PLAINTIFF'S EXHIBIT

UC-4089

Yale University *New Haven, Connecticut 06510*

CONNECTICUT CANCER EPIDEMIOLOGY UNIT
30 COLLEGE STREET

(203) 436-8904

J. WISTER MEIGS, M.D., *Director*

October 13, 1980

Dr. Hilton C. Lewinsohn
Raybestos-Manhatten, Inc.
100 Oakview Drive
Trumbull, Connecticut 06611

Dear Dr. Lewinsohn,

Please review and give me a call. I haven't yet included the sample of the listing. I haven't heard from Dr. Vidone yet. I outlined your section briefly.

Very truly yours,

Jane Teta, M.P.H.
Research Associate

JT:bav

Enclosure

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UCC 017514

~~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

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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, 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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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 ~~verify~~ suggest, a thorough review of available histological material is being undertaken.

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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). ~~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 ~~increasing~~ awareness of mesothelioma associated with this earlier ~~the later~~ time period (1935-1977). The Price and Lee City Directories were searched for job title and name of specific employer or industry for cases, controls and spouses at 1, 10, 20, 30, 40 and 50 years prior to date of diagnosis, death or until the subject was less than twenty years old. An occupational history search was attempted for spouses to coincide with these intervals for their corresponding cases.

~~The three-digit~~ 1970 U. S. Census industrial and occupational codes (U. S. Dept. of Commerce, 1971) were assigned to the employment information ascertained from medical histories, death certificates, and City Directories. A machine readable listing of job and industry titles has been developed for all cases, spouses, and controls, 1935-1977. This will form the basis for classification of study subjects

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

[a] WHO (1976)

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

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

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

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

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III. Results

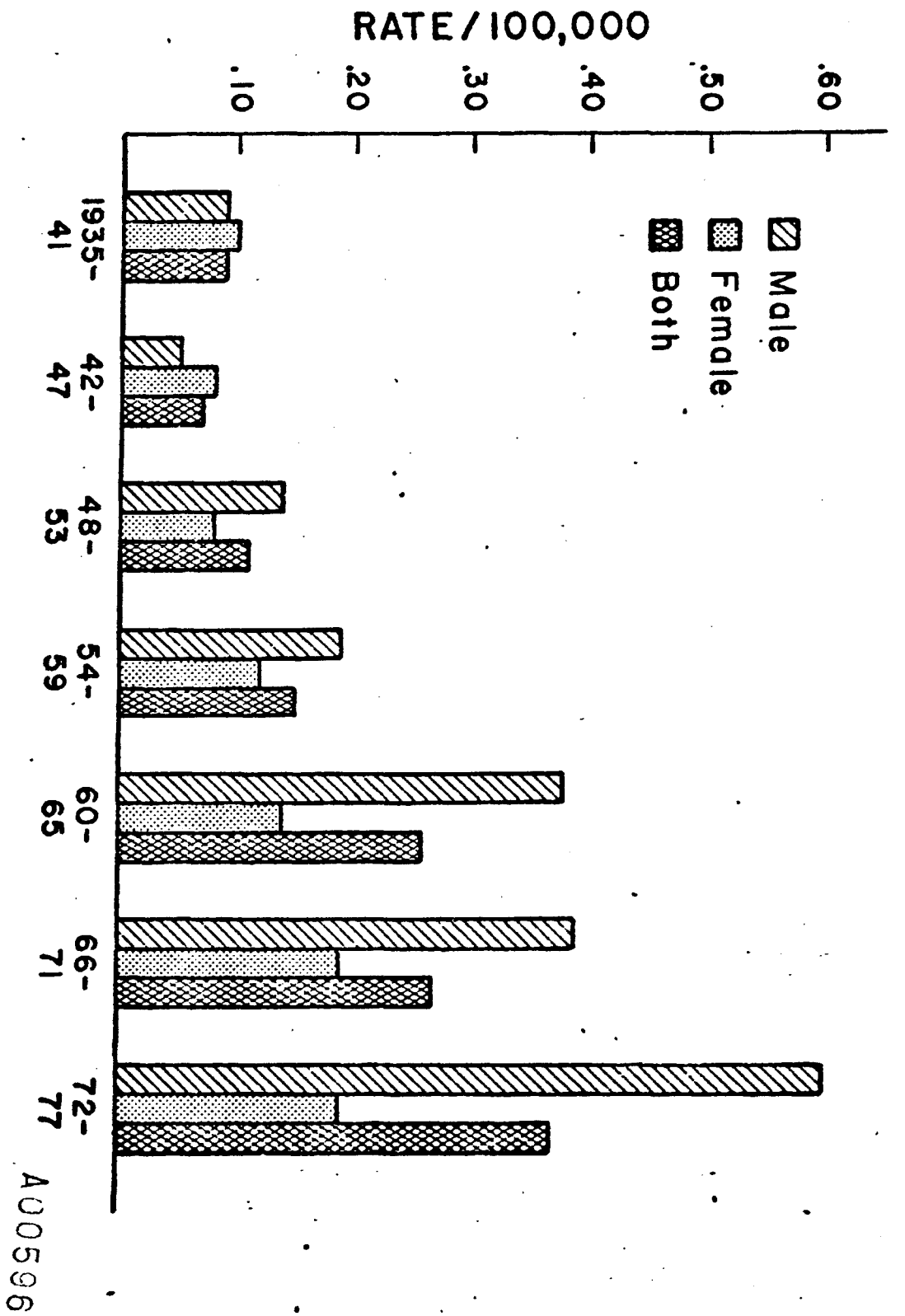
Descriptive Epidemiology

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 incidence rate for males ~~with the Bridgeport LMA the highest overall~~. The Stamford LMA's mesothelioma rate shows an unexplained sharp increase since 1965 (Fig. 4).

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

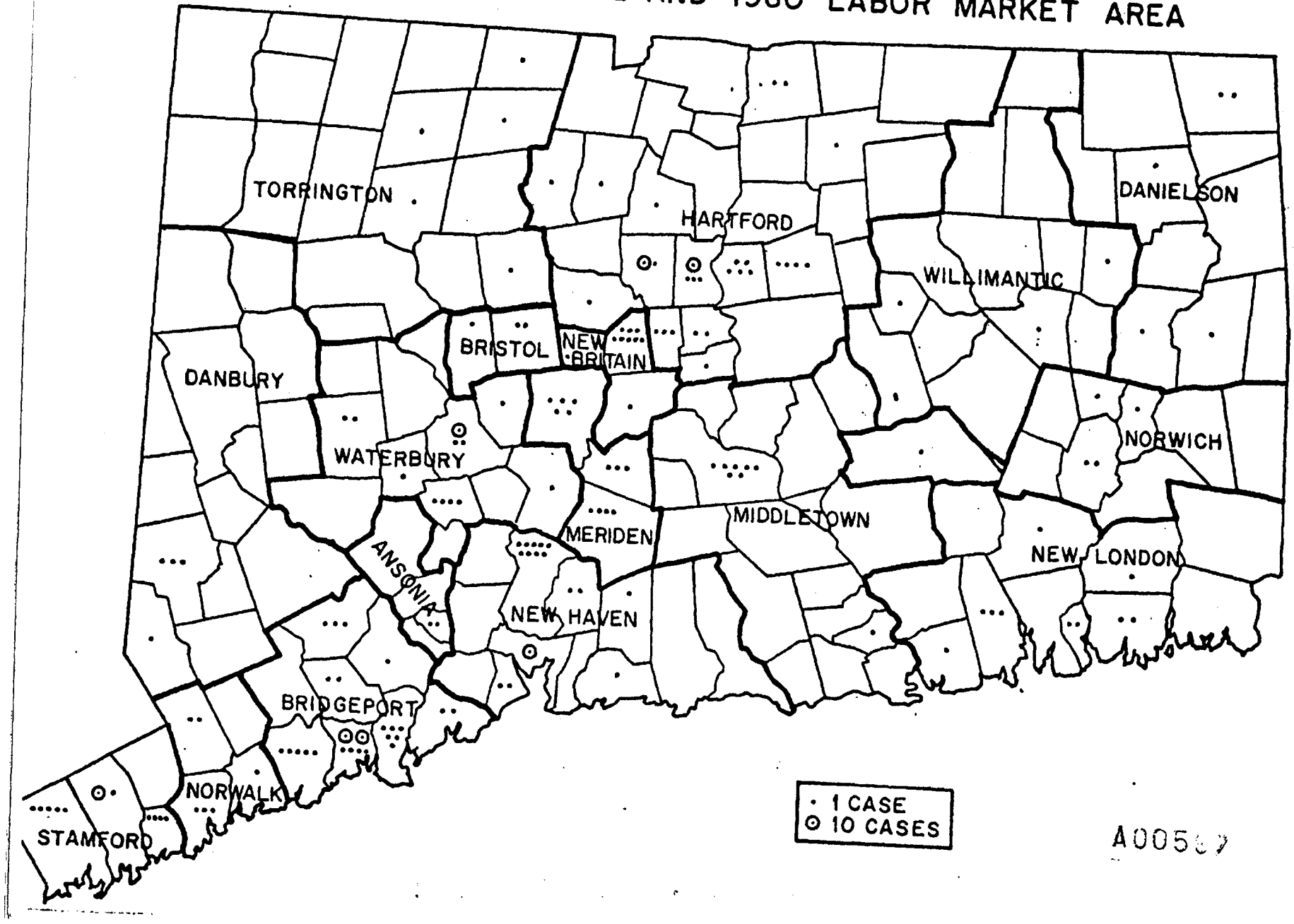
Fig 2

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



- 8 -

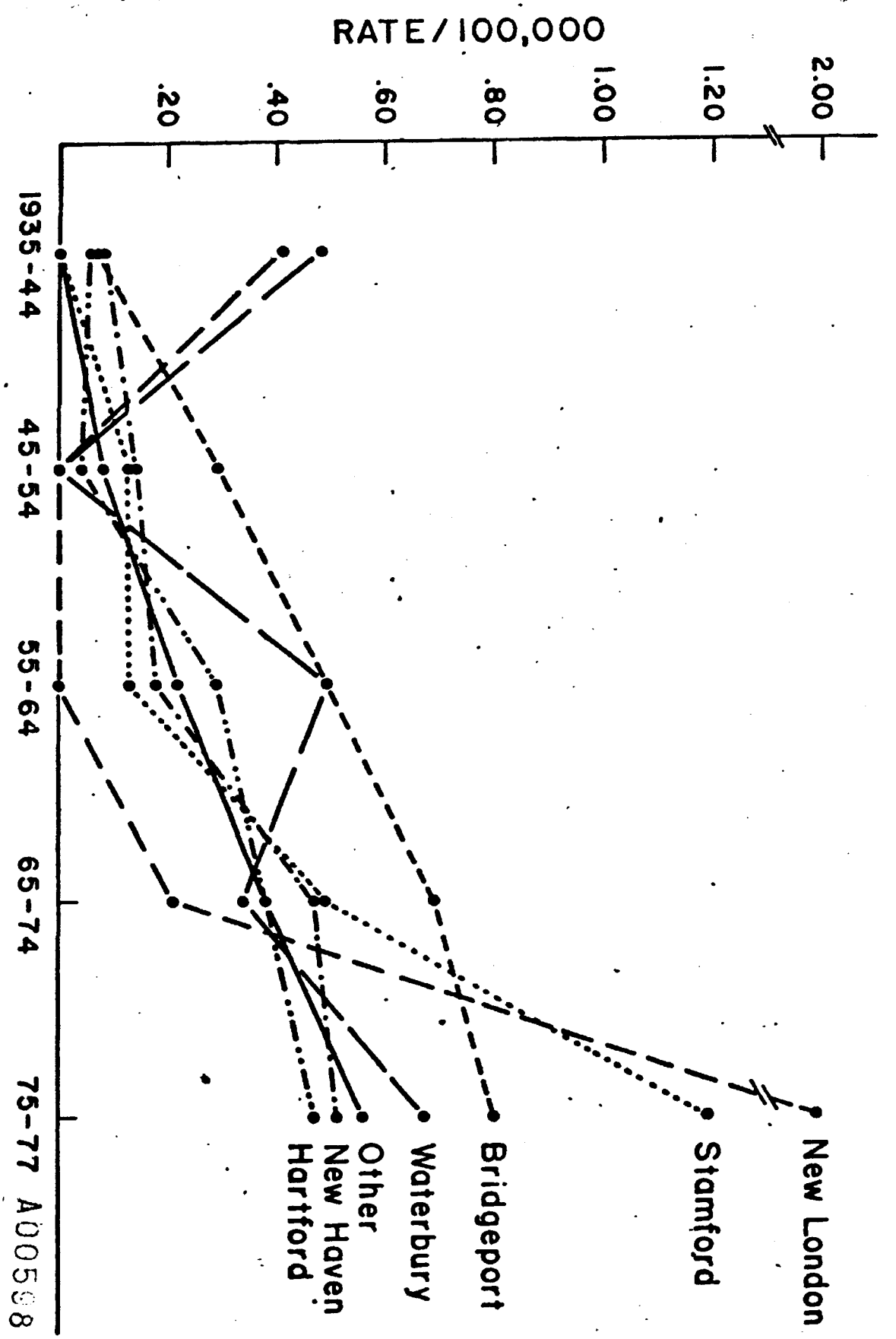
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Fig 7

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



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SLIDE REVIEW

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

~~In addition to its rarity and the subsequent lack of awareness,~~ positive diagnosis of mesothelioma is 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~~ at time of diagnosis, while available ~~specimens vary from biopsy to D & C tissue.~~

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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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	(clerk) Not Mic	UNKNOWN	Total
Pleural Mesothelioma	136	3	3	—	1	4	147
Pleural Tumor (other than 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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TABLE 3: Frequency of Autopsy for Cases of Malignant Mesothel
Tumor and Pleural Tumors other than mesothelioma Diagnosed i
Connecticut, 1935 -1977

	(1)	(3)	(4)	(5)	(7)	(8)	(9)		
Diagnosis[a]	Microscopic Evidence of Ca.	Gross Evid. of Cancer	GROSS, Evid Unk		Autopsy Type Unk	No Autopsy	Unk	No Dead	Aut Dc
Pleural Mesothelioma	43	3	—	1	7	62	18	134	4
Pleural Tumor (other than mesothelioma)	8	1	1	—	3	13	11	37	3
Peritoneal Mesothelioma	21	4	—	—	—	2	1	28	8
Mesothelioma at other sites & Unk sites	11	—	—	—	2	21	5	39	3
Total	83	8	1	1	12	98	35	238	4

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Dr. 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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Mary Jane Teta, Associate in Research, Connecticut Cancer Epidemiology Unit, Yale School of Epidemiology and Public Health
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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, ~~namely~~ 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.

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

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

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[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.

Loren T. Dewing, 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. Gelon, MD
Alton 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 (242:1656, 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.

Jean Spencer Felton, 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
Children's Orthopedic Hospital
and Medical Center
American Association
of Poison Control Centers
Seattle

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by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

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The Influence of Occupational and Environmental Asbestos Exposure on the Incidence of Malignant Mesothelioma in Connecticut.

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

Introduction

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 $30 ng/m^3$, measured over a thirty-day interval. The rapid increase in the State's mesothelioma incidence

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reported in 1977 is referred to as justification for this proposal.

The present study has been designed to re-examine the identified cases of malignant mesothelioma recorded in the CTR and attempt to determine the role of various etiological factors, such as occupational and environmental asbestos exposures. In view of the acknowledged possible diagnostic errors, which our results verify, a thorough review of available histological material will be undertaken.

Methodology

The CTR has identified 267 cases of malignant mesothelioma of the pleura (147) and peritoneum (33), other mesotheliomas, including breast, ovary, synovial membrane, testis, spermatic cord, perivesical tissue, cervical glands, brain, esophagus, bone and sternum (49), and other pleural malignant tumors, not mesothelioma (38), 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 their respective spouses. Similar information has been gathered for a random sample of approximately 700 decedents (1935-76) aged 20 to 98 years from the Division of Health Statistics of the Connecticut Department of Health (Table 2).

Descriptive epidemiology for this research pertains primarily to the forty-three year time interval. Statistical modeling and future

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case-control comparisons include cases (215) diagnosed after 1954 (Table 1), and controls (605) whose deaths occurred during this same time period. This procedure yields a case-control ratio of approximately 1:3, while reducing sources of error resulting from the limited occupational and medical data prior to 1955 and the increasing awareness of mesothelioma associated with the later time period (1955-1977).

The Price and Lee City Directories, utilized as an occupational data source for the three populations, were available for approximately sixty-six percent of Connecticut towns from 1890 to date (with the exception of smaller towns). 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. 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. Industrial coding was determined on the basis of product descriptions for each specific employer which were found in the manufacturing directories of Connecticut, published by the State Department of Labor (1957, 1966, 1973) and from the Price and Lee Directories for non-manufacturing industries. From the complete listing of job and industrial codes a subset was selected by H. C. Lewinsohn, utilizing published sources indicating occupations

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and products associated with asbestos (Hutchison, 1976; Levine, 1978; Weston, 1976). This will form the basis for probable asbestos expsoure classifications. The City Directory data over five decades provides information on duration of exposure.

With a categorical response variable of occupational asbestos exposure, two fundamental research interests can be tested: 1. Whether cases and controls differ significantly with respect to job-related asbestos exposure (Relative Risk) and 2. The nature of the relative contributions of occupation, spouse occupation and geographical residence to the incidence of mesothelioma in Connecticut (Logistic Regression). In addition, the health experience of spouses of occupationally exposed cases and spouses of non-exposed cases can be compared.

Results

Of all cases diagnosed as pleural mesothelioma, twenty-one percent (31) had unknown staging (SEER, 1976) and sixty percent did not have an autopsy. The forty-nine cases of mesothelioma of other or unknown site have a mean age of fifty-two years and sixty-seven percent are without autopsies. The male-female ratio is approximately 1.5:1 (Table 3). The question of the accuracy of classification of cases of malignant pleural tumors into mesothelioma and other pleural tumors naturally arises. The mean ages and the male-female ratios are similar for these two groups and the "other pleural tumor"

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group exhibits weak diagnostic confirmation, i.e., seventy-one percent positive histology and only thirty-five percent autopsied. A discriminant function analysis of these two groups of cases (diagnosed after 1954) on the basis of age, sex, survival, time, stage, and number of tumors yields a sixty percent misclassification. This result suggests that: 1. Either these variables are not sufficiently powerful discriminators of pleural mesothelioma from other pleural tumors, or 2. The two groups, as a result of mis-assignment of a substantial number of cases to the incorrect category, now lack the heterogeneity one would expect from distinct categories.

If consideration is limited to cases identified after 1954, when recorded clinical detail in general improved, as well as an increasing awareness of this form of cancer, the number of cases with solid diagnostic confirmation and characteristics consistent with the natural history of mesothelioma are strikingly few. Of the 131 cases classified as pleural mesothelioma, 124 (95%) had histological material, (specimen from biopsy, frozen section, surgery, autopsy or D and C) examined and autopsies were performed on forty-five cases (38%). The proportion autopsied is disappointingly small.

Table 4. shows the percentages of subjects with these two diagnostic critieria for mesothelioma cases of other or unknown site, for peritoneal mesothelioma, and cases of pleural tumors, not mesothelioma.

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As a result of these findings, it is imperative that a slide review and a re-examination of hospital clinical reports for all cases of mesothelioma and other pleural tumors be undertaken. A commitment has been received from an independent pathologist for this aspect of the study. The following data analyses are subject to change subsequent to this procedure.

Descriptive Epidemiology

Between 1935 and 1977, the CTR identified 229 cases of mesothelioma, yielding an overall crude incidence rate of ~~four~~ 2.2 per million. See tele
Age-adjusted incidence rates per 100,000 population (using 1950 U. S. population as a standard) for pleural and peritoneal mesothelioma consistently increase and exhibit a rapid rise beginning about 1955 - .04 (1935 - 44); .07 (1945 - 54); .18 (1955 - 64) (Figure 1.).
We are in the process of generating these rates through 1977. Of these cases, 195 (85%) were reported after 1954. The male-female ratio is approximately 2:1; the mean age at diagnosis is fifty-nine years. Survival time from date of diagnosis to date of death is approximately ten months.

A logistic regression model of the form:

$$\text{Log}\left(\frac{P}{1-P}\right) = A + B_1 X_1 + B_2 X_2 + B_3 X_3.$$

was fit in order to examine the incidence of pleural mesothelioma (binary response variable) as a function of the categorical explanatory variables - time, age and sex (X_1, X_2, X_3). Connecticut population figures supplied by the Connecticut State Department of Health were used for denominator data in the estimate of disease probability ($\hat{P}$).

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The three and two-way interactions of time, age and sex were found to be unimportant and the main effects model provided a reasonably good fit ($p > 0.1$).

From the estimates of the model parameters ($\hat{B}_1$, $\hat{B}_2$, $\hat{B}_3$), changes in relative risk (here approximated by the odds ratio) over time intervals, age categories, and sex groups are approximated. Persons exposed between 1975 - 77 carry 3.5 times the risk of pleural mesothelioma as those exposed between 1955 - 64. With progression across the age intervals: 45-54, 55-64, 65-74,...the individual risk of this disease is 1.5 times greater than in the preceding ten year age group. As one might expect, males have three times the risk of females. In assessing these results, the poor diagnostic confirmation outlined in Table 3 should be borne in mind.

The geographical distribution of cases of mesothelioma throughout Connecticut shows evidence of urban clusters in the five largest cities where 30% of the cases resided at the time of diagnosis. Since these locations have comprised from 37% to 20% of Connecticut's population (1940 - 1977), the suggested urban effect reduces to merely being a factor of population density.

These five large cities are also centers of Labor Market Areas (LMA) of which there are eighteen in the State. Application of the Cochran-Mantel-Haenszel Test of Average Partial Association (Landis et al., 1978) between these five LMA's and time of diagnosis (1935-77), while controlling for population age differences, suggests the following:

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1. Incidence trends (i.e., the manner in which an area's cases distribute over given time intervals) are primarily the same for four out of five LMA's tested. One region suggests a greater proportion of its cases appearing in more recent years than the others (p=.04). This is readily explicable by the substantial in-migration experienced by this one area and its increasing industrialization as opposed to the other highly industrialized areas whose populations have gradually decreased over time and are, therefore, more comparable for analysis.

2. With the exclusion of this one LMA, the others indicate a similar distribution of their cases of mesothelioma over time (p=.17)

This possibly implies similar patterns of asbestos exposure for the four large industrial regions of Connecticut. Until such time as the mesothelioma incidence has been adjusted for the previously mentioned diagnostic weaknesses and possible misclassifications and until the occupationally exposed cases have been identified, it is not possible to determine the role of environmental asbestos exposure, if any, in the remaining cases.

Summary

Medical, occupational, and demographic data were collected for 267 cases of malignant mesothelioma and other pleural tumors, their spouses, and 605 controls. Methodology was developed for classification of subjects into probable asbestos exposure categories on the basis of product and job descriptions. Although disease incidence rates exhibit a rapid increase from 1955 to 1977, there remains a serious question of diagnostic reliability. A case review will be undertaken.

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Figure 1. Age-adjusted Incidence Rates by Decade of Diagnosis, Pleural and Peritoneal Mesothelioma, Connecticut, 1935 - 1974

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Table 1. CTR Reported Cases of Mesothelioma and Other Pleural Tumors Diagnosed Between 1935 and 1977

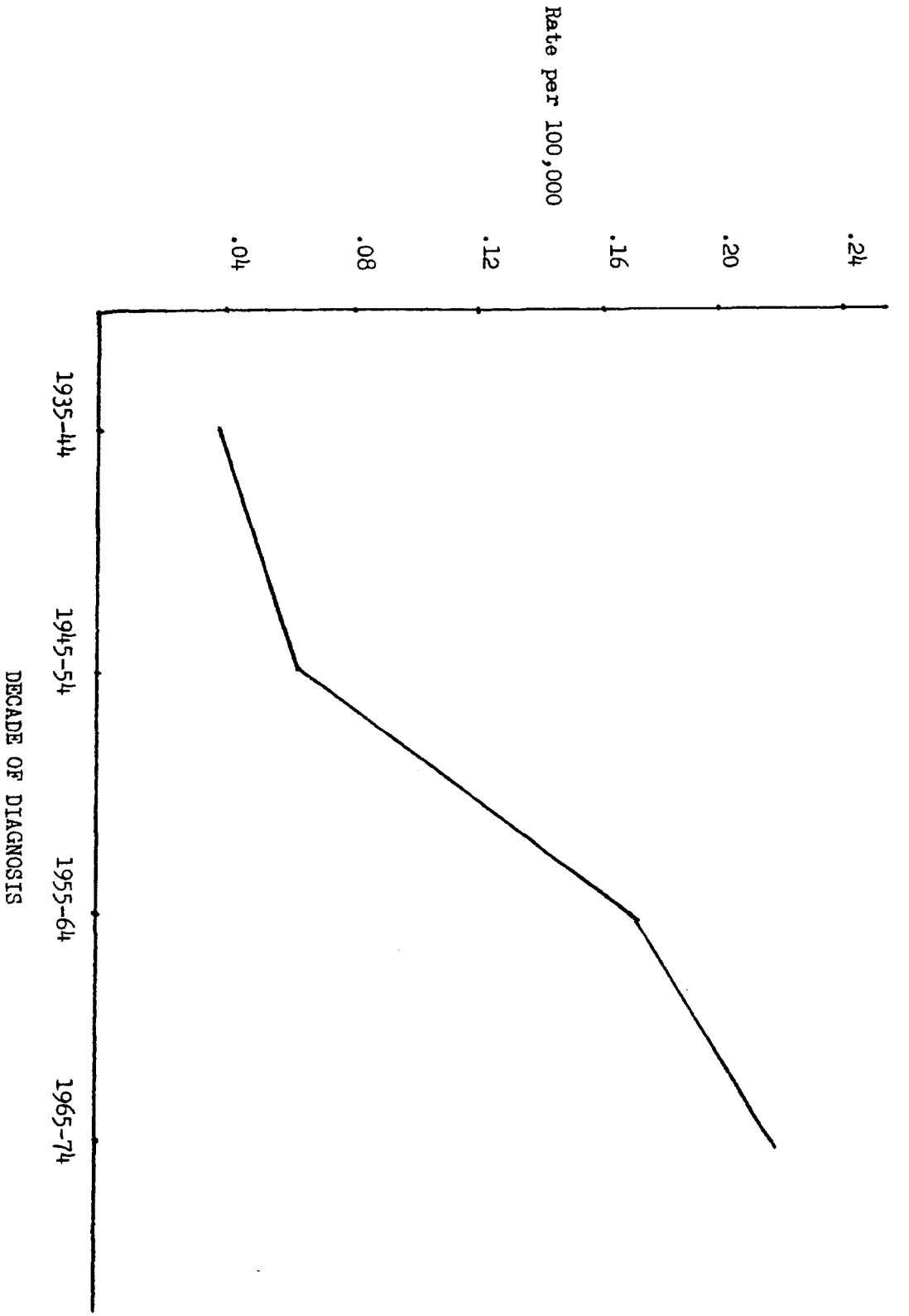
Table 2. Sources of Data and Variables

Table 3. Sex, Age and Diagnostic Characteristics of Malignant Mesothelioma Cases and Other Pleural Tumors Diagnosed in Connecticut, 1935 - 1977

Table 4 Diagnostic Evidence for Disease Groups

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Table 1.

Diagnosis	Period 1935-77		Period 1955-77	
Primary Pleural Tumors (T63)	185		151	
Mesothelioma (M905)		147		131
Other		38		20
Peritoneal Mesothelioma (T58, M905)	33		29	
Mesothelioma Elsewhere	49		35	
Site not pleura or peritoneum		37		27
Site unknown (T99)		12		8
	267	267	215	215

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Table 2.

Source	Population	Variables
Ct. Tumor Registry Tape & Paper File	Cases	Demographic, diagnostic, clinical, follow-up, employment
Vital Statistics Tape of Ct. Residents, matched with case surname, first name, residence, spouse's name	Spouses	Death Cert. No., cause of death, demographic
Death Certificates (1935-1978)	Cases, Controls, Spouses	Demographic, Cause of death, employment, spouse name
Manufacturing Directories of Connecticut 1957, 1966, 1973	Cases, Controls, Spouses	Product Descriptions for specific employers
Price and Lee City Directories	Cases, Controls, Spouses	Middle initial, spouse name, address, employment product descriptions for non-manufacturing employers
1970 U. S. Census industrial and occupational codes	Cases, Controls, Spouses	Job Codes, Industry Codes

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Table 3.

Diagnosis	No.	Male	Female	Mean Age	"Positive"[1] Hist.	Autopsy, if Dead
Pleural Mesothelioma	147	102	45	61	93%	40%
Pleural (not Mesothelioma)	38	24	14	62	71%	35%
Peritoneal Mesothelioma	33	20	13	58	94%	89%
Mesothelioma Other sites & site unknown	49	29	20	52	84%	33%
Total	267	175	92	59	88%	44%

1. SEER, 1976 Code/Field Number 19

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Table 4.

Diagnosis	No.	"Positive Histology"[1].	Autopsy
Peritoneal Mesothelioma	29	96%	88%
Other mesothelioma (not pleural or peritoneal)	35	88%	40%
Pleural tumors, not mesothelioma	20	85%	36%

1. SEER, 1976, Code/Field Number 19

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