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Title in CAPITAL LETTERS

Author names underlined

Laboratory where research was done, city, state and country

STUDIES ON SEA-SNAKE VENOMS: CRYSTALLIZATION OF ERABUTOXINS
a AND b FROM LATICAUDA SEMIFASCIATA VENOM. N. Tamiya* &
H. Arai**. *Chem. Dept., Tohoku Univ., Japan and Med. School,
Tokyo Med. and Dent. Univ., Tokyo, Japan.

.....
The toxic principles in the venom of the sea-snake
Laticauda semifasciata were separated into two components
by CM-cellulose chromatography and obtained in crystalline
forms by salting out with $(\text{NH}_4)_2\text{SO}_4$. They were named 'era-
butoxins a and b'. The homogeneity of each toxin was shown
by rechromatography, by disc electrophoresis, by ultracentri-
fuging, by toxicity measurements before and after repeated
crystallizations and by N-terminal amino acid analysis.
They had molecular weights of about 7000 as measured by

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(Abstract may be extended to fill the rectangle.)

A00443

MAY 16 1976

THE INFLUENCE OF OCCUPATIONAL AND ENVIRONMENTAL ASBESTOS EXPOSURE ON THE INCIDENCE OF MALIGNANT MESOTHELIOMA IN CT. J.C. Lewinsohn, J.W. Meigs, M.J. Teta, Ct. Cancer Epid. Unit, Yale Univ. New Haven, Ct. 06510, U.S.A.

Medical, demographic, and occupational data were collected for the 229 cases of malignant mesothelioma ascertained by the Ct. Tumor Registry between 1935 and 1977 and for a random sample of approximately 700 decedents (1935-1977) from the Division of Health Statistics of the Ct. State Dept. of Health. Sources of information include the files of the CTR, death certificates, and city directories. A vital statistics tape of Ct. decedents was utilized to match spouses of cases. An asbestos-product listing with its associated industrial and employer codes has been created from the occupational histories of cases and controls. A substantial increase in registrations of mesothelioma over this 42 yr. period is evident with 85% of the cases enumerated after 1954. Changes in patterns of diagnosis and the possibility of misclassification are suggested. This hypothesis is supported by: a) only 40% of cases have ^{autopsy} diagnostic confirmation; b) discriminant function analysis performed on the 56 confirmed cases of pleural mesothelioma and the 20 cases of primary pleural tumors (not mesothelioma) with respect to age, sex, survival, stage, and number of tumors yielded 59% misclassification. Geographical clustering is evident in certain industrial cities and Labor Market Areas. [Final results will include case-control comparisons with respect to occupational asbestos exposure, an analysis of the health status of spouses of these cases, and the occupational histories of spouses of non-occupationally exposed cases.]

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The CTR has identified 329 cases of malignant mesothelioma of the pleura (147) and peritoneum (33), other mesos (49) and 38 other pleural tumors not mesothelioma which were diagnosed in the state between 1935 and 1977.

Medical, demographic and occupational data have been collected for the cases and for their respective spouses.

Of all cases diagnosed as pleural mesothelioma, 21% (31) had unknown staging and 60% did not have an autopsy. ~~The 49 cases of mesothelioma of other or unknown site have a~~ The question of the accuracy of classification of cases of malignant pleural tumors into mesothelioma and other pleural tumors naturally arises.

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The geographical distribution of cases of mesothelioma throughout CT 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 20-37% of CT'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 of which there are 18 in the State.

Summary

A00451

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

by

H. C. Lewinsohn

J. W. Meigs

M. J. Teta

A00452

UCC 004888

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 $30\text{ng}/\text{m}^3$, 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 229 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), 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-0 (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 exposure 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 criteria 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~~^{3.2} per million. 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.

A00460

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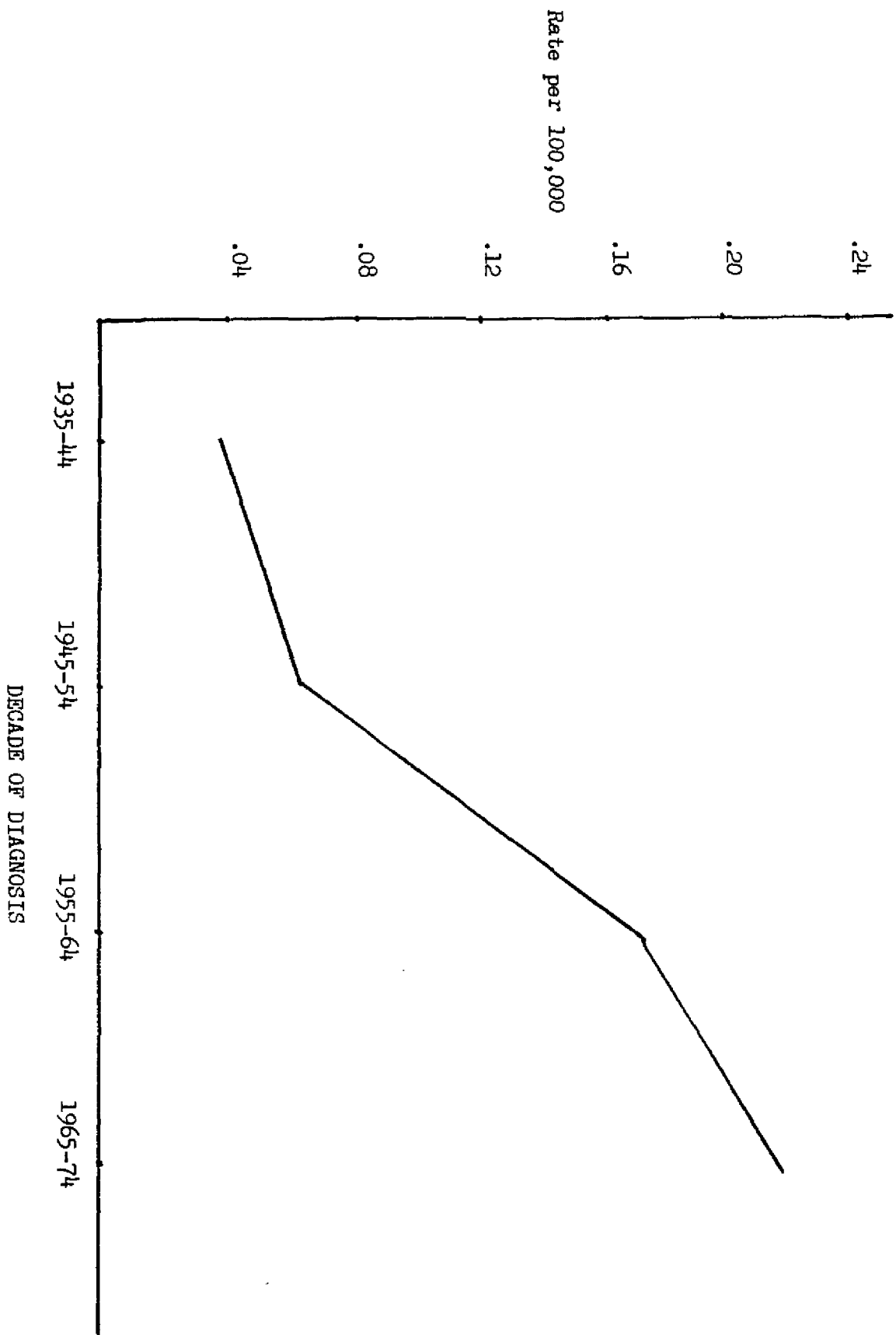
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Figure 1. Age-adjusted Incidence Rates by Decade of Diagnosis,
Pleural and Peritoneal Mesothelioma, Connecticut, 1935 - 1974

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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.

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

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Table 2.

<u>Source</u>	<u>Population</u>	<u>Variables</u>
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

Table 3.

<u>Diagnosis</u>	<u>No.</u>	<u>Male</u>	<u>Female</u>	<u>Mean Age</u>	<u>"Positive"¹. Hist.</u>	<u>Autopsy, if Dead</u>
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.

<u>Diagnosis</u>	<u>No.</u>	<u>"Positive Histology"¹</u>	<u>Autopsy</u>
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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