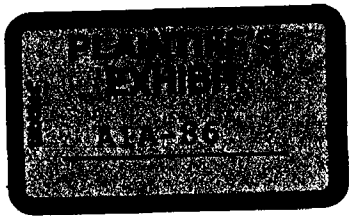

STATE OF FLORIDA

COUNTY OF _____

AFFIDAVIT OF PHILIP E. ENTERLINE

PHILIP E. ENTERLINE being duly sworn deposes and says:

1. I reside at 37 St. Clair Drive, Pittsburgh, Pennsylvania 15228.

2. I am a Professor Emeritus of biostatistics at the University of Pittsburgh.

3. My field of specialty is biostatistics.

4. I have reviewed all the medical literature published on asbestos and cancer during the period 1934-1964.

5. In 1978, I prepared a book entitled Asbestos and Cancer which summarized that review.

6. That book was updated in 1980.

7. The review was conducted at the request of the Asbestos Information Association ("A.I.A.").

8. As part of this review, I read an article entitled "Experimental Studies of Asbestosis" published in the Archives of Industrial Hygiene and Occupational Medicine, Volume 3, dated 1951.

9. This article was authored by A. J. Vorwald, T.M. Durkin and P.C. Pratt ("Vorwald Article").

10. As a result of my review of the published literature, I concluded that in the United States there was a twenty-year lag in the acceptance of the causal connection between asbestos exposure and cancer.

11. I have recently reviewed a document entitled "Outline of Proposed Monograph on Asbestosis" written by Dr. Leroy Gardner ("Monograph Outline"). (A copy of which is attached as Exhibit 1.)

12. This Monograph Outline contained information not contained in the Vorwald article.

PREFACE

In the Spring of 1976 I was asked by the Asbestos Information Association if I might have a student or students who, under my direction, could do a literature review for the purpose of preparing a history of the development of knowledge about the health effects of asbestos. The idea was to determine how, at different points in time, the medical profession interpreted the research literature then available to it. I saw an important area for research here in regard to the relationship between asbestos and cancer, an area of interest to me since 1961 when I first became involved with occupational health. At that time I had joined the Division of Occupational Health of the U.S. Public Health Service — a predecessor of the present National Institute of Occupational Safety and Health. One of my first projects was to develop epidemiological data with regard to any relationship between asbestos dust exposure and lung cancer in the United States. The basis for this was an internal document that reviewed the literature and posed the question, "Does asbestosis predispose to lung cancer?"* I assumed at that time that this was an important but unanswered question. Since then, many of my colleagues have indicated to me that this issue was settled long before 1961. I, therefore, welcomed the opportunity to carry out a project aimed at seeing what were the attitudes and opinions about this and when, in fact, did the debate really end. I was fairly sure this was no later than 1964 when an international meeting was held in New York City on the biological effects of asbestos in which I participated.

The project was carried out in three stages. First, two of my students collected and read all of the literature referenced in the Index Medicus and elsewhere for the years 1934-1965. This included building on references in each article found. In addition, they examined every issue of Lancet, the British Medical Journal, and the Journal of the American Medical Association for these years for any editorials or communications which mentioned asbestos and cancer. Also, all available textbooks on occupational medicine, toxicology, or pulmonary cancer were examined. An abstract of each article was prepared and where attitudes were expressed on the question of does asbestos cause cancer, that section of the article was zeroxed for subsequent study. The Asbestos Information Association had all foreign language articles translated in their entirety.

The second stage included classifying each article or writing as to whether the author thought asbestos definitely caused cancer, possibly caused cancer, or felt the issue was unproven or that asbestos did not cause cancer. Classifying was done separately for lung cancer and for mesothelioma. For those writers who believed asbestos definitely or possibly caused lung cancer, an additional classification was made as to whether they believed asbestosis was or was not a prerequisite. Two reviewers independently classified the material by using the zeroxed sheets prepared by my student assistants or by reading entire articles where necessary. There were surprisingly few disagreements. These were worked out by discussion, and in some cases, by compromise.

In the third stage, I prepared a narrative literature review in which I tried to link the literature together to see who was quoting who, who was given credit for discovering the relationship between asbestos and cancer, what articles and reports stimulated others, and to trace individual writers' attitudes and opinions over time. In this review, I tried not to evaluate the data presented or criticize what was said about it, since my objective was to see what people thought about what they were seeing at the time, rather than what I saw in the data. Nor did I try to judge the writers, neither in terms of their technical or professional competences nor in terms of any biases or motives they might have had. I did at times comment, however, on their knowledge of the literature.

While my major focus was on asbestos and lung cancer, by 1960 I found I could not ignore the mounting volume of literature on asbestos and mesotheliomas and, at that point, I briefly summarized what had gone before and included subsequent writings on mesothelioma in my narrative. In addition, I addressed directly the question of when the relationship between asbestos and cancer actually was accepted in the United States. This represents only my own view. Obviously, my feelings about the role epidemiologic observations played in the acceptance of a relationship is a central issue here.

Among the things I gained from this research was a deep respect for the clinicians and pathologists who contributed to the early literature. They showed remarkable insight into the meaning of their observations, and the logic of their conclusions was far more reasoned than I had expected. I became far less sure that the sharp distinction made by many writers between epidemiological as contrasted with clinical-pathological observation served as a useful purpose. Even a single case report is a kind of epidemiologic observation, since the basis of such reports is usually a feeling, unexpressed, that the case is somehow aberrant for a human population.

*"Ad hoc meeting to discuss the status of knowledge concerning the effects of exposure to asbestos dust on health" for internal distribution only, May 19, 1961.

Asbestos and Lung Cancer

As a method of summarizing how at different points in time, the writers were interpreting the literature and observations then available on the subject of asbestos (or asbestosis) and lung cancer, I classified the impression about the relationship between asbestos and lung cancer gained from reading each of the 104 articles as: (1) asbestos definitely causes lung cancer, (2) asbestos possibly causes lung cancer, and (3) the relationship is unproven or asbestos does not cause lung cancer. For the first two categories, a subdivision was made as to whether I felt the writer thought asbestosis must or must not be present.* Entirely independently, I.T.T. Higgins kindly classified the same articles in the same manner, using the same material.** Where disagreements occurred between Higgins and myself, they were discussed and resolved. The end product appears in Table A. This table also indicates the type of article, whether the original article was in some language other than English, and whether the author conditioned this opinion on type of asbestos fiber. In a few cases involving negative animal experiments, the paper has been put under the unproven column even though the writer may have personally believed in an association between asbestos and cancer (eg: Hueper 1955). Generally, however, where original data were presented, the writer's opinion coincides with what the data seem to show. Table A provides sufficient information to locate any single writing in the bibliography. Where textbooks had chapters written by other than the author or editor, the name of that writer appears in parenthesis after the name of the textbook author or editor.

Data in Table A clearly parallels the narrative in the preceding section. A shift in opinion can be seen with the passage of time up to the year 1942. A retreat from a definite decision in 1956 can clearly be seen, and there appears to be not much movement toward the "definitely" column until 1965. The decade 1956-1965 seemed to be one of uncertainty with little change in the position of individual writers. In fact, with the exception of Bohlig, individual writers rarely changed their position on the subject.

Nordmann was the first to make up his mind, followed closely by other German writers. The American, Hueper, was not far behind. Gloyne and Lynch never moved to the "definitely" column, while even as late as 1965 here is an entry in the unproven column. Textbook writers were among the last to acknowledge a relationship, whereas writers of editorials were among the first. Note, for example, that after 1951 there are no editorials in the nproven column but five textbooks.

Starting in 1955 there was a shift to the notion that asbestos can cause lung cancer without asbestosis, lthough this issue was somewhat clouded with the introduction of the idea of microscopic asbestosis — that is, sbestosis that causes no clinical signs or symptoms but which was seen at autopsy. English language articles were early in the majority after WWII.

sbestos and Mesothelioma

Rare diseases, like malignant mesothelioma, are relatively easy to identify with occupational exposure so at many of the problems in linking lung cancer with asbestos exposure did not apply here. Those who dealt with :sothelioma did not demand epidemiological evidence. Their main problem was in agreeing that the tumor :ually existed and how it should be defined. Pleural and abdominal cancers were sometimes mentioned in ation to asbestosis but until the report by Wagner, Sleggs and Marchand in 1960, this was not a major focus of earch.

A review of opinions similar to that for lung cancer was done only by myself with the results shown in ble B. Few authors ever expressed doubt about the relationship between this rare tumor and asbestos exposure l by 1953, the issue was fairly well resolved. A flood of articles following the appearance in 1960 of the paper by gner, Sleggs, and Marchand is apparent. In 1965, not a single writer expressed doubts about the relationship. ny did condition their opinions on the type of fiber involved, however, believing that crocidolite asbestos was st likely to be related to mesothelioma.

: Periods in Knowledge and Attitudes

In this literature review, I see five distinct periods in the development of knowledge and in attitudes about stos and lung cancer from the American point of view: The Pre-World War II period, characterized by a ral rejection of a relationship; The Period 1939-45; characterized by a sharply divided opinion on the subject 'een German writers and the rest of the world; The Post-War World War II Period 1946-55, in which there was idual acceptance of a relationship first in England and then in America; The Period 1955-63, during which

e of my student assistants (N.S.) checked and often improved my classification.

Higgins is a Professor of Epidemiology, School of Public Health, University of Michigan.

TABLE 8

Opinions of Authors Publishing 1933 - 1965
Regarding the Causal Relationship Between
Asbestos and Mesothelioma

Year	Definitely Causes Mesothelioma	Possibly Causes Mesothelioma	Unproven or Does Not Cause Mesothelioma
1933			Gloyne [O]
1934			Wood [O]
1943	*Wedler [R] *Wedler [O]		
1949		Doig [R]	
1951			*Behrens [O, a]
1952		Smith [R]	Smith (Cartier) [R]
1953	*Weiss [O]		
1954	*Leicher [O]		
1955		Bonser [O]	
1956		*Bohlig [R]	
1958		*Van der Schoot [O]	
1960	Schilling (Gilson) [T, f] *Konig [O]	Keal [O] Wagner [O] Fleming (Schepers) [T, f]	
1961	Sleggs [O] Frenkel [O]	Heard [O]	Knox [C]

TABLE B (cont.)

Opinions of Authors Publishing 1933 - 1965
Regarding the Causal Relationship Between
Asbestos and Mesothelioma

Year	Definitely Causes Mesothelioma	Possibly Causes Mesothelioma	Unproven or Does Not Cause Mesothelioma
1962	McNutty [O, f] Thompson [O] Wagner [O, a] McCaughey [C] Enticknap [C]	Smither [C] Hunter [T]	
1963	Leatheart (Smither) [R, f] Mancuso [O] Walters [R] Thomson [C] Lawson [C] Lawson [C]	Castleman [O] Thompson [O]	
'64	Buchanan [O, f] Enticknap [O] Hourihane [O] *Noeninckx [O] Oettle [O] Owen [O] Smith [O, a]	Gafafer [T] Murray [R, f] Elwood [O, f] Fowler [O] Selikoff [O] Brit. Med. J. [E, f]	Dis. of Chest [R, f]
	Dutra [O, q] Elmes [O] Hinson [R] Selikoff [O] Smith [O, a, f] Steel [O] *Anspach [O] N. Eng. J. M. [E] Can. M.A.J. [E,f] IUAC [E]		

cancer in a group of asbestos-exposed workers in England greatly exceeded that in a comparable group in the general population. This marked an end to a period when conclusions were based largely on pathological and clinical observations, and opened the door for contributions by biostatisticians and epidemiologists. It probably also set back acceptance of a relationship between asbestos and cancer in the United States by another decade.

The epidemiologists demanded epidemiological evidence. In 1956, for example, Hammond and Machle stated that with regard to a relationship between asbestos and lung cancer ". . . there are at present too few cases and too little epidemiologic data to establish a significant relationship." In 1958, the Committee on Occupational Cancer of the AMA council on Industrial health concluded that individual case reports contribute little to an understanding of occupational cancers and that "specific increases in age, sex, and site-specific cancer incidence above normal incidences for the same age, sex, and site represent the only reliable evidence for the existence of an occupational cancer hazard."

The first two epidemiological studies of this kind on asbestos and lung cancer in North America in 1958 and 1960 were considered to be negative. Thus, as late as 1961, it could be said that "there is no epidemiological evidence [of an association between asbestos and lung cancer] among American workers."

So what ended the debate in the United States? Probably three things: positive epidemiological studies in the United States in 1963 and 1964; a widely read 1960 study that showed that asbestos was associated with a rare tumor — malignant mesothelioma; and experimental evidence in 1962 and 1964 that asbestos had carcinogenic properties. So the kind of evidence demanded by Bridge and Henry, and which would have satisfied Gloyne, was finally developed 30 years after Gloyne made his initial observations, and over two decades after the acceptance of a relationship between asbestos and lung cancer in Germany.

Clearly, the matter involved a question of what is acceptable and conclusive evidence. Perhaps a special set of rules are needed for relationships like asbestos and lung cancer where some other biologic response, such as asbestosis, can be used as evidence of significant exposure and the rules proposed by Bridge and Henry were not appropriate after all. Many writers were convinced of a relationship long before epidemiological and experimental evidence was available. Aside from the high incidence of lung cancer in asbestotics, they were impressed by the predominance of cancer in the lower lobes, the time lapse between exposure and disease, the high incidence in females, and the young age of many of the cases seen. Moreover, there were reasonable theories regarding mechanisms by which asbestos could cause cancer. These arguments were seldom acknowledged by the epidemiologists and biostatisticians.

In any event, the issue was definitely settled for the United States at a conference on the Biologic Effects of Asbestos held in New York City in 1964. At that conference additional epidemiologic evidence was presented, and of 20 papers presented in which an opinion was expressed, none dissented from the view that asbestos is a cause of cancer.