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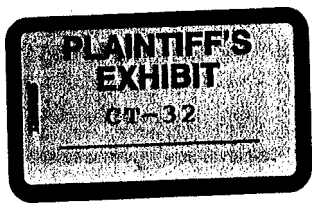

James J. La Penna
513 Stahlman Building
Nashville, Tennessee 37201

Dear Mr. La Penna:

You are correct in surmising that my statements are based on the medical literature. Enclosed are two examples. If you care to read further, there are 27 references in the 1966 Cumulated Index Medicus which link asbestos with cancer, and an additional 14 such references in the 1965 Cumulated Index Medicus. They are listed under the heading "Asbestosis."

The relationship of asbestos exposure to cancer of the lung has been well known for several years, being listed on page 708 of Rubin's Thoracic Diseases published in 1961. The original relationships were noted only in people working within industries using a lot of asbestos. About six months ago, however, in a pathology conference we discussed a patient who died of a mesothelioma (a malignant tumor) and was found to have asbestos fibers associated with the tumor despite never working in industries associated with asbestos exposure. Our pathologist stated he was seeing more of these tumors than ever before, and in people not working in areas of known exposure. We discussed the fact that asbestos was being put into many things these days, and that somehow it seemed to be involving more people than just miners or manufacturers.

When I saw that water pipe was being made from asbestos, it really upset me. The Food and Drug Administration has taken drugs off the market for producing tumors only in experimental animals. Yet, somehow, an agent known to cause cancer in humans has been allowed to contaminate drinking water. The only possible defense is that the amount of asbestos each person gets from the water will be so small that only a very rare, susceptible, individual will develop cancer. Do you want to gamble on whether you or your family are the susceptible ones — just to save a little money? I do not.

Respectfully,

James D. Snell, Jr., M.D.

JDS:jd
Enclosures

SUMMARY

Two methods of measuring the resistance or sensi[illegible] of *Staph. pyogenes* to mercury salts have been [illegible]pared. Little difference was noted, but the agar [illegible] method is preferred as it is technically easier to [illegible]form. Resistance to mercury appears to be associ[illegible] with antibiotic resistance, but no difference in [illegible]ence between the two groups was demonstrated [illegible] means of intracerebral injection of mice. The [illegible]ercury test may have a place as a screening procedure [illegible] view of the relationship between the resistance to [illegible]ercury and to antibiotics.

We are grateful to Miss Thibeaudeau and Mrs. J. Small for their technical assistance.

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SPECIAL REPORT

Asbestos and Cancer

The Report and Recommendations of a Working Group Convened Under the Auspices of the Geographical Pathology Committee of the International Union Against Cancer

EDITOR'S NOTE—In October 1964, the New York [illegible]ademy of Sciences sponsored an international meet[illegible] on the biological effects of asbestos. Following [illegible] meeting, some 40 delegates from Australia, Canada, [illegible]land, France, Germany, Great Britain and Ireland, Italy, South Africa and the United States were invited to study the vast amount of information which had been presented with a view to the organization of an international study of asbestos and cancer. The terms of reference of this Working Group covered three major aspects of the problem: epidemiology, pathology and experimental pathology, and physics and chemistry.

The findings of the Working Group and their recommendations arising from these studies are recorded, in slightly abridged form, in the following report.

THE ASSOCIATION OF EXPOSURE TO ASBESTOS DUST AND CANCER

THE main types of asbestos of commercial interest are amosite, anthophyllite, chrysotile, crocidolite and tremolite. There is evidence of an association between exposure to asbestos and malignant neoplasia. This has been established mainly on information from Germany, Italy, South Africa, the United Kingdom and the United States of America.

The types of tumours which have been shown to be associated with exposure to asbestos dust are:

1. Carcinoma of the lung.
2. Diffuse mesothelioma of the pleura and peritoneum.

There is [illegible]e suggestion of an association also with gastrointestinal carcinoma, and possibly with ovarian tumours.

The latent period between first exposure to the dust and detection of the related tumours is many years, usually 20 or more. Instances up to 60 years have been reported. For this reason, further cases of these associated tumours will be expected to occur for many years to come, even if dust exposures are now greatly reduced.

Present evidence indicates that the associated carcinomas of the lung are not limited to exposure to any one type of asbestos fibre. However, further investigations are urgently needed to establish whether the degree of risk is importantly related to the type of fibre inhaled.

In the case of mesotheliomas evidence from several countries suggests that exposure to crocidolite (blue fibre) may be of particular importance, but it cannot be concluded that only this type of fibre is concerned with these tumours, and further investigation of this problem is needed.

Certain types of asbestos fibres in the virgin state have been found to contain oils, waxes and other organic matter. In addition, asbestos fibres readily absorb hydrocarbons subsequent to mining. Small or trace amounts of various elements such as nickel and chromium are also found associated with some types of fibre. The possible role of such associated materials in the development of tumours following exposure to asbestos dust is not yet clear.

These findings, when considered in relation to the great increase in the use of asbestos for many purposes in all countries, suggest that a more serious and widespread hazard from exposure to asbestos dust may exist than is widely appreciated.

NEOPLASIA AMONG INSULATION WORKERS IN THE UNITED STATES WITH SPECIAL REFERENCE TO INTRA-ABDOMINAL NEOPLASIA

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Before presenting the findings in our study of insulation workers, we would like to discuss briefly some considerations which we believe to be important.

Malignant neoplasms produced by exposure to chemical agents or ionizing radiation typically have a long latent period. That is to say, there is a long delay between first exposure and the appearance of the neoplasm. In the case of carcinogens which can be eliminated from the body, repeated contacts over a long period of time may be required. However, in the case of agents which are not eliminated, exposure of the tissues is continuous from time of first exposure. The probability that neoplasia will occur and how soon it appears generally depend upon the degree of exposure.

Now let us consider the effects of exposure to an agent which can produce neoplasia but which can also produce some other type of disease. Here we are dealing with the problem of competitive risks. If exposure results in death from some other disease within ten or fifteen years, then, because of the long latent period, it is very unlikely that neoplasia will result from such exposure.

In these situations, the outcome depends in part upon the time required to produce the other disease in relation to the time required for the development of neoplasia; and this in turn depends upon the degree of exposure. Of equal importance is whether or not the other disease can be cured, or death delayed.

An historical review of the literature from this point of view is most interesting.

All of the early reports apparently concerned workers who were very heavily exposed to asbestos dust. This was long before the development of the sulfa drugs and antibiotics. Pulmonary diseases including tuberculosis and pneumonia were among the leading causes of death. Life expectancy in the general population was far shorter than it is today, and a relatively small percentage of people lived to an age where the incidence of cancer becomes high.

In 1906, Auribault reported the results of what was probably the first study of mortality among asbestos workers.[1] His account is interesting.

In 1890 an asbestos spinning mill and weaving factory was established in the neighborhood of Conde-sur-Noireau (Calvados). During the first five years of operation there was no artificial ventilation and the employees were heavily exposed to dust from the looms. According to Auribault, fifty workers died during this five-year period. Furthermore, the director, previously owner of a cotton mill, had recruited seventeen of his former employees and "sixteen of them were wiped out by the Chalicosis."

In 1918, Hoffmann was able to present some data from the industrial experience of the Prudential Life Insurance Company.[3] From 1897 to 1914 there were 13 deaths of asbestos workers and three of these were attributed to pulmonary tuberculosis. It is of interest that nine of these 13 asbestos workers died under the age of 44. This is in contrast with a much older average age at death reported for potters, molders, marble workers, and stone workers. Hoffmann notes that "in the practice of American and Canadian life insurance companies, asbestos workers are generally declined on account of the assumed health-injurious conditions of the industry." He also quotes E. L. Collins (Annual Report of the Chief Inspector of Factories and Workshops for England and Wales for 1910) as having found five deaths in people having pulmonary tuberculosis in five years among a staff of under 40 workers in a factory weaving asbestos.

Since Hoffmann's time, many authors have reported findings in series of cases of asbestosis. Until after 1940, emphasis was placed upon the role of secondary infections, particularly pulmonary tuberculosis and bronchopneumonia. For example, Merewether[3], writing in 1933 commented:

> Usually, the fatal issue is determined by the onset of some acute infection with which the remaining undamaged tissue is quite unable to cope: this is commonly a low grade bronchopneumonia.

The same year, Gloyne[4] stated that, "the writer has so far only seen one asbestos patient recover from bronchopneumonia."

In two series of cases reported by Wood and Gloyne[5] in 1934 and Stone[6] in 1940, bronchitis, bronchopneumonia and pulmonary tuberculosis were the commonest terminal complications of asbestosis. However, Wood and Gloyne found two lung cancers and one cancer of the pleura in 26 deaths of patients with asbestosis.

With the passage of time, pulmonary infections were found less frequently and lung cancer was found more frequently in cases of asbestosis. We will not take the time to review the more recent literature, a large part of which was written by people present at the Conference and adequately covered by other papers in this Annal. It is sufficient to say that since the advent of the antibiotics, workers have generally been saved from death due to infectious pulmonary diseases resulting as a complication of asbestosis. Thus they began to live long enough for the neoplastic effects of exposure to asbestos to become manifest.

Our study differs from the early studies in two important respects:

TABLE 1
OBSERVED AND EXPECTED NUMBER OF DEATHS AMONG 632 ASBESTOS WORKERS EXPOSED TO ASBESTOS DUST 20 YEARS OR LONGER

CAUSE OF DEATH	Years				Total
	1943-1947	1948-1952	1953-1957	1958-1962	1943-1962
Total, all causes					
Observed (asbestos workers)	28	54	85	88	225
Expected (US white males)	39.7	50.8	56.6	54.4	203.5
Total cancer, all sites					
Observed (asbestos workers)	13	17	26	39	95
Expected (US white males)	5.7	8.1	13.0	9.7	36.5
Cancer of lung and pleura					
Observed (asbestos workers)	6	8	13	18	45
Expected (US white males)	0.8	1.4	2.0	2.4	6.6
Cancer of stomach, colon, and rectum					
Observed (asbestos workers)	4	4	7	14	29
Expected (US white males)	2.0	2.5	2.6	2.3	9.4
Cancer of all other sites combined					
Observed (asbestos workers)	3	5	6	7	21
Expected (US white males)	2.9	4.2	8.4	5.0	20.5
Asbestosis					
Observed (asbestos workers)	0	1	4	7	12

(1) The subjects had very light and intermittent exposure to asbestos dust as compared with the daily heavy exposure of subjects included in the old studies; and (2) We are reporting deaths which occurred after 1942; that is, after antibiotics became available for the treatment of pneumonia and after death rates from tuberculosis had been greatly reduced in this country. It also differs from most other studies in that we were able to trace an entire group of workers including those who had retired and those who had left the trade.

The data we are presenting here is an extension of data we published last year.[1] Therefore, we will start by briefly reviewing our first report, the results of which are summarized in TABLE 1. The data shown here are confined to the experience of 632 men. They composed the total membership of New York Local 12 and Newark Local 32 of the International Association of Heat and Frost Insulators and Asbestos Workers as of January 1, 1943. All of them were traced through December 31, 1962 and 255 of them died during that period of time. Most of them had been first exposed to asbestos dust at least 20 years prior to 1943. The remainder passed the 20-year point between 1943 and 1962; and we counted their experience only after they reached this point.

TABLE 1 shows the total number of deaths and the number of deaths from selected causes during each of four successive 5-year periods. For comparison, we show the number of deaths which would have been expected among these asbestos workers had their age specific death rates been exactly the same as those reported for all white males in the United States during the same intervals of time.

First note the total number of deaths. During the first five-year period, fewer deaths occurred among the asbestos workers than would have been expected on the basis of general U. S. death rates. This is accounted for by the fact that all of the workers were actively at work in 1943; and seriously ill men are unemployable. Thus their total death rates were low. This selective effect gradually wore off. During the last 5-year period, 88 of the workers died compared with 54.4 expected. During the entire 20-year period, 255 asbestos workers died compared with 203.5 expected.

Now observe the number of deaths from cancer of the lung and pleura. During every 5-year period, far more than the expected number of asbestos workers died of this cause. Altogether there were 45 deaths from cancer of the lung and pleura compared with 6.6 expected; a mortality ratio of nearly 7 to 1.

To our surprise, these asbestos workers also had extremely high death rates attributed to cancer of the stomach, colon and rectum. The observed number of deaths from these cancers was 29 compared with an expected 9.4; a mortality ratio of 3 to 1.

It is of interest that out of a total of 255 deaths only 12 were attributed to asbestosis.

As previously mentioned, our first report was based upon the records of 632 men who were members of the two locals on December 31, 1942. An additional 890 men joined between January 1, 1943 and December 31, 1962. Thus a total of 1,522 were in the two locals at some time between 1943 and 1962. We have traced all of them through August 1964 and Dr. Selikoff had medically examined most of those who were living as of the end of 1962. Of the 1,522 men, 264 were dead as of January 1, 1963 and an additional 43 died between January 1, 1963 and August 31, 1964. The findings shown in TABLE 2 are based upon these 307 deaths.

TABLE 2
N. Y. C. ASBESTOS INSULATION WORKERS
307 CONSECUTIVE DEATHS JANUARY 1, 1943 – AUGUST 31, 1964

Total deaths	307	
All neoplasia	124	40.4%
Bronchogenic carcinoma	53	17.3%
Mesothelioma	10	3.3%
G.I. carcinoma	34	11.1%
Upper respiratory	6	1.9%
Bladder	4	1.3%
Generalized carcinomatosis	7	2.3%
All other	10	2.2%
Asbestosis	17	5.5%
All other causes	166	54.1%

Of the 307 deaths, 124 (40.4 per cent) were attributed to cancer, 17 (5.5 per cent) were attributed to asbestosis and 166 (54.1 per cent) were attributed to various other causes. The Table shows the 124 neoplastic deaths classified by type of neoplasm. Fifty-three (or 43 per cent of the cancer deaths) were attributed to bronchogenic carcinoma. Ten were attributed to mesothelioma, 34 to gastrointestinal carcinoma, 6 to upper respiratory cancer, 4 to cancer of the bladder, 7 to generalized carcinomatosis and 10 to various other cancers.

In studies of this type, accuracy of diagnosis is of prime importance. Of the 53 deaths attributed to bronchogenic carcinoma, 34 occurred in

hospitals. In 18 the diagnosis was based upon post-mortem examination and in 15 the diagnosis was based upon histologic examination of operative specimens. The remaining 20 were based upon clinical evidence or information reported on death certificates. J. Churg has personally examined specimens from 15 of these 53 cases.

J. Churg has also personally examined sections on all of the 10 deaths attributed to mesothelioma. Four of the 10 were pleural mesotheliomas and six were peritoneal mesotheliomas.

Of the 34 deaths attributed to gastrointestinal cancer (cancer of the stomach, colon and rectum plus one cancer of the esophagus), 20 occurred in hospitals. Six of the diagnoses were based upon post-mortem examination, 19 were based upon operative specimens and nine were based upon less reliable evidence. J. Churg personally reviewed sections from 12 of these cases.

Of the 27 other cancer deaths, 16 occurred in hospitals. Fifteen of the diagnoses were based upon autopsy or operative specimens, and 12 were based upon less reliable evidence.

Of the 17 asbestosis deaths, 6 diagnoses were based upon post-mortem evidence and 11 upon clinical evidence only.

In most prospective epidemiological studies, the investigators are forced to be content with information from death certificates plus a little additional information. We think it fair to say that in this study we were able to obtain a reliable diagnosis on cause of death in the majority of cases. This does not imply that all of the cases were correctly diagnosed. For example, the diagnosis is certainly open to question in those cases where it was based upon clinical evidence or death certificate information only. This is particularly true in the case of deaths attributed to generalized carcinomatosis (with primary site unknown), and deaths attributed to stomach cancer or liver cancer. Furthermore, it is not unlikely that a few mesotheliomas were missed. Indeed, in addition to the 10 deaths attributed to mesothelioma there is one lesion which looks suspiciously like this disease, but the diagnosis is not certain.

Taken at face value, it would appear that asbestos workers have an abnormally high risk of dying of gastrointestinal cancer. However, we will refrain from drawing conclusions on this matter at the present time.

Returning to the subject of pulmonary neoplasms, TABLE 3 shows the lapsed time from onset of exposure to time of death of 57 of our subjects who died of cancer of the lung and pleura. (A few recent cases are not included here.) Not a single one of these deaths occurred in less than 20 years after first exposure. The majority did not occur until after 30 years and many did not occur until after 40 years.

Obviously, light exposure to asbestos dust does not lead rapidly to pulmonary neoplasia. Equally obviously, this disease is unlikely to appear