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PULMONARY NEOPLASIA AMONG DRESDEN ASBESTOS WORKERS

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PLAINTIFF'S EXHIBIT

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PREVIOUS DRESDEN STUDIES

Dresden has been a center of the German asbestos industry for approximately forty years. It was here that Saupe undertook the extensive radiological studies which led to the well-known classification proposed by him,¹ a classification still officially recognized in the German Democratic Republic.

It is of interest that Saupe's early studies of asbestosis in Dresden contain no reference to personal observations concerning an association between asbestosis and lung cancer. This omission can hardly be ascribed to lack of interest on Saupe's part, since he had already completed important pioneer studies in occupational lung cancer of the Schneeberg miners with Rostoski and Schmorl in 1926.² Moreover, he made references to the cases published by Lynch and Smith³ and Egbert and Geiger,⁴ as well as having had personal communication from Nordmann⁵ concerning two cases of asbestosis and lung cancer observed by the latter, together with Nordmann's opinion⁶ that this association represented a new occupational cancer.

It would appear, therefore, that the absence of instances of combined asbestosis and lung cancer in the early asbestosis studies in Dresden can best be explained by the suggestion that such cases did not occur in the material studied in Dresden during the 1930s. This assumption fits well with our later experiences in the Dresden asbestos industry, described below, and with developing observations of our own and others concerning the period of latency between onset of exposure to asbestos and the development of lung cancer associated with such exposure.

CURRENT INVESTIGATIONS

Problems of asbestosis and its complications have been reinvestigated among workers in the Dresden asbestos industry since 1952, with the results of these investigations reported in a number of papers.⁷⁻¹⁴ These investigations formed the basis for a monograph on asbestosis published in 1960.¹⁵ In this monograph the question of lung cancer associated with asbestosis was critically examined with reference to the observations then available in Dresden. Although it was emphasized that the conclusions reached did not warrant removal of lung cancer associated with asbestosis

from the schedule of compensable occupational cancers, neither did the data then available clearly support, on a statistical basis, an unquestioned association between the two conditions.

The uncertainties expressed by Dohlig and Jacob¹ were based upon comparison of the frequency of lung cancer among German, especially Dresden, asbestos workers, in comparison with lung cancer rates of the population as a whole. A number of statistical difficulties were recognized, including the relatively small number of cases observed, the widespread asbestos industry, the variation in numbers of asbestos workers, and the difficulties encountered in comparing the various groups of asbestos workers studied by different investigators. An additional problem, which had to be allowed for in the calculation of incidence rates of cancer over a period of time, was the significant increase of lung cancer in the general population over the period of observation.

These difficulties, coupled with the knowledge that the latent period for occupational cancers may be anticipated to be relatively long, necessitated studies that required observation of as many individuals as possible, in well controlled population groups, for periods as long as feasible. Observations made after relatively short periods of study run the risk of incompleteness and inaccuracy.

In 1952, Silicosis Registration Offices (Silikose-Erhebungsstellen) were set up in the German Central Institute of Occupational Health, German Democratic Republic (Holstein) for cases of asbestosis in Dresden, as well as for all other asbestos workers in that city. The creation of this central registry for the first time provided an opportunity to study workers exposed to asbestos, and those already suffering from asbestosis, respectively. The registry is an inclusive one and provides for the registration of asbestos workers regardless of whether they belong to different trade unions, and without concern for such questions as compensation. Continuity of observation is also ensured since the registration is not affected by change of employment or change of residence.

The data which follow summarize the observations made among workers in the Dresden asbestos industry from 1952 to mid-September, 1964, with particular reference to the question of the association between asbestosis and lung cancer. These data now take precedence over previous published data from the Dresden area, being based upon significantly longer periods of observation.

Materials and Methods

Two thousand six hundred and thirty-six individuals have been registered as occupationally exposed to asbestos (1,512 men and 1,124 women); they are the subject of this report. Unfortunately, it has been impossible at this time to categorize the exact occupational exposures in this group;

these people being exposed to a variety of occupations in contrast to the well-defined group of insulation workers studied by Selikoff and his colleagues.²⁰ Thus, exposure has occurred in occupations in the mixing, weaving, and grinding departments of a brake-lining factory; in the production and processing of asbestos textiles, asbestos cement products, etc. Similarly, it was not possible for this report to detail such factors as degree and duration of exposure, quantitative dust counts, etc.

The asbestos used in the Dresden asbestos industry includes asbestos from Canadian, Soviet, and South African sources, in varying amounts at different times. For this reason, we are unable to offer valid observations concerning effects of the different varieties of asbestos. Should there be different effects with these different varieties of asbestos, it may be predicted that all these effects might be observed since, practically speaking, exposure has taken place to all sorts of asbestos.

Results

There have been 721 registered cases of asbestosis in the Dresden area, in the group studied by us. These have included 426 males and 295 females. Utilizing Saupe's classification,¹ 249 of these cases were categorized as "suspect," 269 were radiologically stage I, 141 stage II and 62 stage III. There have been 150 deaths among the asbestos workers, including 132 patients suffering from asbestosis. TABLE 1 details the causes of death among these individuals. TABLE 2 contains an analysis of the extent of radiologically evident pulmonary asbestosis among the deaths, including correlations with neoplasms of the lung and pleura, and cor pulmonale. Data in these TABLES include observations in the Dresden asbestos industry to September 15, 1964.

It is of interest to note (TABLE 2) that of the 39 deaths due to cor pulmonale, 13 had radiological evidence of asbestosis of but limited extent. This discrepancy between radiological appearance and functional capacity of individuals with asbestosis has been commented upon before and has been observed much more frequently in asbestosis than in silicosis.^{12,19,21}

Analysis of our data indicates that there have been important changes in the percentages of deaths caused by the several major causes of death during the period of our observations. TABLE 3 contains an analysis of deaths caused by neoplasms of the lung and pleura and by cor pulmonale during three periods covered by our analysis, 1952, 1953-1957 and 1958-1964. Not only has there been an increase in the total number of deaths per annum (almost certainly the result of factors associated with initiation of registration in 1952), but there has been a significant increase in the number of cases of lung cancer associated with asbestosis lately. Thus, there were no cases of cancer associated with asbestosis to 1952, there

TABLE 1
CAUSES OF DEATH AMONG 150 DRESDEN ASBESTOS WORKERS, INCLUDING 132
CASES OF ASBESTOSIS (1952-1964)

Cause of death	Asbestosis						All cases		
	absent			present			Total	Male	Female
	Total	Male	Female	Total	Male	Female			
Right heart failure (cor pulmonale)	—	—	—	39	25	14	39	25	14
Lung cancer	6	6	—	22	16	6	28	22	6
Pleural mesothelioma	—	—	—	6	—	6	6	—	6
Peritoneal tumor	1	1	—	—	—	—	1	1	—
Cancer of gastrointestinal tract	2	2	—	4	3	1	6	5	1
Other malignant tumors	1	—	1	3	—	3	4	—	4
Pulmonary tuberculosis	—	—	—	9	8	1	9	8	1
Other causes	8	7	1	19	13	6	27	20	7
All cases	18	16	2	102	65	37	120*	81	39

*In 30 cases the cause of death could not be ascertained (16 M, 14 F).

TABLE 2
RADIOLOGICAL CLASSIFICATION OF ASBESTOSIS (SAUPE¹) IN 150 DEATHS AMONG
DRESDEN ASBESTOS WORKERS, INCLUDING CORRELATION WITH COR PULMONALE
AND LUNG AND PLEURAL NEOPLASMS (1952-1964)

Radiological stage	Number of cases of asbestosis observed			Deaths of lung cancer (+ pleura)			Deaths of right heart failure (cor pulmonale)		
	Number	Deaths	Per cent	Number	Per cent of deaths	Per cent of those observed	Number	Per cent of deaths	Per cent of those observed
0	—	18	—	6	17.6	—	—	—	—
0 - I ("suspect")	249	24	9.6	3	8.8	1.2	4	10.2	1.6
I	269	30	11.4	4	11.8	1.5	9	23.1	3.35
II	141	43	30.5	12	35.3	8.5	11	28.2	7.8
III	62	35	56.5	9	26.5	14.5	15	38.5	24.2
Total	721	150	20.8	34	22.7	4.7	39	26.0	5.4

TABLE 3
SECULAR CHANGES IN PERCENTAGES OF DEATHS DUE TO NEOPLASMS OF LUNG
AND PLEURA AND TO COR PULMONALE, IN 150 DEATHS AMONG DRESDEN ASBESTOS
WORKERS (1952-1964)

Period	Total deaths			Deaths of lung cancer (+ pleura)			Deaths of right heart failure (cor pulmonale)		
	Number	Per cent of total	Per cent of period	Number	Per cent of all lung cancer deaths	Per cent of deaths in period	Number	Per cent of all cor pulmonale deaths	Per cent of deaths in period
1952	18	12.0	100	0	0	0	8	20.6	44.4
1953 - 1957	47	31.3	100	9	26.5	19.2	20	51.1	42.6
1958 - 1964	85	56.7	100	25(+2)*	73.5	29.4	11	28.3	12.9
Total	150			34(+2)*		22.7	39		26.0

*Two alive; diagnosis by biopsy.

were 9 from 1953 to 1957 and 25 from 1958 to 1964. In addition to the absolute increase in numbers, the relative proportion of deaths due to lung cancer rose from 19.2 per cent of all deaths in the period 1953-1957 to 29.4 per cent of all deaths in the period 1958-1964. This is in contrast with the percentage of deaths due to cor pulmonale. To 1952, almost half of the 18 deaths recorded were caused by right heart failure, and in the period from 1953-1957 a similar proportion was noted, with 20 of 47 deaths due to this cause. On the other hand, in the period 1958-1964 only 11 of the 85 deaths were due to cor pulmonale, or 12.9 per cent. It is apparent that lung cancer has now displaced cor pulmonale as the leading cause of death among asbestos workers in Dresden.

The shift in frequency of these two leading causes of death among Dresden asbestos workers may be understood by reference to the effect of two important variables; the degree of severity of pulmonary fibrosis in cases of asbestosis, and the duration of the latent period between onset of exposure and the occurrence of cancer associated with such exposure.

The more quickly pulmonary fibrosis develops, and the more severe its degree, the more rapidly will cor pulmonale occur. If the period for the development of fatal cor pulmonale is shorter than the latent period for the development of asbestos cancer, it may be anticipated that relatively few cases of the latter will be observed. Our data indicate (see below) that the latent period for asbestos lung cancer among Dresden asbestos workers is approximately 31 years from onset to exposure. On the other hand, among patients with asbestosis in Dresden who die of cor pulmonale, the average elapsed period from the onset of asbestos exposure to death averages only 25.7 years. These data tally well with the fact that average age at death from cor pulmonale is 55.1 years, whereas that from asbestos lung cancer is 60.9 years. Thus, if asbestotic pulmonary fibrosis develops rapidly and extensively, death from right heart failure will precede lung cancer, and in such circumstances deaths from cor pulmonale will significantly exceed those from lung cancer.

Previous studies in the Dresden area¹² have shown that with improved industrial hygiene procedures with consequent decrease in the severity of dust exposure, not only have death rates secondary to asbestosis and its complications been reduced, but the incidence of extensive asbestosis has similarly decreased. These observations suggested the possibility that lung cancer rates associated with asbestos exposure might be found to rise. We have analyzed the incidence of lung cancer among Dresden asbestos workers to September 15, 1964 and have summarized our results in TABLE 4. These data have been supplied with relation to age and sex, and comparison has been made with corresponding lung cancer death rates in the local population.^{22,23,24} In this Table, too, we have given the occurrence of lung cancer among Dresden asbestos workers with and without observable pulmonary asbestosis.

TABLE 4
OCCURRENCE OF LUNG CANCER (EXPECTED AND OBSERVED) AMONG DRESDEN
ASBESTOS WORKERS, 1952-1964, COMPARED WITH EXPECTED LUNG CANCER RATES
FOR DRESDEN GENERAL POPULATION OF CORRESPONDING AGE

Period	1952-1957		1958-1964		1952-1964	
	Exp.	Obs.	Exp.	Obs.	Exp.	Obs.
1521 Asbestos workers (male)	5.4	6	5.9	17	11.1	23
426 Cases of asbestosis (male)	1.5	4	1.7	13	3.1	17
1124 Asbestos workers (female)	0.4	3	0.4	10	0.8	13
295 Cases of asbestosis (female)	0.09	3	0.1	10	0.2	13

It will be seen from TABLE 4 that the incidence of lung cancer among asbestos workers in Dresden, with or without asbestosis, was not significantly increased in the period 1952-1957 and these data mirror the reports of Bohlig and Jacob, based upon observations made during those years in Dresden.^{10,11,16,17}

For the period 1952-1957, if the lung cancer death rate for asbestos workers were the same as those for the Dresden general population of corresponding ages, we would have expected 5.4 lung cancers among the 1521 male asbestos workers. Six were actually observed. Among the 1124 female asbestos workers we would have anticipated 0.4 lung cancer deaths. Three were observed. Analyzing only those asbestos workers with recorded asbestosis, we would have expected 1.5 lung cancers among 426 male cases of asbestosis; four were observed. Among 295 female cases of asbestosis, we would have expected 0.09 deaths due to lung cancer; three were observed.

Analysis of experiences among Dresden asbestos workers for the period 1958-1964 (to September 15, 1964) demonstrates a very sharp rise in the incidence of lung cancer. For this period, the expected number of deaths among 1521 male asbestos workers was 5.9, while 17 were observed. Among 426 male cases of asbestosis, 1.7 lung cancers were expected and 13 were observed. Even more striking were the observations among female asbestos workers. Only 0.4 lung cancers were expected among 1124 female workers, but 10 were observed. In 295 female cases of asbestosis, 0.1 lung cancers were expected, yet 10 were observed.

Although these data did not then provide a reliable statistical basis for the recognition of lung cancer associated with asbestos exposure as an occupational cancer, other factors were considered, in part by examination of the available published literature, which pointed to suggestive "peculiarities" of lung cancers associated with asbestosis. Nordmann¹⁸ in his early papers had commented upon such "peculiarities" and the Dresden experience had been examined with these aspects in mind.^{11,16,19}

TABLE 5
ANALYSIS OF PULMONARY AND PLEURAL NEOPLASMS AMONG DRESDEN ASBESTOS
WORKERS (1952-1964)

I. Duration of asbestos exposure		
Between 2 and 42 years—average: 14.2 years		
II. Latent period from onset of exposure		
Between 4 and 46 years—average: 30.7 years (Pleural tumors alone —average: 31.8 years)		
III. Age at occurrence of lung cancer		
	Associated with asbestos	Lung cancer (Dresden)
Males	60.0	60.0
Females	61.2	60.0
Total	60.2	60.0
(Pleural tumors alone)	62.7	
IV. Sex Distribution		
1. Asbestos tumors*	males/females	1.8/1.0
2. Asbestos lung cancer	males/females	3.7/1.0
3. Lung cancer (Dresden)	males/females	9.9/1.0
V. Topographical distribution in lungs		
Asbestos lung cancer	upper lobe/lower lobe	1.0/2.2
Lung cancer (Dresden)	upper lobe/lower lobe	2.5/1.0
VI. Histology		
A. Lung cancer		
Asbestos lung cancer	74.0 per cent "mature forms"	
Lung cancer (Dresden)	49.4 per cent "mature forms"	
B. Serosal tumors		
1. <i>Pleura</i>		
a. Asbestos cases	19.4 per cent of all pulmonary tumors	
b. Autopsy-statistics (Walter, ²⁵ Switzerland)	4.0 per cent of all pulmonary tumors	
2. <i>Peritoneum</i>		
Only one case observed by us.		

*Includes pleural tumors. All pleural tumors observed by us to this point have been in female asbestos workers.

We also analyzed the lung cancer death among Dresden asbestos workers with regard to a number of specific features of the neoplasms found. Observations obtained from this analysis are summarized in TABLE 5. Asbestos dust exposure averaged 14.2 years, with a range of from 2 to 42 years. The latent period between onset of exposure and death due to lung cancer averaged 30.7 years, with a range of from between 4 to 46 years. This included all thoracic neoplasms. Analysis of those deaths associated with pleural neoplasms showed a similar period of latency, with an average of 31.8 years.

It was interesting to note that age at death with lung cancer associated with asbestos exposure was very much the same as that seen with lung cancer in general, in Dresden. In this area, average age at onset of lung cancer is 60.0 years. Among male asbestos workers, it was also 60.0 years, among females it was 61.2 years and for the entire group, it was 60.2 years. Again, analyzing the pleural tumors separately, some difference is noted, with an average age at onset of lung cancer of 62.7 years.

As might be expected from TABLE 4, the sex distribution of lung cancers showed a marked increase of these neoplasms among women. In the Dresden general population, the ratio of male to female lung cancer deaths is 9.9 : 1.0. The ratio of males to females among all thoracic neoplasms associated with asbestos exposure in our series was 1.8 : 1.0. This includes pleural tumors, and since all pleural tumors so far observed by us have been among women, this significantly alters the ratio in favor of women. If we analyze only lung cancer deaths among all asbestos workers, the ratio of males to females was 3.7 : 1.0.

The location of lung cancer associated with asbestos exposure has been noted to be unusual in many previously reported series. Our observations are quite in accord with these previous experiences. Lung cancers observed among the general population in Dresden have been predominantly upper lobe, with an upper lobe to lower lobe ratio of 2.5 : 1.0. In contrast, the lung cancers occurring among Dresden asbestos workers have been predominantly lower lobe, with an upper lobe to lower lobe ratio of 1.0 : 2.2.

With regard to the histological appearances of the observed tumors, there has also been some variation among the asbestos cancers, when compared with general observations in the Dresden area. Thus, mature histological appearances were observed in 74 per cent of the asbestos cancers, in comparison to 49.4 per cent of those observed among the Dresden general population.

The high incidence of pleural tumors is noteworthy. Among our cases, 19.4 per cent of all pulmonary tumors were primary in the pleura. In contrast, Walter²⁵ has reported such an origin in only 4 per cent of cases. In addition, we have observed one case of a peritoneal neoplasm.

These data are striking in several respects. First, the incidence among women is most unusual as is the lower lobe preponderance. In addition, the frequency of serosal tumors, especially those of the pleura, is noteworthy. These observations concerning pleural tumors in the Dresden area may be compared with those of other investigators.^{29,30,31} Investigations are continuing with reference to this aspect of the problem of neoplasia associated with asbestos exposure in the Dresden area (Anspach) and will be subsequently reported.

It is of interest to note that although only one pleural neoplasm had been observed to 1960 in the Dresden area, the reported cases of such tumors associated with asbestos exposure elsewhere had been commented upon by Dresden investigators in their overall analysis of the problem.¹⁶ There are now six such cases among the asbestos workers observed by us. This indicates the importance of completing adequate periods of observations, when comparing the results obtained by various investigators.

As noted, we have observed so far only one case of a peritoneal tumor in an asbestos worker. We are unable to compare this fragmentary experience with the observations of other workers,^{29,30,32} and will await additional observations among the cases studied by us.

A final word may be said with regard to our observations and the question of "inverse association" of asbestos cancers, proposed by Peller.^{31,34} Analysis of early observations made in the Dresden area suggested that Peller's concept was correct. However, our current extended observations require reevaluation of the problem and this is being undertaken (Anspach) and will be reported later. This analysis will consider the fact that the observed total cancer rate was some 30 per cent higher than expected from the projected experiences of the general population. Although the factor of selectivity among the asbestos deaths may be present, this factor may not explain the observed results. It is hoped that further studies will clarify this problem.

SUMMARY

Analysis of experiences among workers in the Dresden asbestos industry has been completed from 1952 to September 15, 1964. This progress report summarizes these observations with special reference to neoplasia observed among these workers. Lung cancer and neoplasms of the pleura are significantly increased among asbestos workers in the Dresden area when compared with the general population of this area of corresponding age and sex. Neoplasms of the lung and pleura were found to have increased both in relative incidence and in absolute numbers, with increasing duration of the latent period from first exposure. Thus, while an increased incidence of statistical significance was not observed in the period 1952-1957, a sharp increase was noted in lung cancer among men from 1958

to 1964, and in both lung cancers and pleural tumors among women from 1958 to 1964.

Right heart failure (*cor pulmonale*) is no longer the leading cause of death among Dresden asbestos workers, a position it held from 1952 to 1957. In the period 1958-1964, it has been replaced by neoplasms of the lung and pleura as the most common cause of death among these asbestos workers. Data are presented which indicate that the reduction in deaths due to *cor pulmonale* is a consequence of improved industrial hygiene measures. However, since the latent period from onset of exposure to death from *cor pulmonale* is considerably shorter (25.7 years) than the latent period of lung cancer associated with asbestos exposure (30.7 years), it is suggested that this has been a factor in the observed increased incidence of lung cancer. More asbestos workers are surviving long enough to reach the period in which the lung cancer rate is important.

Analysis of the lung cancer deaths has been undertaken and several features associated with asbestos lung cancers are documented. The remarkable increase of lung cancer among female asbestos workers is detailed, as is the preponderance of lower lobe localization of the observed tumors. The high incidence of pleural neoplasms is noteworthy. We observed six cases of pleural tumors, all in women. We have also observed one peritoneal tumor.

These observations are presented as a progress report and investigations continue. Among current studies are investigations of serosal neoplasms and an analysis of our data with reference to the "inverse association" proposed by Peller. These studies will be subsequently reported.

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