# Asbestos Exposure, Smoking, and Neoplasia

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**Asbestos insulation workers, as a group, have a high risk of dying of bronchogenic carcinoma (about seven or eight times expected). We have observed 370 such workmen from Jan 1, 1963 to April 30, 1967. Our findings indicate that asbestos exposure alone is not the entire explanation. Of 87 noncigarette smokers, none died of bronchogenic carcinoma. Of 283 workmen with a history of regular cigarette smoking, 24 died of bronchogenic carcinoma, although only three were expected to die of this disease. Calculations suggest that asbestos workers who smoke have about 92 times the risk of dying of bronchogenic carcinoma as men who neither work with asbestos nor smoke cigarettes. We conclude that asbestos exposure should be minimized, that asbestos workers who do not smoke should never start, and that those now smoking should stop immediately.**

In 1964, we reported on deaths occurring between Jan 1, 1943, and Dec 31, 1962, among 632 members of the International Association of Heat and Frost Insulators and Asbestos Workers.[1] All of these men had been occupationally exposed to asbestos dust for many years. Their death rate from lung cancer was found to be 6.8 times as high as that reported for the general white male population of the United States during the same years, with age taken into consideration. Three of the men died of diffuse pleural mesothelioma and one died of a neoplasm histologically suggestive of peritoneal mesothelioma. This was of interest since mesothelioma is a very rare disease in the general population but is reported to be associated with exposure to asbestos dust.[2] In addition, their death rate from cancer of the stomach, colon, and rectum was higher than expected; but this may have been due to chance, the number of such deaths being small. During the latter part of the study, we obtained information on the smoking habits of most of the survivors, but we could not obtain reliable information on the smoking habits of those who had died at an earlier date. Therefore, we could not at that time investigate death rates in relation to smoking habits and exposure to asbestos dust which were considered both separately and jointly.

There is abundant evidence that cigarette smoking leads to a high rate of death from lung cancer in the absence of occupational exposure to asbestos dust.[3-7] Our findings outlined above suggested (but did not prove) that exposure to asbestos dust may lead to a high rate of death from lung cancer in the absence of cigarette smoking. If the latter be so, then the combined effect of both types of exposure might or might not be equal to or greater than the sum of the two effects. On the other hand, it was possible that exposure to asbestos dust increases the risk of lung cancer among cigarette smokers but does not lead to lung cancer among nonsmokers.

The present study was undertaken primarily to investigate these possibilities. In addition, we wished to obtain more information on the occurrence of mesothelioma and gastrointestinal cancer among asbestos workers.

## Material

From records of New York Local 12 and Newark, N.J., Local 32 of the International Association of Heat and Frost Insulators and Asbestos Workers, a list was made of every man who was a member of either one of these locals on Dec 31, 1942, or who joined between that date and Dec 31, 1962. No one was omitted regardless of his subsequent work history.

Personnel data from union records indicated that of the 632 on the union rolls on Jan 1, 1943, 339 of the men had first been occupationally exposed to asbestos dust prior to 1922, and an additional

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93 men had first been exposed between the beginning of 1923 and the end of 1942. All of these men were successfully traced through Dec 31, 1962, and 262 of them were found to have died up to that time. Of the 262 deaths, seven occurred prior to the 20th anniversary of the man's first exposure to asbestos dust and 255 occurred after the 20th anniversary. Thus, of the 632 men, 370 were still living on Jan 1, 1963.

These 370 men were the subjects of the present investigation. Table 1 shows their age distribution as of Jan 1, 1963, and the lapsed time from first exposure up to that date. All of them have been traced, and 94 of them were found to have died during the four-year and four-month interval from Jan 1, 1963, to April 30, 1967.

Table 1.—Subjects Classified by Age as of Jan 1, 1963, and by Years From First Occupational Exposure to Asbestos Dust up to Jan 1, 1963

| Age, Yr | Total No. of Subjects | No. of Years Since First Exposure to Asbestos | | | | | | | No. of Deaths, 52 Mo |
|---|---|---|---|---|---|---|---|---|---|
| | | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | 45-49 | 50+ | |
| 35-39 | 2 | 2 | ... | ... | ... | ... | ... | ... | ... |
| 40-44 | 13 | 12 | 1 | ... | ... | ... | ... | ... | 1 |
| 45-49 | 32 | 17 | 2 | 13 | ... | ... | ... | ... | 2 |
| 50-54 | 109 | ... | 1 | 80 | 28 | ... | ... | ... | 18 |
| 55-59 | 60 | ... | 1 | 16 | 34 | 8 | 1 | ... | 11 |
| 60-64 | 42 | ... | 1 | 3 | 11 | 19 | 8 | ... | 16 |
| 65-69 | 40 | ... | ... | 1 | 10 | 18 | 18 | 2 | 17 |
| 70-74 | 38 | ... | ... | ... | 3 | 12 | 6 | 17 | 18 |
| 75-79 | 21 | ... | ... | ... | ... | 1 | 5 | 15 | 8 |
| 80-84 | 4 | ... | ... | ... | ... | 1 | 1 | 2 | 3 |
| Total | 370 | 31 | 6 | 113 | 86 | 59 | 39 | 36 | 94 |

Table 2.—Subjects Classified by Age and by Smoking Habits on or about Jan 1, 1963

| Age, Yr | Total No. | Never Smoked Regularly | Pipe, Cigar Only | Ex-cigarette Smokers* | Current Cigarette Smokers* | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | 1-9 a Day | 10-19 a Day | 20-39 a Day | 40+ a Day |
| 35-39 | 2 | 1 | ... | 1 | ... | ... | ... | ... |
| 40-44 | 13 | 2 | ... | 2 | ... | ... | 5 | 4 |
| 45-49 | 32 | 2 | 1 | 5 | ... | ... | 12 | 12 |
| 50-54 | 109 | 12 | 6 | 26 | 3 | 5 | 33 | 24 |
| 55-59 | 60 | 6 | 5 | 16 | ... | 3 | 20 | 10 |
| 60-64 | 42 | 7 | 4 | 15 | 1 | ... | 11 | 4 |
| 65-69 | 40 | 6 | 8 | 17 | ... | 4 | 9 | 5 |
| 70-74 | 38 | 7 | 7 | 12 | 1 | 4 | 4 | 3 |
| 75-79 | 21 | 3 | 7 | 6 | ... | 1 | 3 | 1 |
| 80-84 | 4 | 2 | 1 | 1 | ... | ... | ... | ... |
| Total | 370 | 48 | 39 | 101 | 5 | 17 | 97 | 63 |

*Includes cigarette smokers who also smoked pipes or cigars

Beginning in October 1962, we made arrangements to examine these men periodically, once every six to twelve months; the interval depended upon age and physical condition. The examinations include chest x-ray films as well as physical examination and cover past and present smoking habits, occupational history, medical history, and current physical complaints. Altogether, we have examined 338 (91.4%) of the men at least once and have repeatedly examined most of those who are still living.

Information on smoking habits was obtained by personal interview with the 338 men who were examined. Of the 32 men who were not examined, six told us their smoking habits by telephone and five gave us the information by mail. The local union secretaries (who personally knew these men well) ascertained the smoking habits of 18 men, and family members supplied the information on the remaining three men. This accounts for all of the 370 men. Table 2 shows their smoking habits on or about Jan 1, 1963, the men being classified by their ages on that date, even though some changed their smoking habits between 1963 and 1967.

Of the 370 men, 48 never smoked regularly, 39 smoked or had smoked pipes or cigars but never smoked cigarettes regularly, and 283 had smoked cigarettes regularly. Some of those with history of cigarette smoking also smoked pipes or cigars. Of the 283 with a history of regular cigarette smoking, 101 were excigarette smokers, five currently smoked one to nine cigarettes a day, 17 smoked 10 to 19 cigarettes a day, 97 smoked 20 to 39 cigarettes a day, and 63 smoked 40 or more cigarettes a day.

The smoking habits of the 370 subjects were compared with the smoking habits of a large number of men selected from the general population.[5] There were proportionally more cigarette smokers among the 370 subjects than were found in the general population sample; age was taken into consideration.

*Causes of Death.*—A copy of the death certificate was obtained for each of the 94 deaths. In addition, we examined hospital records, postmortem findings (41 cases), as well as the surgical and pathologic reports when surgery was performed (39 cases). We also reexamined histologic specimens. It was found that the death certificate was inaccurate in 14 instances. However, this did not alter the picture as much as might have been expected since there were several compensating errors. For example, in one instance the death certificate indicated bronchogenic carcinoma as the cause of death while a review of the histologic specimen showed that death was due to pleural mesothelioma; but in another instance exactly the reverse was found. Likewise, review in one instance resulted in changing the reported cause of death from bronchogenic carcinoma to cancer of the stomach with metastasis to the lungs while review in another instance resulted in exactly the opposite change. The 94 deaths were ascribed to the following causes: bronchogenic carcinoma, 24; pleural

Table 3.—Observed and Expected Number of Deaths [illegible] 370 Asbestos Workers During the 52 Month Period

| Cause of Death | Observed Deaths | Expected Deaths* |
|---|---|---|
| Total, cancer (all sites) | 49 | [illegible] |
| Cancer of lung, pleura, bronchus, and trachea | 27 | [illegible] |
| Bronchogenic carcinoma | 24 | † |
| Pleural mesothelioma | 3 | † |
| Peritoneal mesothelioma | 7 | † |
| Cancer of stomach | 3 | 0.6 |
| Cancer of colon and rectum | 5 | 1.2 |
| Cancer of all other sites combined | 7 | 4.5 |
| Asbestosis | 15 | [illegible] |
| Heart and circulatory disease including stroke | 22 | 28.5 |
| All other causes of death | 8 | 10.4 |
| Total, all causes | 94 | 47.5 |

*Based upon US mortality data disregarding smoking habits.
†United States data not available, but figure should be only slightly less than 2.3.
‡United States data not available, but these are rare causes of death in general population.

mesothelioma, three; peritoneal mesothelioma, seven; cancer of the colon, four; cancer of the rectum, one; cancer of the stomach, three; cancer of the pancreas, two; cancer of buccal cavity and pharynx, two; cancer of bladder, one; cancer of undetermined primary site, two; asbestosis, 15; cor pulmonale, one; cornary heart disease, 17; congestive heart failure, one; cerebral vascular lesion, two; aortic aneurysm, one; cirrhosis of the liver, three; bronchopneumonia, one; encephalopathy, one; acute pancreatitis, one; Wegener's granulomatosis, one; and accidental fall, one.

*Expected Deaths.*—For purposes of comparison, we wished to ascertain how many of the 370 subjects would have died during the 52-month period (Jan 1, 1963, to April 30, 1967) if their age-specific death rates had been exactly the same as for the general white male population of the United States. For this purpose, we made use of the United States 1964 life table for white males; this provided the most stable basis for comparison. It should be noted that for white males total death rates and death rates from respiratory cancer were slightly higher in the industrial states of New York and New Jersey than in the United States as a whole.[7] On the other hand, respiratory cancer death rates in white men aged 20 to 64 are reported to be a trifle lower than average among laborers, not elsewhere classified employed in construction work.[8]

From the life table we determined for each of the 370 men the probability of his dying within a period of 52 months, considering his age on Jan 1, 1963, and assuming that the life table probability applied to him. Summing these probabilities for the 370 men yielded an estimate of the "expected" number of deaths under the null hypothesis that the age-specific death rates of these asbestos workers are the same as for United States white males in general. The computation indicated that 47.5 deaths would have been expected.

Next, we wished to estimate the expected number of deaths from each of several causes. For this, we made use of the percentage distribution of deaths by cause of death among United States white males of various ages during the year 1964 as reported by the National Center for Health Statistics. These percentages were then standardized for age according to the age distribution at time of the 47.5 expected deaths. The results are shown in Table 3.

*Expected vs Observed Deaths.*—As shown in Table 3, there were 94 observed deaths (ie, 94 of the 370 asbestos workers died) as compared with 47.5 deaths expected on the basis of the age-specific death rates of all white males in the United States in 1964. Thus, there were 94 minus 47.5 = 46.5 excess deaths. The excess deaths were due to bronchogenic carcinoma, mesothelioma of the pleura and peritoneum, asbestosis, and cancer of the stomach, colon, and rectum.

*Cancer of Lung, Pleura, and Trachea.*—In published mortality data for the United States showing deaths each year from various causes by age, sex, and race, the following diseases are combined: cancer of the lung (including sarcoma of the lung), cancer of the bronchus, cancer of the pleura, and cancer of the trachea. For this group of diseases, there were 27 observed deaths and only 2.3 expected deaths, a ratio of nearly 12 to 1.

It is well known that, for the United States as a whole, all except a very few of the deaths reported in the combined category are due to bronchogenic carcinoma. Thus, it may be assumed that there were close to 2.3 expected deaths from this cause as compared with 24 observed deaths, a ratio of over 10 to 1.

*Mesothelioma.*—Ten of the 94 observed deaths were due to mesothelioma, three were due to pleural mesothelioma, and seven were due to peritoneal mesotheliomas. This is such a rare disease that if the 370 subjects had been selected as a random sample from the general population, one would not have expected any of them to die of mesothelioma within a period of 52 months.

All three of the men who died of pleural mesothelioma had a history of regular cigarette smoking. Of the seven who died of peritoneal mesothelioma, one never smoked regularly, one smoked only pipes and cigars, and five had a history of regular cigarette smoking.

*Cancer of Stomach, Colon, and Rectum.*—In our earlier study of asbestos workers,[1] there were more deaths than expected from cancer of the stomach, colon, and rectum (9.4 expected, 29 observed). As compared with a total of 1.8 expected deaths from these causes, there were eight observed deaths in this study, due to cancer of the following sites: stomach, three; colon, four; and rectum, one. Although this bears out our earlier findings, the number of deaths from these causes was so small that we still refrain from drawing any conclusion at this time.

*Asbestosis.*—Asbestosis accounted for 15 of the 94 deaths. While it is not surprising that deaths from this disease occur among men exposed to asbestos dust, attention must be called to the fact

that these subjects were primarily insulation workers. While all of them were occupationally exposed to asbestos dust, their degree of exposure was light as compared with the degree of exposure of asbestos miners, processors, and weavers in earlier times.

Table 4.—Estimated Number of Lung Cancer Deaths Expected to Occur During a Period of 52 Months per 10,000 Men Living at the Start of Period; by Age and by Smoking Habits*

| Age, Yr (Jan 1, 1963) | Never Smoked Regularly | Pipe, Cigar Only | Excigarette Smokers† | Current Cigarette Smokers† | | | |
|---|---|---|---|---|---|---|---|
| | | | | 1-9 a Day | 10-19 a Day | 20-39 a Day | 40+ a Day |
| 35-39 | 0 | ...‡ | 5 | ... | ... | ... | ... |
| 40-44 | 2 | ... | 7§ | ... | ... | 15 | 15 |
| 45-49 | 2 | 2 | 10 | ... | ... | 39 | 46 |
| 50-54 | 7 | 12 | 22 | 28 | 44 | 69 | 90 |
| 55-59 | 6 | 15 | 53 | ... | 91 | 117 | 185 |
| 60-64 | 16 | 31 | 71 | 80 | ... | 190 | 256 |
| 65-69 | 14 | 32 | 97 | ... | 157 | 305 | 350§ |
| 70-74 | 12 | 52 | 100 | 103 | 206 | 288 | 450§ |
| 75-79 | 28 | 53 | 100 | ... | 185 | 341 | 379 |
| 80-84 | 25 | 12 | 148 | ... | ... | ... | ... |

*Based upon data from a prospective study with adjustment for US mortality experience.
†Rates substituted for categories with no subjects in this study. See Table 2.
‡Includes cigarette smokers who also smoked pipe or cigar. Men with a history of only cigarette smoking have higher lung cancer rates than shown here.
§Rates obtained by smoothing the data.

*Bronchogenic Carcinoma.*—Bronchogenic carcinoma accounted for 24 deaths while only about 2.3 were expected on the basis of general United States mortality data for white males. However, as previously mentioned, evidence at hand suggests that there were proportionally somewhat more cigarette smokers among the 370 subjects than among white males in the United States as a whole, age being taken into consideration. This might have partially accounted for the high bronchogenic carcinoma death rate of the subjects. For this and other reasons we made estimates of the expected number of bronchogenic carcinoma deaths, the smoking habits of the men being taken into consideration. This was done as follows:

Data are available on lung cancer deaths in relation to the smoking habits of 440,000 men enrolled by American Cancer Society volunteers in a prospective epidemiological study between October 1959 and March 1960 and traced through Sept 30, 1964. Causes of death were ascertained from death certificates, but whenever cancer was mentioned on a death certificate inquiry was made of the physician who signed the certificate. In case of disagreement between the two sources of information, the physician's statement was accepted. For the purpose at hand, we only made use of data covering the 52-month period beginning on June 1, 1960, and ending on Sept 30, 1964. The number of lung cancer deaths occurring during the 52-month period was divided by the number of men alive at the beginning of the period. This was done by five-year age groups for men in each of the following smoking categories: (1) never smoked regularly (nonsmokers and occasional smokers being combined); (2) history of regular pipe or cigar smoking, past or present, but never smoked cigarettes regularly; (3) excigarette smokers (including those who had smoked or currently smoked pipes or cigars); and (4) current regular cigarette smokers (including those who also had smoked or currently smoked pipes or cigars). The last of these categories was further divided by current number of cigarettes smoked per day: (4a) one to nine cigarettes a day; (4b) 10 to 19 cigarettes a day; (4c) 20 to 39 cigarettes a day; and (4d) 40 or more cigarettes a day. Since the men were divided into seven groups by smoking habits and further subdivided into many five-year age groups, some of the subgroups contained only a small number of men. In consequence, the lung cancer death rate was statistically unstable in some of the very small subgroups. In three instances where the observed rate in a small subgroup appeared to be badly out of line, we arbitrarily made an adjustment to bring it more into line with adjacent figures in the table. These adjusted figures which are indicated with symbols in Table 4 carry very little weight in the final calculation. All of the rates were then adjusted as follows:

Lung cancer death rates in the United States have risen steadily year by year and were higher in 1964 than during the period 1960 to 1964 as a whole. Furthermore, in the study described above, we avoided enrolling seriously ill people and, as of the cut-off date for preparing the computer tape, we had not yet received death certificates for all of the men now known to have died during the specified period of time. For these reasons, lung cancer death rates in the study population were appreciably lower than those reported for white males in the United States in 1964. To compensate for this, we raised the rate of each individual smoking category so that the total lung cancer death rate (disregarding smoking habits) in each five-year age group would be the same as that of all United States white males (based upon the 1964 life table and the 1964 distribution of deaths by causes of death). The results of these computations are shown in Table 4. (It should be noted that Table 4 shows only such rates as were required for further calculations.)

The rates shown in Table 4 were then applied to the number of asbestos workers shown in each of the corresponding internal cells of Table 2. This yielded an estimate of the number of lung cancer deaths expected to occur during a 52-month period among the 370 asbestos workers classified by their smoking habits. By "expected" number, we here mean an estimate of the number of lung cancer deaths which would have occurred under the null hypothesis that asbestos workers do not differ from other men in respect to their lung cancer death rates, both age and smoking habits being taken

Table 5.—Observed and Expected Bronchogenic Carcinoma Deaths by Smoking Habits for 370 Asbestos Workers

| Smoking Habits | Observed Deaths | Expected Deaths |
|---|---|---|
| Never smoked regularly | 0 | [illegible] |
| History of pipe, cigar smoking only | 0 | [illegible] |
| History of regular cigarette smoking† | 24 | [illegible] |
| Total | 24 | 3.16 |

*Based upon data in Table 2 and Table 4.
†Includes cigarette smokers who also smoked pipe or cigar.

Table 6.—Expected and Observed Deaths Among 632 Asbestos Workers Exposed to Asbesto Dust 20 years or Longer

| | 1943-1962 | 1963-1967 | Total 1943-1967 |
|---|---|---|---|
| Total deaths: all causes | | | |
| Expected | 203.5 | 47.5 | 251 |
| Observed | 255 | 94 | 349 |
| Total cancer: all sites | | | |
| Expected | 36.5 | 8.6 | 45.1 |
| Observed | 95 | 49 | 144 |
| Cancer of lung, trachea, pleura | | | |
| Expected | 6.6 | 2.3 | 8.9 |
| Observed | 45 | 27 | 72 |
| Cancer of stomach, colon, rectum | | | |
| Expected | 9.4 | 1.8 | 11.2 |
| Observed | 29 | 8 | 37 |
| Cancer all other sites combined | | | |
| Expected | 20.5 | 4.5 | 25 |
| Observed | 21 | 14 | 35 |
| Asbestosis | | | |
| Expected | 0 | 0 | 0 |
| Observed | 12 | 15 | 27 |
| All other causes | | | |
| Expected | 167 | 38.9 | 205.9 |
| Observed | 148 | 30 | 178 |

into consideration. The results are summarized in Table 5 which shows the expected and observed number of lung cancer deaths in each of three smoking categories.

Taking smoking habits as well as age into consideration (Table 5) a total of 3.2 bronchogenic carcinoma deaths were expected whereas taking only age into consideration 2.3 deaths were expected from this cause (Table 3). Thus, perhaps one of the excess bronchogenic carcinoma deaths might be attributed to the fact that there appear to have been proportionally somewhat more cigarette smokers among the 370 subjects than among men of the same ages in the general population.

The following statements are based upon the data shown in Table 5. Twenty-four deaths from bronchogenic carcinoma occurred among the 370 subjects compared with only 3.16 expected, a ratio of about 7.6 to 1. This is slightly higher than found in our earlier study which indicated a ratio of 6.8 to 1 (not taking smoking habits into consideration). It should be noted in this connection that the 370 subjects in this study had been exposed to asbestos dust somewhat longer than the subjects of our previous study (the present 370 subjects are survivors as of Jan 1, 1963, of subjects in the previous study).

Of the subjects who never smoked regularly and those who smoked only pipes or cigars, none died of bronchogenic carcinoma whereas 0.18 of these men were expected to die of lung cancer. This suggests that exposure to asbestos dust does not increase the risk of bronchogenic carcinoma among men who never smoked *cigarettes regularly*. However, considering the small number of such subjects in this study, we only conclude that exposure to asbestos dust does not *greatly* increase the risk of bronchogenic carcinoma among men who never smoked cigarettes regularly.

Twenty-four of the men with a history of regular cigarette smoking died of bronchogenic carcinoma whereas only 2.98 were expected to die of it, a ratio of 8.05 to 1. From this it appears that exposure to asbestos dust greatly increases the risk of lung cancer among cigarette smokers.

Now we may ask how greatly is the risk of bronchogenic carcinoma increased by the combined effects of cigarette smoking and exposure to asbestos dust. To answer this question, we applied rates shown in Table 4 for nonasbestos workers who never smoked regularly to the number of subjects with a history of regular cigarette smoking as shown in Table 2. This indicated that only 0.26 of the subjects with a history of regular cigarette smoking would have been expected to die of bronchogenic carcinoma if they had never smoked regularly and had never been occupationally exposed to asbestos dust. Since 24 of them actually died of this cause, the ratio of observed to expected deaths is 92 to 1 (ie, 24 divided by 0.26=92). This appears to indicate that cigarette smoking plus occupational exposure to asbestos dust increases the risk of bronchogenic carcinoma by a factor in the order of magnitude of 92 to 1. It should be noted that this estimate does not take current amount of cigarette smoking into consideration.

*Comparison With Earlier Findings.*—As explained, we started with a cohort of 632 asbestos insulation workers, the entire membership of the union locals on Jan 1, 1943. We have now traced each man through April 30, 1967. Table 6 shows the observed and expected number of deaths for each of two periods (the first, 1943 to 1962, being previously reported[1]) and for the entire period. In respect to respiratory cancer (lung, trachea, and pleura) and in respect to cancer of the stomach, colon, and rectum, the findings in the two periods are in close agreement.

## Comment

The increased risk of neoplasia (mainly bronchogenic carcinoma and mesothelioma) among insulation workers reported here should be evaluated in the knowledge that these men have comparatively light exposure as asbestos trades go. Primarily employed in construction work, many of the materials they use contain little or no asbestos and others have only 5% to 15%. Conditions of work vary; these men often work outdoors unlike asbestos operators in factory work. Comparatively few dust-exposure surveys have been made in this trade but their results have generally been within the 5 million particles per cubic foot permissible limits currently accepted by the American Conference of Governmental Industrial Hygienists.[9,10] Nor have

ditional potentially carcinogenic substances been ntified among the other materials used."

Heavier or even lighter exposure may result in fferent degrees of risk of neoplasia. Heavy factory posure in the past has in some instances resulted considerable lung cancer risk." In others, paraxically, little lung cancer was seen because asstosis was so common and so severe as to cause ath of the exposed workers before they could live ng enough to develop lung cancer. Once exposure as reduced by improved industrial hygiene pracces, early death from asbestosis sharply diminhed and lung cancer became common."

In any case, heavy exposure is not likely to be e most important problem in the future, unless ere be sheer carelessness or unconcern. Rather, ght exposure, similar to that in insulation work, ll be much more common, both in direct asbestos rking trades and as the result of indirect occupaonal exposure, as in the construction and shipilding industries.

There is another type of "light exposure" which ay affect many more people than those industrialexposed. In the past several years, it has been monstrated that asbestos bodies can be found in e lungs of 25% to 50% of adults examined at topsy in large cities, such as Belfast, Northern eland, Capetown, Republic of South Africa, iami, Fla, Pittsburgh, and Montreal. This is resumably due to "asbestos air pollution" by bers derived from industrial "spillover" (as dust om construction sites or factory wastes) or from d-product use. Such community asbestos air llution may be important since there is already idence that in certain circumstances, as living thin half mile of an asbestos plant or in the ousehold of an asbestos worker, intimate environental contamination can be associated with some sk of mesothelioma.[3] What is not now known is hether the minimal amounts inhaled by the genral public carry a similar risk."

Nor do we know whether inhalation of the very nall amounts of asbestos present in the air of some mmunities is associated with a special lung ncer risk in cigarette smokers (or, conversely, hether cigarette smoking makes the inhalation of ry small amounts of asbestos particularly hazardus). It will be important to ascertain whether such carcinogenic or potentiating or precipitating relaonships exist because, with the rapid growth of sbestos use (500,000 tons per year would produc on in 1930 has risen to over 4,000,000 tons per ar now), it may be difficult for cigarette smokers avoid inhaling air contaminated with asbestos.

It may not be easy to unravel the interrelationhips which might exist between community asestos air pollution and cigarette smoking. Both sbestos exposure and cigarette smoking have a ng-lapsed period between onset of exposure and ccurrence of neoplasia, yet for current smokers hese two exposures may not have begun simultaneously; there was much less asbestos used 20 to 40 years ago. Youngsters who start smoking now have a much greater chance of having both exposure simultaneously.

*Significance of Findings for Asbestos Workers.*—The import of the data reported here seems clear. There is an extraordinary risk of developing and dying from lung cancer for asbestos workers who smoke cigarettes regularly. In the group studied, the combination of asbestos exposure and cigarette smoking increased the risk approximately 90 times compared with men who neither work with asbestos nor smoke!

Of 283 asbestos workers who had a history of cigarette smoking, 78 died within a period of 52 months whereas only 32.4 would have been expected to die within that length of time if their age specific death rates had been the same as for the general white male population of the United States. Of the 78 deaths, 24 (31%) were due to bronchogenic carcinoma. It is estimated that if these men had smoked cigarettes but had not been exposed to asbestos dust, only 2.98 would have died of bronchogenic carcinoma within the same length of time. If they had neither smoked nor been exposed to asbestos dust, only 0.26 would have been expected to die of the disease within a period of 52 months.

Of 87 asbestos workers who never smoked cigarettes regularly, none died of lung cancer within the 52-month period (although three died of asbestosis and one died of peritoneal mesothelioma). This finding, being based upon the experience of only 87 men, does not prove that exposure to asbestos dust has no influence on the risk of lung cancer among nonsmokers. However, it suggests that exposure to asbestos dust does not lead to an extremely high risk of lung cancer among nonsmokers.

The conclusions are evident:

1. Occupational exposure to asbestos dust should be reduced to as low a level as possible; but there may be an irreducible minimum level if asbestos, a very useful material, is to be used at all. Such reduction in exposure will benefit asbestos workers of the future. However, we are also concerned with workers who have already been exposed at significant levels for many years. Asbestos fibers will remain in their tissues for the remainder of their lives.

2. All people incur a great increase in risk of lung cancer if they smoke cigarettes; for asbestos workers the increase in risk is tremendous. Asbestos workers who do not now smoke cigarettes should never begin. Those who do smoke, should stop immediately. We may hope that the decrease in risk which results from cessation of smoking among "the general public" will be the good fortune of the asbestos workers as well.

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## Just Words:

Many, possibly most, of the words in the dictionary stand there as representatives of a whole family of forms. Not even the timidest of the linguistically timid will run to the dictionary for encouragement when, for instance, they want to refer to a spell of "hiccuping," provided they are certain that Webster does know "to hiccup."

All the tense forms, the participles, the gerunds are assumed to be authorized by implication the moment the infinitive is known to exist. The plurals of nouns are similarly taken for granted, and the forms of comparison and the adverbial forms of adjectives.

This phenomenon is generally covered by the assertion that a dictionary is not a grammar and that each individual entry in a dictionary stands simultaneously for all its grammatically possible forms. (For details, consult your grammar.)

But is a gerund a grammatical form? Or is it a suffix-derived noun?

I am not really looking for an answer. I ask those questions to suggest that the dividing line between grammatical form and derived neologism is both hard to define and artificial. If I distinguish among men the "hunting" from the "hunted," I have done no more than form (grammatically) two nouns from two adjectives which are forms (grammatically) implied in the existence of "to hunt." But if "hunting" is implied, why not "hunter"? Why not "huntee" and "huntable" and "huntabilize"?

The question of when a new word is a new word and when it is merely an "implied" form of a conventional term is indeed more complex than is grossly apparent. Take "dehairability" as an example. Can I claim the word is implied in the existence of "hair," or must I assume the responsibility for having spawned a monster?

Or take "unequivocably," which indeed was the starting point of all this reasoning and wondering, for it was spotted as a bold neologism in *JAMA* in the sentence, "Research at the Public Health Service Hospital at Lexington, Ky, has unequivocably proven that methadone has all of the euphoric properties of morphine. . . "

Now, clearly, the adverb "unequivocably" is grammatically implied in the adjective "unequivocable," and this in turn is implied grammatically or semi-grammatically or otherwise in "equivocable." If we grant further that formations in "-able" of "-ible" are likewise legitimate without special dispensation, we shall conclude that "unequivocably" is in no sense a bold departure since "to equivocate" is a firmly established, standard English word.

But there is a hitch and a flaw in the argument. "To equivocate" means "to use ambiguous language" and (by extension) "to render ambiguous." Hence, "equivocable" can only suggest the trait of "being apt or able to be made ambiguous," and that, I fear, was not intended. Which means, by (nongrammatical) implication, that the discrepancy between the obviously intended meaning of "unequivocably" and its structurally supported significance was the cause of the unpleasant jolt experienced by the spotting reader.

*PS.* It is of course possible, and even likely, that "unequivocably" was just a typo for "equivocally."

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J. Sprawl

# CELLULAR IMMUNITY IN ASBESTOSIS*

by

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*A highly statistically significant correlation was found between asbestosis and impaired responsiveness in skin reaction to intermediate and second strength tuberculin and SK-SD. Considering ANA incidence these antibodies were found with higher frequency in asbestos workers who lacked a cutaneous response to the recall antigens. In asbestosis cases peripheral blood lymphocyte profiles are also abnormal demonstrating low proportions of E-RFC. Moreover, MIF test results showed the impairment of this cytokine generation when lymphocytes were stimulated with SK-SD, PPD and PHA in asbestosis cases. The lymphocyte transformation study documents an impaired response mainly to a lower dose of PHA and ConA in asbestosis cases and in asbestos workers with ANA.*

The occurence of rheumatoid factor and antinuclear antibodies (ANA) in asbestosis is well documented[6, 8, 11]. Furthemore, it was shown that abnormalites in humoral immunity are accompanied by changes in immunological cell-mediated reactions in asbestosis namely low proportions and absolute numbers of T-lymphocytes were found[2, 3, 4]. Moreover, skin reactions to recall antigens were also impaired in these patients as well as abnormal responses to PHA[1].

The problem to what extent lymphocyte malfunction is involved in the pathogenesis of asbestosis has become the most challenging problem in view of the data documenting the high incidence of neoplasmas in asbestos workers[10].



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## MATERIAL AND METHODS

All people investigated except the controls came from asbestos textile plant. They underwent a thorough medical examinations when blood was collected for immunological studies. The groups of people which were compared to each other were matched for age and sex. Details about these people are given in the tables. Hospital staff who were in apparent good health served as controls for lymphocyte studies.

*Autoantibodies* in sera were detected with the use of the immunofluorescence method.

*Delayed hypersensitivity skin testing.* As recall antigens tuberculin and streptokinase-streptodornase (SK-SD), (Serum and Vaccine Factory, Warsaw) were used. Intermediate test strength were 2 U and 5 U for tuberculin and SK-SD, respectively. The second strength was 5 U for tuberculin and 40 U for SK-SD. The results were read 48 hrs after injections. Induration at least 5 mm in diameters was regarded as positive.

*Erythrocyte (E-) and complement (EAC-) rosettes forming cells (RFC) study.* Lymphocytes were obtained from peripheral blood by centrifugation at a density gradient Ficoll (Pharmacia-Uppsala) – Uropolinum (Polfa, Poland). To determine E-RFC 0.25 ml of 1% SRBC suspension in Hanks' balanced salt solution (HBSS) was mixed with 0.4 ml previously absorbed with SRBC heat inactivated calf serum and with $0.5-1.0\times10^6$ lymphocytes suspended in 0.1 ml HBSS and with 0.4 ml HBSS. EAC-rosettes were measured using IgM antibody sensitized SRBC and fresh mouse serum. Details of the method are given elsewhere [5, 12].

*Direct migration inhibitory factor (MIF) assay.* This test was performed according to the method given by ROCKLIN[9]. The following stimulants were used: PHA (Wellcome) 2 μg and 8 μg/ml of medium, PPD (Serum and Vaccine Factory, Warsaw) 1 μg and 10 μg/ml of medium and SK-SD (Serum and Vaccine Factory, Warsaw) 100 U and 200 U/ml of medium. Inhibition of macrophage migration was never observed with cells obtained from guinea pig peritoneal exudate with addition of only stimulants without human lymphocytes.

*Mitogen-induced lymphocyte transformation test.* This test was performed with the use of microassay of DNA synthesis. In general the method given by OPPENHEIM and SCHECTER[7] was followed with some modifications. The following mitogens were used (in brackets are given the intermediate and the higher concentrations of mitogens which were used): PHA (Wellcome; 5 μg/ml and 20 μg/ml), ConA (Sigma; 2 μg/ml and 10 μg/ml), PWM (Gibco, Grand Island; 0.01 ml/ml).

Titriated thymidyne (0.5 μCi/well, specific activity 28 Ci/mmole) was purchased from Institute for Research Production and Application of Radioisotopes, Prague. Statistical analysis was made with the chi² test with Yates modification.

## RESULTS

*Skin testing.* 271 asbestos workers were examined with SK-SD and tuberculin. 48 of them did not respond to any of the antigens when they were used in intermediate strength. In this group of people, asbestosis was found more frequently when compared to workers responding at least to one antigen (19% versus 4%; $chi^2 = 11.0$, $p < 0.001$). ANA positive cases regardless of the presence or absence of asbestosis, were also more frequently found in this group of non-responding asbestos workers when compared to responders (31% versus 11%; $chi^2 = 11.0$, $p < 0.001$). However, when asbestosis patients were excluded from the calculation this difference became weaker and statistically non-significant (18% versus 7%; $chi^2 = 3.2$, $p < 0.1$). 44 of the non-responders to both antigens intermediate strength were retested with second strength antigens. 29 of them failed to respond again. Asbestosis cases were

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found in 17% and ANA in 28% of this group. The percentage for responders equaled 5% and 12% for asbestosis and ANA occurence, respectively.

*E-and EAC-RFC study.* This work confirmed our previous work[4] showing that proportions of E-RFC were significantly lower in asbestosis cases (n = 14) as compared to asbestos workers without lung fibrosis (n = 51; 46%±7 versus 52±10, $p < 0.05$). However, no statistically significant difference was found in respect to absolute number of E-RFC. On the other hand, in asbestosis cases higher proportions of cells lacking E-and C-receptors were found when compared to non-asbestosis cases (32%±7 versus 25%±11; $p < 0.05$). No difference in the proportion and absolute number of EAC-RFC was found.

In ANA positive cases regardless of the presence or absence of asbestosis a lower percentage but not absolute number of E-RFC were found when compared to people lacking ANA (47%±8 versus 52±9; $p < 0.05$). However, this difference became insignificant when patients with asbestosis were excluded from the calculation.

*MIF study.* A majority of patients with asbestosis lacked responsiveness to PPD, SK-SD and PHA, when these stimulants were used at their first strength to generate MIF production. The percentage of people who did not respond to any of the stimulants were 67%, 30% 35%, 33% for asbestosis cases with ANA, asbestos workers with ANA but lacking asbestosis, asbestos workers cases without asbestosis and

*Table 1.* Summary of migration inhibition test results

| | Asbestosis with ANA $n = 12$ (9/3)* mean age = 52 yrs duration of employment from 13 to 26 yrs | Without asbestosis with ANA $n = 10$ (8/2) mean age = 47 yrs, duration of employment from 7 to 25 yrs | Without asbestosis and without ANA $n = 17$ (13/4) mean age = 46 yrs, duration of employment from 4 to 30 yrs | Control group $n = 16$ (14/2) mean age = 38 yrs |
|---|---|---|---|---|
| All results with first strength of stimulants | 30/36[ab]** (83%) | 19/25 (65%) | 29/50[a] (58%) | 26/45[b] (57%) |
| All results without second strength of stimulants | 23/26 (64%) | 16/29 (55%) | 24/49 (50%) | 22/45 (48%) |

* Number of people investigated (in brackets female/male); ** ratio of the numbers of tests with impaired MIF generation to numbers of all test performed (in brackets are given percentages of impaired responses); [a] the difference statistically significant between groups labeled a ($chi^2 = 5.11$; $p < 0.05$); [b] the difference statistically significant between groups labeled b ($chi^2 = 4.98$; $p < 0.05$).

ANA, and in controls, respectively. When the results of second strength stimulants are considered, the differences were less pronounced and these percentages were as follows: 42%, 30%, 24% and 27% for asbestosis, asbestos workers without asbestosis

but with ANA, asbestos workers without ANA and asbestosis, control group. Summary of MIF results are presented in Table 1. When MIF results obtained with the first strength stimulants were taken together within the groups, it showed that asbestosis cases differed significantly from the controls in the number of test results demonstrating a lack of significant macrophage migration inhibition.

*Lymphocyte transformation study.* Lymphocyte transformation test results are considerably scattered in all groups investigated but mainly in asbestosis cases. To evaluate the results expressed in counts per minute it was judged that all results below the mean value of the control group minus one SD were considered as abnormal. Table 2 shows the number of patients test results below this value. This clearly

*Table 2.* Frequency of impaired response of lymphocyte microcultures *in vitro* to mitogens

| | Asbestosis with ANA $n = 12$ (9/3)* mean age = 52 yrs | Without asbestosis with ANA $n = 5$ (3/2) mean age = 50 yrs | Without asbestosis and without ANA $n = 11$ (9/2) mean age 44 yrs |
|---|---|---|---|
| PHA (20 μg/ml) | 6/12 (50%)** | 3/5 (60%) | 2/11 (18%) |
| PHA (5 μg/ml) | 8/12 (67%) | 3/5 (60%) | 3/11 (27%) |
| ConA (10 μg/ml) | 8/11 (73%) | 4/5 (80%) | 5/9 (55%) |
| ConA (2 μg/ml) | 8/11 (73%) | 3/5 (60%) | 3/9 (33%) |
| PWM (0.01 ml/ml) | 8/11 (73%) | 4/5 (80%) | 3/9 (33%) |

Results of the test were expressed as mean counts per minute of tritiated thymidine incorporated by quadruplicate microcultures. Impaired response means those results below mean value of control group minus SD; * number of people investigated (in brackets female/male); ** ratio of numbers of impaired response results to all number of patients tested (in brackets are given percentages of impaired responses).

demonstrates that in asbestosis cases 67% and 73% of cases are in the abnormal range when PHA and ConA were used in the intermediate concentration. Similar results were also found in the asbestosis negative but ANA positive group. Only 27% and 33% of asbestos workers with prolonged employment but lacking asbestosis and ANA were in the abnormal range with the same concentration of PHA and ConA. When indices of stimulation were considered the percentages of abnormal results in the asbestosis group and in asbestos workers without asbestosis and ANA were comparable. The highest percentages of abnormal results were found in groups of asbestos workers using the intermediate concentration of PHA (73% to 100%) and ConA (40% to 64%). Interestingly stimulation indices of PWM activated cultures in asbestos groups of people were in almost all cases within normal range.

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## DISCUSSION

This is a preliminary report of our work on the range of lymphocyte functional abnormalites in asbestos workers. It was clearly documented with the use of four different technics that cell-mediated immunity is impaired to the greatest extent in asbestosis cases and to lesser extent in asbestos workers without asbestosis but with ANA. The abnormalites found in the group of people with ANA points to the close relationship between humoral and cell-mediated immunity abnormalites in asbestos workers. However, the most pronounced abnormalites are found in cases with lung fibrosis. This implies that impairment of cell-mediated immunity is closely linked to the disease process in asbestosis, which is connected with a high risk of cancer.

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