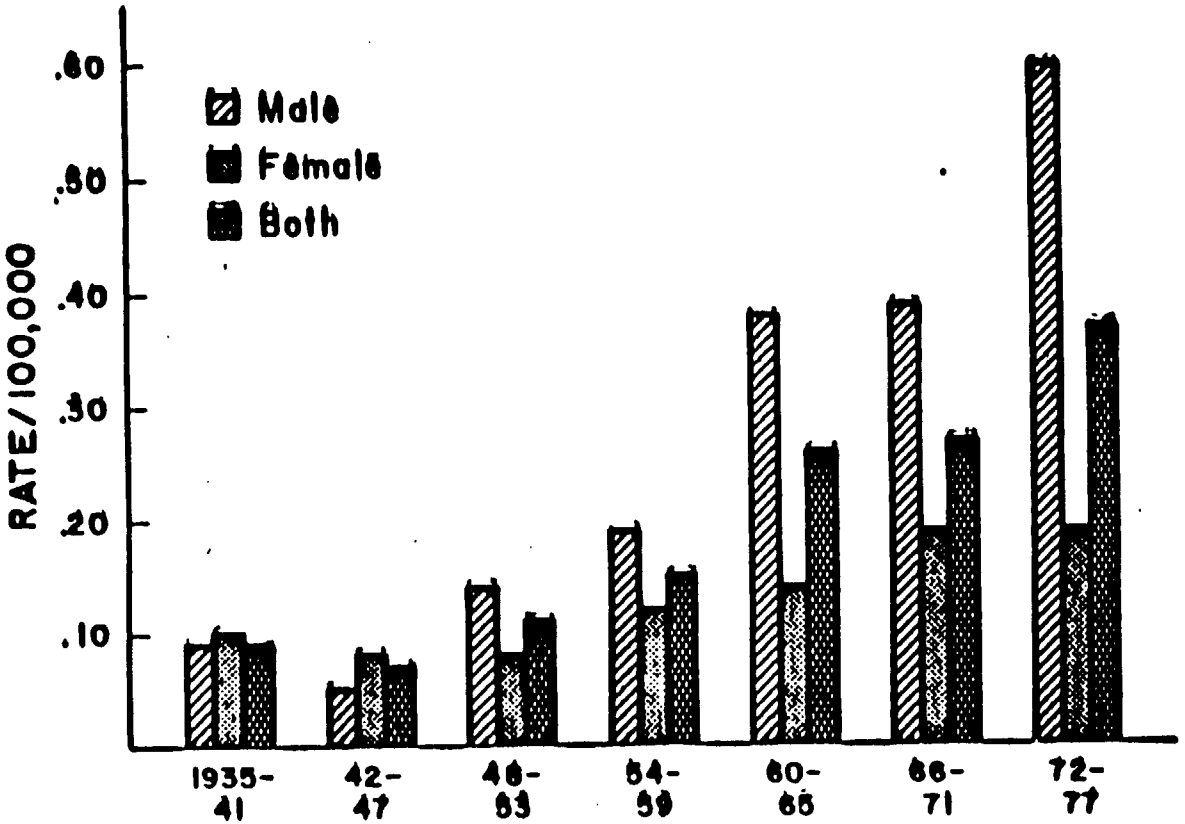


Figure 2

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ACL Doc 16428 · Page 84 of 111
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Talk to Medical Society, [illegible] 12/12/77

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" ~~in part~~ 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 ~~able to be~~ employed in a factory in the United Kingdom which has preserved its personnel records ~~from~~ since the turn of the last century ~~onwards~~ and which has good medical records going back to the late 1940's-early 1950's. ~~and which~~ These had previously been studied by my predecessor, John Knox in association with Richard Doll who is now Sir the Professor of Medicine at Oxford University and whom I am sure you all know of as a leading epidemiologist ~~in the field~~. It was Sir 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. ~~Before we start~~, I think it would be ~~is always~~ worthwhile to ~~go through the old pot boiling mechanisms of telling you exactly~~ describe what asbestos is ~~well not exactly but just giving~~ and give you some idea of the material we are talking about. ~~what~~ ~~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

A00903

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!" ~~If we could just have the first slide and the lights off then I could illustrate to you just briefly that~~ Asbestos is a

SLIDE 1. 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, Cyprus, ~~South Africa~~, Swaziland and the United States, is the type of fiber which comprises about 95% of the world's usage of this material. It is a hydrated fibrous magnesium silicate. Crocidolite, which is a blue ~~pallet~~ fiber, ~~comes from~~ is mined in South Africa at the present time ~~from~~ in 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 ~~accounts~~ the incidence of mesothelioma among the miners. Amosite is not ~~an acceptable~~ a reasonable mineralogical terms because it merely ~~stands~~ is an abbreviation for "Asbestos Mines of South Africa" ~~and that~~ It is unique in that it only comes from one fiber a part of the world i.e. ~~and that's from~~ this the Northeast Transvaal. The amosite and crocidolite from the Northeast Transvaal often ~~occurred~~ occur in the same rock seam ~~in the rock~~ and therefore it is ~~always~~ possible ~~to say~~ that amosite ~~is~~ may be ~~not~~ contaminated with ~~some~~ crocidolite and vice versa. ~~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~~. ~~Its~~ Amosite ~~really a part of~~ belongs to the ~~cummintinate grunatie~~ cummingtonite-grunerite (?) 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 ~~Co~~ found itself ~~enbattled~~ embattled with EPA, the State of

A00904

Minnesota and various others ~~people~~ regarding the dumping of tailings from its Taconite mines in Silver Bay into Lake Superior, ~~and/Dr. Selikoff 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 CC~~ The fiber in the tailings and the lake which is apparently similar to commercially used amosite. ~~Apart from the fact that a lot of the fibers initially discovered were Diatimatic skeletons (?~~ Anthophyllite isn't very widely used in industry. It's one of the oldest ~~used~~ known asbestos fibers in particularly 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 fiber because no cases of mesothelioma have as yet been described ~~with the~~ in association ~~of~~ with anthophyllite exposure, ~~and we can forget about the other two except the bottom one~~ SLIDE 2 Tremolite ~~which~~ is a fibre which is often found in commercial talc or industrial talc. ~~Just to give you some idea of the fact that chrysotile crocidolite/is blue amosite is sort of an in between color~~. ~~Those are both iron containing fibers this~~ is really ~~magnesium and various anthophyllite 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 ~~and this is~~ which shows what we did with asbestos in Rochdale in England. ~~That's a~~ The rock, ~~it was opened~~ is crushed and graded at the mine and the opened to some extent. It ~~was~~ is further opened at the factory in the process ~~of what we~~ called fiberizing. ~~and~~ After carding it ~~was used as~~ is formed into a sliver and then ~~we~~ spun into a yarn. ~~and that is the process and then~~ The yarn ~~would be~~ is 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, solar curtain etc. ~~Another think~~ 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

A00305

in 1933, ~~when~~ 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 ~~Merrywhether~~ Merriwether and Price in 1929 and published in 1930 ~~which~~ and it became is ~~one of the most famous study in this field and is~~ a milestone in the history of the ~~xxxxxxx~~ British asbestos industry. What they found was that in people who had been employed for 20 or more years, ~~xxx~~ - 81% had pulmonary fibrosis. We are talking about asbestosis, ~~and it's important to remember that asbestosis xxx x 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 ~~x 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 ~~xxxxx~~ association until the work of Richard Doll in 1955, although the same ~~Merrywhether~~ Meriwether 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~~ Is the development of ~~where~~ asbestosis ~~is~~ a prerequisite for the development of lung cancer or ~~that~~ can lung cancer occur in an asbestos ~~worker~~x without asbestosis, ~~is nevertheless an occupational disease and we would only enter in many arguments~~ into especially in view of the known multiplicative effect which cigarette~~s~~ ~~xx~~ smoking has on lung cancer in asbestos workers.

AJU906

~~However, I show that simply to point out what the situation was in 1930 with regard to asbestos~~is. In 1929 ~~This~~ Pulmonary fibrosis ~~was of crippling and killing people and~~ 81% of those worked 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%. ~~which~~ This obviously is still ~~xx~~ unacceptable but ~~what you have to remember is that~~ some of ~~those~~ the cases in this population were in fact exposed before the 1931 regulations. They were still ~~working~~ employed and as this ~~xxx x~~ is a table of prevalence not incidence ~~and consequently~~ they were there and ~~counted~~ were included. 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~~ This co-hort whose mortality experience ~~that~~ we are describing ~~in the paper~~ has been the subject of ~~2~~ 3 previous reports and the last of these ~~reports~~s was published in 1968. ~~the one prior to this and~~ They dealt particulary with mortality from 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~~ In the 1968 paper the cohort was divided into 6 groups. ~~with this~~ Group 1 had more than 10 years of exposure before 1933 but ~~xxxx~~ groups 1, 2, 3 and 4 had all had more than 20 years total exposure ~~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 ~~4~~ 3 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, ~~you see that the observed was 15 and the expected~~ 15 cases were observed where were expected 1.6 so there is was about an 11 times

A00907

excess incidence of lung cancer in ~~that~~ the 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 ~~interesting~~ satisfying observation but the authors were wise ~~and they~~ pointed out that no ~~further~~ firm conclusions could be drawn because little carcinogenic effect 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 those figures here we have~~ In the men and women all exposed since 1933 ~~and you can see that~~ for cancer of the lung and pleura 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 ~~and~~ but 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 group with less than 20 years or 10 to 19 years and you see no difference in the observed to the expected rate of incidence of lung cancer.~~ In men employed 20 years or more, those who worked before 1933 ~~as we have said before~~ there were 11 lung cancers observed to 0.8 expected (11 to 1) and for all neoplasms observed 15 to 3 expected, ~~and since~~ 1933 there were 3 observed to 2.9 expected ~~and so~~ Therefore, it appeard from this information, men exposed only since that people who had worked since 1933 were ~~now~~ no longer at risk and, if you accepted this, because the dust levels ~~that~~ had been brought down had been achieved a disappearance of the lung cancer. Furthermore this was against a diminishing background of incidence of asbestosis ~~and~~ as ~~you see~~ in 1975 the prevalence of asbestosis was only 0.8% in the factory population studied compared with 26% in 1929. 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~~

A00908

~~were~~ higher than the present ~~xxxxxxx~~ 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 ~~has~~ have been roughly sub-divided in the same way except that you will see there are only 5 groups instead of 6. ~~and xxxx the previous group 3 and 4 have been combined. It 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 ~~xxxx~~ 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 ~~xxxxx~~ interested in 10 to 19 and then females with 10 or more. Well there may be some ~~xxxxx~~ 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 ~~xxx~~ 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 ~~have~~ had completed 10 years employment since June ~~xx~~ 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 ~~xxxx~~ 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 registery as having imigrated or were not currently registered with ~~the~~ a 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 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 ~~that~~ the column ~~which is~~ for the ~~xxx~~ cause of death, ~~which is~~ heading lung cancer and mesothelioma, other cancers, respiratory diseases and other causes, and if you will just look at the ones ~~which is~~ show statistically ~~xxxxxxxxxxxxxx~~ significant ~~there~~ you will see that ~~again~~ in Group 1 (which ~~we knew before~~ previously ~~we~~ had the ~~10 or 11~~ 15:0.8 observed to expected ratio) ~~xxx~~ in ~~xxxxx~~ Table II 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 ~~xxxx~~ residue of asbestosis in ~~xxx~~ 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 ~~members~~ numbers are not underestimated, imigrants 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 ~~xxxx~~ age of 85 are ignored and expected members are calculated accordingly. In Rochdale itself lung cancer mortality was lower than the national average ~~among the men~~ for males, which is interesting, ~~in that~~ This is the ~~xxxx~~ largest asbestos textile factory in the world. Rochdale ~~has~~ with a population of about 80,000 people ~~and it~~ had a lower than average lung cancer mortality. It doesn't prove anything but ~~you xx know 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 ~~x~~, this doesn't seem to make sense. The A00910

standardized mortality ratio ~~xx~~ in Rochdale is 87, and ~~similar~~ for women ~~104 that's~~ (1959 to 1963 Register General 1971.). Workers first exposed before 1933 ~~that's fir xx~~ cohorts 1 and 2, suffered from excess of lung cancer and respiratory disease, ~~xxxxx~~ particularly those with 10 or more years exposure prior to 33. ~~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, ~~xx~~ 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 those 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 ~~incidence~~ inference that this was probably a chance observation seemed confirmed. There were 16 deaths attributable to gastro-intestinal cancer comapred 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 ~~xxxxx~~ 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

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ACL Doc 16428 · Page 93 of 111 asbestosclaims.law/library/16428/93

exposed worker 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 ~~this~~ as excess of gastro-intestinal carcinoma has never been found ~~in Rochdale~~ I think ~~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 for ~~any of those that is~~ gastro-intestinal carcinoma approached statistical significance in any cohorts and no peritoneal 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 as the start of the modern period in that factory. ~~because~~ It was the year in which the routine dust sampling was initiated. Although Merrywhether had, way back in the 1930's, had tried to give some indication as to what he considered to be an unacceptable dust level, the instrumentation and the techniques were not available to assess dustiness ~~numerically and to assess~~ accurately. It was only in 1951 when the thermal precipitator came into use in that factory, ~~and then subsequently~~ was followed by the long-running thermal precipitator and then, in 1961, by the membrane filter method, that it was possible to attempt to measure ~~what~~ the exposure of these people and to control the environment ~~according to~~ using 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 IV ~~but I think before we get there, no we got there, Men and women first exposed 1933 to 1950 there were 616 Men and women first exposed 1951 or later lung cancer 33 to 50 observed 30 expected 16 with a 2 to 1 ratio~~. Here we find that the 1968 authors were

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ACL Doc 16428 · Page 94 of 111 asbestosclaims.law/library/16428/94

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 something they didn't find and that is a slight excess ~~& its 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 about those first exposed after 1951? ~~Well we have it again~~. We have a ratio of 1.9, observed to expected lung cancer deaths ie ~~That is only~~ 6 cases observed to 3.2 expected. The numbers ~~might~~ at this stage are 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 following ~~But even~~ people who first entered since 1951 ~~up to 1974 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 the medical records but we do 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 is recorded ~~records~~ kept in the medical records ~~of 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 wont go into how those are defined just suffice to say that that's the way they were at the time~~. There were 22% who were non-smokers, 13% who had given up smoking and there were

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ACL Doc 16428 · Page 95 of 111 asbestosclaims.law/library/16428/95

65% who still smoked. ~~and~~ These were comparable to the national figures, ~~in a way~~. This population was no different ~~xxx xx~~ in its smoking habits from the general population. ~~What do you do about smoking? I don't know~~. Table # shows deaths ~~of~~ from lung cancer (including ~~peritineal~~ mesothelioma) in the men and women first exposed 1933 to 1950 and men and women first exposed 1951 or later. They are distributed according to ~~the day by day~~ date of 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~~ In the the 20 years or more ~~2xx~~ group the ~~o~~ ratio~~x~~ is 2 to 1. ~~In those two groups it probably is not significant.~~ In Men and women first exposed 1951 ~~or later 20 years or more if you take xxxifxxxxxxxxx~~ 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 you get~~ there are 5 observed, 1.8 expected (2.7 ~~as your~~ the 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, ~~x~~ although in view of the long latent period, ~~not~~ none would yet be expected. ~~An approximately~~ A multiplicative effect of asbestos exposure and cigarette smoking ~~x~~ on lung cancer/incidence 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 ~~x~~ an 8 times greater chance of dying from lung cancer than a non-exposed 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

found by the Pneumoconiosis Medical Board ~~at examinations of~~ in three of the six cases. They all came to post-mortem. All asbestos workers in Rochdale ~~x~~ who die have their ~~x~~ deaths reported to the ~~coroner~~ either by their doctors, ~~to the coroner or~~ the hospital, ~~report to the~~ ~~coroner~~ or by the ~~xixxxx~~ ~~register~~ Registrar of Births, marriges and deaths. This has been done since 1930. The post mortem rate when I once looked into it was ~~merely~~ nearly 70%, ~~of our ex employees~~ which is pretty high. ~~and~~ I used to go nearly every post mortem that took place. ~~xxxxxxxx~~ There is a lot of interesting work which will come out of the post mortem work which was done in Rochdale. The numbers ~~of~~ are too small for the magnitude of excess of lung cancer in those first employed after 1950 to be estimated with any precision. The implementation of the asbestos industry regulations started a drive to improve dust levels and as I explained to you the ~~xxxxxxxx~~ process ~~were~~ of fiberizing ~~xxxxxxx~~ where the fiber came from the mines, ~~xxx~~ was opened, mixed and ~~there were~~ involved certain operations such as mixing, opening, bag slitting, mechanical bagging. ~~Then they went on the to~~ The carding ~~xx~~ process followed. ~~and~~ If you are familiar with the textile industry the carding is simply a matter of teasing out the fibers, layering them all in one direction ~~and you do this~~ by passing them through two rollers moving in opposite directions with ~~chopped~~ short needles projecting from ~~them so~~ to you tease them out. ~~and you get~~ A fine web is formed which subdivides and spun (or twisted) and ~~then you take that web and you spin it and~~ There are different grades of yarn, ~~fine or whatever and then you beaning~~ (?) Yarn is woven into cloth. ~~x is a winding is the~~ _____ ~~and if you ever get confused with the weaving loom as to what the wheft and the wharp are the wheft goes from wheft to white and the wharp goes whap and down and you x can't forget it that way and that's how you weave.~~ ~~Platting~~ Plaiting is obviously used for packings. ~~You do things with~~ plaiting is used ~~like impregnating with~~ can be impregnated with ~~xxxxx~~ grease or graphite and this ~~got~~ ~~xxxxx~~ stuck into valves. ~~xx~~ You can see here years 52, ~~xxxx~~ 60, 61 66, 70 for packing.

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 operation, I'll show you in a moment, is totally closed. Of course that is the way to deal with anything dusty. If you ever close it you won't got no dust. But those gradually went down 6 fiber in 1961 to 3 in 74. This factory population was used and studied by the British Occupational Hygiene Society in 1966 and on the morbidity study which was done at that time not a mortality but a morbidity study the present hygiene standard for asbestos fiber was developed. and To the dismay of the people who developed it it became widely accepted throughout the world and is now the current US standard (or threshold limit value) for asbestos of 2 fiber/cc. Originally it was a cumulative standard of 100 fibers years/cc. so If a man worked for 50 year in 2 fiber/cc he stood a 1% risk of getting asbestosis. The standard was not designed for lung cancer. Although there is some indication, as that I have shown you, if that the incidence of 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 to 2 fiber/cc or less. No population has been followed for long enough 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. 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 their "gut feeling" felt that 2 fibers/cc was a reasonable level because of the health experience

A00916

of that weaving shed. No single population in the world has been followed-up for long enough at a 2 fiber/cc or less level to enable us to say, based upon human experience, whether this is an adequate level or not. Let's look at Table 11 which shows the mean dust levels over the period of observation and the number of men exposed to them. From 1936 to 1967 obviously I told you we didn't have dust counts. In 1936 they didn't start having dust counts until 51. that is _____ but it is based on calculations made by the committee of the British Occupational Hygiene Society (and the status statistician involved was Geoffrey Berry of the Medical Research Council's Pneumonociosis Unit in Penarth) and they arrived at a means of calculating based upon present levels that 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 the beginning of a period of modernization of the factory which was completed in about 1954, and a lot of engineering work was done, a lot of jobs were changed, a lot of many processes were altered and it all resulted in a better working environment. In 1969 new Regulations were made. Those new regulations were called 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 asbestos dust was giving off in such excess concentrations as was liable to be harmful to the health of the exposed person. As opposed to the American method of doing it, the British have not put a figure in the asbestos standard in the regulations, there is no legally enforceable figure. The way it has been done is by publishing, as an addendum to the standard, if you like guidelines for the benefit of those people who have to apply the standard. The guidelines to whom the standard applies which indicate what the current thinking of the factory inspectorate is at the present time with regard to the dust levels they are going to enforce. That means that to be achieved. If they want to change those this levels to vary tomorrow (and they have already changed them once since 1969), all they have to do is amend the published guidelines. AD0917 pull that piece of paper out of circulation and publish another. It doesn't require an act of Parliament or any

~~sort of~~ ~~consultated~~ formal consultative mechanisms to do this, although ~~xx~~ obviously ~~they~~ would consult before ~~xxx~~ with all interested parties. It realy makes it very much simplier 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 which~~ don't have to play the "numbers game" and this is the difference ~~xxx~~ between the OSHA standard ~~xxx~~ and the British standard. ~~However, that xx 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 xxx xxxxx we are going to begin to xxxx people out of the cohort~~ losing 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~~ In 1972 , 32% ~~are~~ were exposed at less than 2 fiber/cc. In ~~1936~~ 1936 100% were exposed to ~~xxxxxxx~~ greater than 5 fiber/cc and only 3% now remain ~~In xx 1972~~ in 1972 ~~who are~~ exposed ~~xxx xxx xxxxxx~~ to greater than 5 fiber/cc. What this is ~~really showing you~~ demonstrates is that with time the number of people ~~xxxx~~ng exposed to high concentrations is declining. It is ~~just~~ interesting to present it that way. ~~There are a number of always in this type of thing~~. ~~World War took place and~~ During the ~~war~~ Second World 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 ~~made~~ produced. Overtime was worked, ~~xxx~~ women were brought in to work instead of men and long hours of blackout restrictions made it impossible to operate ventilations ~~and all sorts of things~~ systems adequately. ~~You have this period in World War which~~ I don't know what effect this is going to ~~be~~ 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 ~~modern~~ present day conditions. What we are looking at is a ~~hotchpoth~~ the result 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 level here~~ to 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 ~~and that~~ The next slide is ~~just~~ a ~~plot i of in~~ graph showing the way in which the levels in the factory

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ACL Doc 16428 · Page 100 of 111 asbestosclaims.law/library/16428/100

have been coming down. Even people exposed after 1950 ~~are~~ were 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 excess incidence or 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 don't begin to see any difference in mortality experience, ~~you may see a slight difference~~ until after a latent period of 20 years but you may have to follow up people for 30, 40 or 50 years ~~with occupational cancers~~ from occupational cancer before ~~that~~ an excess mortality becomes apparent. This is why it is important ~~that you~~ to keep records of medical findings, ~~to you~~ keep personnel records which are accurate with regard to ~~date~~ date of employment and types of employment and if possible the type of materials ~~to~~ to which people ~~are~~ were 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 ~~varying~~ bearing 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 ~~predecesors~~ predecesors had no concept of this type of approach ~~to~~ 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 ~~a~~ part of it ~~that's~~ is 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~~ information and analyze it statistically ~~and~~ to obtain an idea as to how ~~this~~ this population compares with another population or with the general population. If you can do all this ~~so that~~ you will find out ~~have an idea~~ whether your industry ~~you are~~ is ~~in~~ in any way ~~in~~ ~~impeding~~ impeding or ~~impairing~~ impairing the health of ~~the~~ persons employed ~~person~~ by it. ~~and~~ I promised that I would show you that improvement had taken place at Rockdale ~~and~~ ~~That~~ doesn't show up very well, but that's a man and those are his legs and what he ~~has~~ is holding is a pitchfork.

There is a hole in the ~~ground~~ floor and he is standing on a big wooden drum. This is asbestos and he is ~~xxxx~~ using his pitchfork to blend it on a open floor throwing it up in the air and letting it settle. ~~and~~ It's blowing ~~xxxxxxxx~~ it about all over the place. That was ~~taken~~ taking place in the factory that I have ~~xxx~~ just ~~xxxxxxxx~~ 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. You have got to be very careful when you read the world literature because working conditions in different countries vary and when ~~xxxx~~ some ~~xx~~ people ~~xxx~~ ~~xxxxxxxxx~~ describe the horror and the disease associated with asbestos, ~~and their findings~~ they 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 ~~x~~ seen conditions and I have got slides to demonstrate the differences between the U.S., somewhere like South Africa, ~~__-~~ Natal, Mombasa, 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~~ So, ~~far~~ 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 ~~xxx~~ well there are ladies present! // That's what happened to ~~the~~ this job - it was totally enclosed. The drum is now ~~in there~~ enclosed. ~~and~~ It revolves and mixes the fibre. ~~and~~ There is a bag opening procedure whereby the bags are fed on to a conveyor belt and fiber go ~~xxx~~ into the drum after mixing it and tips it into another bin down on the floor ~~and that~~ which is also all enclosed and there should be 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

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ACL Doc 16428 · Page 102 of 111 asbestosclaims.law/library/16428/102

looked at ~~the~~ me and asked ~~and I said~~ where ~~do you want~~ I wanted to start. ~~and~~ I said ~~I'll~~ I'll start at the beginning where the fiber comes in. ~~and [illegible] that 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. ~~that~~ It 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. ~~[illegible]~~ I ~~xxx~~ wasn't allowed to visit Rhodesia while I worked for Turner & Newall. However in ~~xx Raybestos~~ American's factories there is plenty of this stuff. The United States hasn't bothered about sanctions. Anyway this was 1966 these were ~~rolled up~~ burlap bags. Every now and then you could see holes in them. Shippers used to love this stuff because it ~~was~~ made ~~xxxx~~ beautiful ~~balaced~~ ballast. 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 xx is~~ them was to plunge a hook into the bags swinging them over their sholders ~~xxx~~ + then ~~chuck~~ it over the side to someone else. ~~and have~~ A horrible mess used to result and these ~~things~~ bags used to arrive at the factory ~~and~~ where the chaps in the warehouse ~~they~~ did not have quite as big hooks so the little holes are theirs. ~~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 ~~f~~ of ~~x~~ fiber stacked to the ceiling. It ~~was~~ held 18 months supply because they knew UDI ~~x~~ was coming and so they brought ~~xx~~ 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, ~~xxxx~~ 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 ~~polyprophylene or polythyne~~ and they are pressure-packed at the mines. They ~~Those~~ are all solid, hard ~~they are~~ like bricks, they are palletized and very often they are covered with an

~~T~~ 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. ~~and~~ It's a nice part of the world to go to in January! // What we have therefore is a story that is unfolding. ~~and~~ This is a rather ~~an~~ old slide ~~and~~ it tells you about asbestosis beginning at the beginning of the century. The incidence declining ~~ing~~ 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 ~~of~~ insulation workers to a large extent Asbestosis and lung cancer ~~overall~~ increasing ~~ing~~ 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 during the War and ~~accelerating~~ accelerated afterwards so that asbestos became a universally ~~widely used~~ utilized material. It was cheap, 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 TSH. Just before I left we completedgoing through our personnel record cards back to ~~1~~19~~8~~18 and collected something like ~~nearly~~ 30,000 records of 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~~ 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

PLAINTIFF'S EXHIBIT
UC-1271

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

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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.

AU0546

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, these 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~~ outcome 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 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 material are also 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 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.~~ It is probable 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

A00543

DRAFT ~~10/17/80~~ 10/24/80

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

A00550

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ACL Doc 16428 · Page 110 of 111
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Malignant Mesothelioma in Connecticut 1935-1977 by H C Lewinsohn, J.W. Meigs, and M.J. Teta

I. Introduction and Aims

The combined sex age-adjusted mesothelioma incidence rate for Connecticut was reported in 1977 to have increased ten-fold since 1935. 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 (Gruskin 1977 ; Brockmann 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

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ACL Doc 16428 · Page 111 of 111
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