248 A

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LUNG CANCER IN ASBESTOSIS PATIENTS

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In the last 12-15 years, such extensive experience in the field of asbestosis has been reported by both German and foreign literature that we are now quite familiar with the dangers to which asbestos workers are subjected, and the clinical picture as well as the development of this occupational disease. Nevertheless, there are still many unanswered pathogenesis-related questions which will eventually be answered through animal experimentation and chemical-physical processing. However, our knowledge of accompanying diseases and complications is based on a much narrower and uncertain basis. At this time, the editor could publish an extensive report on the behavior of lung tuberculosis patients suffering from this type of pneumoconiosis. One question which is as important as it is conclusive is that concerning the correlation to lung cancer, whose incidence in asbestosis patients has been repeatedly observed over the last few years. The interest that this creates is not limited to the fields of social medicine and legal insurance regulations, but extends far into the field of general medicine, since this would produce a new example of the exogenetic appearance of cancer. The number of such observations reported in itself is very small, but is nevertheless so significant in relation to the rare occurrence of this disease that we feel it warrants the publication of a detailed report. This is also justified by the fact that, as yet, from a clinical side, no such work has ever been published.

We shall first mention observations previously published in worldwide literature concerning lung cancer in asbestosis patients, and conclude with the latest experience in that field, as well as the characteristics of the respective clinical image and its diagnosis.

[illegible] of a carcinomatous tumor in the lungs of an asbestosis [illegible] in 1933 by Gloyne, while working with the [illegible] and histology of asbestosis patients. He mentions complications in asbestosis patients which were thought to be related to the origin of the disease (purulent bronchitis, bronchopneumonia, tuberculosis, emphysema and bronchiectasis) and accompanying diseases which, based on the status of medical knowledge at that time, were thought to be correlated to the effects of the dust. Under the latter, he makes the following observation: "There has also been one case of squamous carcinoma of the pleura. There is no evidence at the moment that this was in any way related to the asbestosis".

In 1935, Gloyne was able to provide two additional reports on lung cancer detected in asbestosis patients. At that time, he still was not able to make a definite statement as to the possible etiological correlation of both diseases. Nevertheless, certain histological aspects did appear to indicate this.

The first of these two observations concerned a 35-year-old female who had worked for a period of 8 years as an asbestos spinner, and had then lived 9 years for 9 years without any exposure to the dust. She died, as shown by the autopsy, of moderate asbestosis with a coagulum in the right section of the heart, spleen infarct and a meningeal hemorrhage. On the basis of the right lung upper lobe, a clinically non-identifiable tumor was found, which was approximately the size of a walnut and which extended into the tip of the enlarged pleura. There were no metastases to be observed. The cornified pavement epithelium carcinoma originated from a small bronchus.

The second observation and autopsy also concerned a female who was just turning 71 years of age. Fifteen years prior to her death, she had once worked for a period of 6 months, and another time for a period of 13 months, in a hazardous dusty mattress and processing department of an asbestos plant. In this patient, Gloyne found a moderate case of asbestosis, with a partly-collapsing tumor in the right lung upper lobe, ascites and thrombosis of the left leg vein. Here too there were no metastases to be observed. Histologically, this was also a cornified carcinoma of the pavement epithelium.

In both cases, the cancer did not appear to be spread to the extent that it could promote death by itself. The same applied to asbestosis.

In the same year (1935), a report was issued by Lynch and Smith of the United States concerning lung cancer in asbestosis patients, in which a detailed history of the disease was given. The 57-year-old patient whose case is described had worked for 22 years in a cotton weaving plant, and for 21 years in an asbestos plant, until his hospitalization; he had been complaining of shortness of breath for about 5 years. Three years prior to his death, he started having occasional pains in the back and over the three last ribs on the right, and again complained of shortness of breath in the last few months of his life. He became weak, coughed, lost his appetite, his temperature rose, he had blood in his sputum and suffered

[illegible] years. The clinical findings were characteristic of asbestosis. Underneath to the right above the lungs, the respiratory sound [illegible] was weakened. The clinical diagnosis was asbestosis and chronic indurative pneumonia, with rind (skin) to the bottom right. In addition to asbestosis with right lateral pleuritis and bronchiectasis, a decomposed cystic was found in the right lower lobe through pathological-anatomical examination, which was macroscopically taken as tuberculosis. Only through the microscopic examination was it possible to detect cancer of the parenchyma of the epithelium. There were no metastases to be observed. It is unusual to speak of simultaneous hyaline nodes in the lungs of asbestosis patients. The carcinoma originated from a bronchus with a metaplastic epithelium. The authors felt that this had been caused by chronic irritation of the bronchii. They spoke of the correlation between cancer and asbestosis as a "possible relationship" and tried to find parallels to other occupational diseases of the lungs.

In 1936, Eghert and Geiger (USA) reported on an additional observation which they felt was the first one of this type (with the exception of Gloyne's 1933 report). The 41-year-old male had worked for 18 years as an asbestos weaver. After 9 years in this job, he had a case of pneumonia, followed by coughing and shortness of breath. Eight months prior to a short treatment in the hospital, he began to have occasional back pains. He was emaciated and had trouble moving because of the pain; he coughed, had cyanosis and shortness of breath, as well as bloody and purulent expectoration. In addition to asbestosis, x-rays showed a cluster in the left bottom part of the lung, which had the appearance of an atelectasis or a pneumonic process, but which was recognized as a tumor, due to the fact that metastases were present in the pelvis and in the spinal column. In addition to asbestosis, autopsy revealed a 5:5:4 cm acinose cancer in the left lower lobe of the lung, which had caused the appearance of metastases in the lungs, in the left lateral hilus and aortic glands, in the right suprarenal gland, in the abdominal musculature, the pelvis, the spinal column and the skull. The origin of the tumor was formed by a large secondary branch of the left bronchial lower lobe. He felt that there was very likely an etiological correlation between the two diseases: "That the irritating effects of the inhaled asbestos particles may in this case have been a significant factor concerned in the development of the primary lung cancer seems sufficiently plausible to be worthy of consideration."

In 1936, Gloyne was able to add an additional observation to his three initial ones. He found a non-differentiated carcinoma of the left lower lobe in a 59-year-old male suffering from asbestosis, who had worked for 21 years in the asbestos industry.

In 1938, Sparks, without specific data, stated that in his autopsies, Gloyne had encountered 6 cases of lung cancer in patients suffering from asbestosis. Baader learned from Gloyne himself that these 6 cases of cancer were based on 50 autopsies.

In the same year, Nordmann provided us with two new observations of cancer cases in asbestosis patients that he had previously and consecutively

[illegible] The first was a 45-year-old female. Between her [illegible] of life, she had worked for exactly 7 years in the [illegible] and weaving departments of an asbestos plant. Four [illegible] prior to her death, she began to cough and have shortness of [illegible] three months before she died, she was treated for suspected tuberculosis. Koenig gave a probable diagnosis of cancer in the left lower lobe, due to extensive asbestosis, since there were clinical symptoms of atelectasis and the main bronchus was tomographically found to be displaced. Anatomically, this was a cornified carcinoma of the pavement epithelium, with a walnut-sized decomposed cavity, which also affected the lower lobe bronchus, with pleura callosities and metastases in the liver and kidneys.

The second observation concerned a 55-year-old male who, between his 36th and 43rd years of his life, had been involved the preparation processes of an asbestos plant, for a total of 7 years. Thirteen months prior to his death, there was sudden loss of weight accompanied by bloody expectoration. He was first suspected of suffering from tuberculosis. Above the left lung underneath, respiration was suppressed and weak. X-rays showed a shadow around the left lower field. His treating physician gave a diagnosis of asbestosis with lung cancer. This was confirmed by the autopsy. The cancer, which was in the left lower lobe, had also caused a walnut-sized decomposition of the main bronchus, and also affecting the pericardium, the left chamber wall, the diaphragm, the peritoneum of the left upper part of the abdomen, the retroperitoneal tissues behind the spleen, the lymph node and the lower breast and upper lumbar spinal column. Histologically, this was again a cornified carcinoma of the pavement epithelium. Bronchial carcinoma had also begun to appear in the right lung lower lobe.

In this observation, Nordmann included an evaluation of the various aspects which could possibly lead to occupational cancer. For the first time, there was a definite mention of occupational cancer in asbestos workers.

In 1939, Wedler reported on one additional observation made in Germany, which had originally been made by Bohne, but which had not been reported at that time. The 58-year-old male had, between 1925 and 1935, worked as a part-time craftsman in an asbestos plant. A few years following his exposure to the particles, he began to have respiratory troubles. In 1928, he was transferred for a period of two months. Later, he often underwent cures at cure centers, without tubercle bacillus ever being detected. Because of a worsening of his condition, he stopped working 3 months prior to his death. In the hospital, he showed symptoms of general emaciation, cyanosis, and a probable catarrh, particularly under the upper part of the lung. His sputum contained numerous asbestos particles, but no tubercle bacilli. His blood sedimentation rate sharply accelerated (57-95). To the left above the ninth rib, there was a tumor the size of a chestnut, which had grown together with the skin in the anterior axillary line, which was removed and found to be a carcinogenic metastasis. X-rays showed symptoms of asbestosis as well as multiple indications in the right upper field. Judging from the documents in my possession, there was no intra vitam

[illegible] patient died of cardiac insufficiency [illegible] the asbestosis. The autopsy findings were [illegible] as follows: "The lung had grown together with the chest wall. [illegible] was not enlarged, the musculature was brownish-red in color and somewhat flaccid. The left lung was filled with blood and fluid, the lower lobe was firm and slate-gray colored. The right lung ruptured in the area of the middle lobe when removed. Its tissue was a reddish-yellow, and was decomposed and showed widespread formation of cavities and nodes. The upper lobe was filled with blood and fluid, its consistency was firm and air-free. The lower lobe was slate-gray and reddish-gray in color, and firm to the touch. It was also found to be air-free. The microscopic examination of the lungs showed typical cancerous tissue in the right middle lobe, and all the alterations which are characteristic in the case of asbestosis were present in the lower lobes. More particularly, there were asbestos particles in all the parts examined."

According to Baader (1939), six authors saw a total of 14 cases of asbestosis cancer between the years 1935 and 1938. However, this report did not include any details and, judging from the available documents which are listed above, this cannot be completely confirmed at this time.

In 1941, a detailed clinical and pathological-anatomical report was published by Wedler and Linzbach on an additional patient history which described the complete course of the disease. The 60-year-old male had, between 1921 and 1939, worked a total of 18 years in an asbestos plant. He was only exposed to the strong effects of the particles (preparation) for the first three years. His first problems were experienced shortly after his employment. In 1938, he already presented the picture of an uncomplicated and severe case of asbestosis, which had developed chronically. During the course of his last year of life, an increasing shadow developed over his diaphragm in the right lung lower lobe, with clinical symptoms of atelectasis and later decomposition, as well as severe neuralgic pains in the respective intercostal nerve area. Blood appeared in his sputum. All symptoms seemed to indicate cancer which had already been diagnosed clinically. The autopsy confirmed the diagnosis of a collapsed cornified carcinoma of the pavement epithelium, originating from the right lower lobe bronchus. There were no metastases to be found.

In the meantime, two additional observations have been reported in Germany, but no documentation is as yet available.

The first case was observed by Teutschlaender, who reported twice verbally on the subject. Following is a quotation from a personal communication on the subject: "In 1938, Teutschlaender performed an autopsy on a 40-year-old female, who had been employed in an asbestos plant for a period of 10 years with long interruptions. In her case, a clinical diagnosis was as followed: 'Lung tumor on the right? Lung process on the right? Secondary emphysema on the left, ascites, severe cachexia'. The autopsy revealed no tuberculosis, but rather a widespread asbestosis with massive accumulation of asbestos particles and a right-sided pleura blastoma which was histologically found to be pseudo-alveolar mesothelium. Tumors

[illegible] peritoneum with ascites. The left pleural cavity [illegible] discharge. There was compensatory emphysema in the [illegible] cachectic female died of cardiac insufficiency following [illegible] lung [illegible]."

The second observation was made by Alwens. The autopsy was performed by Fischer-Wasels. As a consultant, I became involved with this case. The 49-year-old male (8/14/81 to 9/19/41) had been working in an asbestos rubber plant for 22 years, until 6 months prior to his death. He became ill in January of 1941 with increasing shortness of breath and loss of weight, with symptoms of left pleural secretion. The respiratory sounds were totally suppressed and sustained, and there was right cardiac repression. His sputum contained considerable amounts of asbestos particles. In the jelly-like red secretion, mostly obtained through puncture, numerous tumorous cells could be found. Above and under the right lung, individual fine bubble-like rattling sounds could be heard. The sedimentation rate quickly increased. There were no tubercle bacilli to be found in the sputum. Based on the x-rays, a moderate asbestosis was diagnosed, with the primary tumor thought to be in the right hilus. The autopsy revealed a mild case of asbestosis, with a diffuse primary mucus-forming glandular cell carcinoma in the left pleura of mostly adematous character, and metastases on the abdominal side of the left diaphragm cupola, the serosa and the small pelvis, and the left side of the chest musculature. The autopsy report on the thoracic organs is quoted here, since no report has yet been made on the subject.

Autopsy of the chest. Moderately developed panniculous adiposes. The thorax is moderately expanded and flexible. The rib cartilage can easily be cut. The diaphragm is on the right, at the level of the fifth intercostal space; on the left side it is folded under, and penetrates far into the abdominal cavity. Its bottom pole here is lower than the neck of the pelvis. In the pneumothoracic test, almost 3,000 ccm of yellowish-brown fibrous fluid is released by the left pleural cavity. The entire mediastinum is displaced to the right. The heart hangs in the shape of a drop in the mediastinum; its left edge lies along the median line. The right lung floats freely in the pleural cavity up to small string-type growths. In the pleura costalis, there are gray and white tendon-like scales about the size of the palm of the hand, with isolated tubular nodes which are also gray and white. In the pleura of the right lung upper lobe, there is a large radiating scar. On the pleura of the right lung, there is a fine moderately firm adhering gray felt-like layer. The right lung itself is normal in size and filled with a moderate amount of air and fluid. The pleura and the surface of the cut show moderately severe black mesh-type markings. Generally, the lung tissues are red in color. There are no clusters to be observed. In the lower lobe branching of the right pulmonary artery, a small brownish-red blood thrombus adheres to the intima. The pulmonary arteries are empty. The left pleura is entirely covered with rind-like skin. On the inner surface, there are massive, tightly-packed tuberosities reaching the size of a walnut, with a mulberry-type surface consisting of blister-like (white on the surface of the cut) tumorous tissues. When cut, the latter secretes a

[illegible] to tumorous tissues, we can also observe [illegible]. The tumorous tissue does not penetrate any [illegible] beyond its base, particularly not the lung tissue. Only in the area of the cutaneous nodes on the left side of the chest, as mentioned in the introduction, can tumorous nodes be found in the intercostal musculature. The left lung is highly atelectatic, and only adheres to the chest wall through a series of growths. The lung tissue is tenacious and grayish-red in color, and shows a black mesh-type marking on the surface of the cut and on the surface itself, which is somewhat thicker than on the right side. No tumors were detected in the lung tissue. The trachea and bronchi of both lungs are normal in size, and the wall is tender. No tumorous tissue was observed here. The hilary lymph nodes are bilaterally black in color, and soft in consistency. The heart is barely the size of the dead patient's fist. The pericardium is smooth and shiny. There is some sub-epicardial fatty tissue. The left ventricle is small; the right one somewhat expanded. The wall of the left ventricle is 5 mm thick; that of the right ventricle 2-3 mm. The entire cardiac valve is soft and conclusive. The coronary artery is moderately enlarged, and its wall is soft. Cardiac musculature is of the same brownish-red in all cuts. The complete aorta is soft and flexible.

MICROSCOPIC FINDINGS

Right lung. The lung structure shows small isolated emphysemal changes. Occasional nodular deposits with a fine granular black pigmentation can be found in the peribronchial tissue. In this area, the peribronchial tissue shows a definite hyaline alteration and fibrosis. In addition to the anthracotic pigmentation deposits, typical asbestosis particles can be seen which are partly fresh and partly disintegrating. For the most part, these are parallel to the anthracotic pigmentation. However, independent from the latter, these can also be found by themselves in the pulmonary alveoli, as well as in the interstitial tissues. Massive accumulations of coal dust and asbestos particles can also be seen underneath the pleura. The large bronchi contain some amounts of mucus as well as epithelial discharge. The bronchioli are greatly expanded. However, they are covered with one layer of glittering epithelium. No epithelial metaplasia can be found. The lung tissue directly underneath the pleura shows a mild collapse of the alveoli. The alveolar epithelium shows a considerable glandular, but never non-typical, character. Generally, there are no pneumonic changes in the lung tissue.

Left lung. In the tissue of the left lung, we find a collapsed induration with desquamatous alveolar catarrh and fibrosis of the interstitium. In the peribronchial tissue, as on the right side, we find considerable anthracotic deposits with hyalinosis of the surrounding tissue. In this lung, we find a larger amount of typical asbestosis particles, both in the development stage and in the decomposition stage. Asbestos needles are considerably more rare. The jelly-like envelope of the particles gives a characteristically positive reaction to iron. In the left lung, moreover, we find several hemorrhaging areas, as well as areas of tissue necrosis saturated with the hemorrhaging blood. These mostly occurred recently, since there are absolutely no signs of demarcation. In these necrotic

[illegible] particles persist, and penetrate sharply through [illegible] of the remaining tissue. In this lung, the same [illegible]ias to the bronchial system are found as in the right lung. No [illegible]helial [illegible]asia can be found in this lung either.

Diagnosis. Numerous asbestosis particles in both lungs with minimal fibrosis (mild pulmonary asbestosis). Compression atelectasis and collapsed induration of the left lung. Hemorrhage, necrosis and minimal bronchopneumonia in the left lung.

Pleural tumor on the left. The tumor grows in its own structure. In a few areas, there are firm cones and strings surrounded by the stroma of a myxomatous, slightly fibrillar, connective tissue. Almost all tumorous areas have large mucus vacuoles; several signet-ring shapes can be seen. Some cells with ruptured vacuoles can be seen where the mucus has penetrated to the surrounding tissue. In another area, the tumor has the appearance of a collection of tightly-packed hollow cavities, which are covered with a smooth, single-layer epitholium. These epithelial cells also contain large amounts of mucus, and are released from the epithelial accumulations in the form of signet-rings, and thus end up in the lumen of the hollow cavities. In the interstitium, however, loose, stringy mucus-forming tumorous cells can be found. Firm epithelial formations without mucus formation of a solid carconoma type can only be found in isolated areas. Tumors can be found all over the pleura parietalis and visceral pleura on the left, and, in some areas, there is minimal growth in the subpleural layers of the pulmonary tissue. Here they are particularly in the septum and some isolated ones can be found in the lymphatic tract.

Diagnosis: Primary mucus-forming glandular cell carcinoma of the pleura of mostly adenomatous character.

The glassy nodes in question on the abdominal side of the left diephragm tip and on the serosa of the small pelvis are mocroscopically found to be metastases with a structure similar to that of the primary tumor.

This completes the observations found in world-wide literature on published cases of lung and pleural cancer in asbestosis patients.

Nordmann and Sorge were the first to undertake a study of the correlation between asbestos particle inhalation and lung cancer through animal experiments on white mice. For these experiments, they used 150 mice, which they sprayed with amounts corresponding to the average amounts received by humans (taking into consideration average age and duration of employment) for a period of 1 1/2 and 3 months. More than half of the animals died prior to the experiment. None of the animals survived for longer than 9 months following inhalation. Twenty per cent of the remaining animals were found to have a cornified multi-centric carcinoma of the pavement epithelium, and 42-57% epithelial regeneration in all stages. Experimentally, this is in support of the importance of asbestos dust in promoting primary pulmonary carcinomas in asbestos workers. The number

[illegible] experiments, and to which the above-[illegible] is very small. Only 2 animals had new growth [illegible] as said to be [illegible] errors. The authors themselves referred to the [illegible]ality in differentiating from simple metaplasia. We must leave it [illegible] experienced morphologist and specialist to decide to what extent [illegible] conclusions of the experimenters are valid and to what extent the [illegible]ary measures with regard to uniformity and use of the animal material were observed, and, within these limits, which spontaneous tumors are to be classified under the type which is the subject of this work. Nordmann and Sorge gave a short report on this.

It is evident that no similar observations have ever been made before in animal experiments with asbestos dust; these experiments in fact concerned other aspects of the disease. Moreover, various dissections of animals (dogs, rats) living in asbestos plants also did not lead to these observations.

In discussing occupational cancer in a specific industry, it is first necessary to produce statistical data in support of the fact that there is a higher incidence of cancer in that industry than in other industrial or social groups, in which case comparative figures of age groups which are similar (as much as possible) are difficult to produce. Even in the case of asbestosis, the statistical method also presents one additional obvious problem. This rather rare disease can only produce small absolute numbers. One single random incident can create considerable percentage differences. Moreover, in the case of Nordmann, we must take into consideration the fact that, particularly over the last few years, the high turnover of personnel in asbestos plants can give a negative value to the results, since a long period of exposure to the dust and a long dust-free interval usually must be present for the development of cancer. Now the number of workers who remain in hazardous plants for longer periods of time is very small. Dust prevention methods against dust injuries to the lungs also work against us. Nevertheless, our severe cases of asbestosis are mostly workers who are carrying the effects of dust absorbed in earlier years, when the working conditions were considerably less proper.

A second aspect of importance in the correlation between cancer and asbestosis should be mentioned here, which concerns particular conditions under which the injuries occurred and the findings made on location, conditions which describe the type of cancer and differentiate from other types of pulmonary cancer.

As keystone for the evidence, there would have to be experimental experience which would make it possible to provoke this type of cancer in animals.

Let us now turn to the statistical method. As reliable material, we can only evaluate here sections with specific anatomical examinations of the lungs, since certain errors can be made in the purely clinical diagnosis. Moreover, purely clinical works on this subject are not available.

[illegible] autopsied in Germany. [illegible] list of these cases according to age, sex, [illegible], stage of asbestosis and cause of death if other than asbestosis, if due to cardiac insufficiency or agonal pneumonia as a result of the disease. The first 18 fatal cases have already been reported. I reviewed the additional 12 cases. The case of a young girl reported under No. 29 can be ignored here, since she had a very short period of exposure to the dust and did not anatomically present a case of asbestosis. Of the remaining 29 autopsies, 4 had bronchial cancer and 2 others had a malignant pleural growth. By performing the necessary calculations, we get a round percentage number of 20% for malignant tumors in the lungs of cases of asbestosis autopsied in Germany. Other malignant growths of the body were found in a total of 3 occasions, namely in the stomach, the esophagus and the prostate. Although the number of lung cancers has statistically increased considerably over the past three decades, it nevertheless remains far lower than the number of cases of cancer of the esophagus, as shown by numerous autopsy statistics. Depending on the various authors, its rate of incidence takes the second to fourth place among the cancer statistics concerning organic cancers. As shown by the above-mentioned figures, lung cancer in patients suffering from asbestosis is a primary one in Germany. The average age at death for lung tumor carriers is considerably lower than for carriers of other types of carcinoma (around 51 to 66 years of age).

These small figures do not allow us to come to any conclusions. In a breakdown by sex, there are 4 males and 2 females with lung tumors. For the sex breakdown of lung cancer in males and females, the figures, otherwise, are: 3-4:1. The number of asbestos workers suffering from lung cancer, based on sex, is of course dependent on the number of females and males working in that industry. In Germany, the females exceed by far the males employed in that industry. For the two aforementioned females, the age at death was relatively low, being 35 and 40 years. All cancer patients were suffering from chronic to severe asbestosis. Only one man with pleural carcinoma (No. 20) suffered from moderate asbestosis; the latter had had a very long, but minimal, exposure to the dust. Nordmann has already pointed out that all these cases involved prolonged employment under dust conditions. According to the above table, this applies to all cancer patients without exception. The duration of exposure was 7 years in 2 cases, 10 years in two cases, and 18 and 42 years in the last two cases, respectively. The dust-free interval prior to the development of the cancer, during which the asbestos particle deposits in the lungs was still effective, varied (6 months to 12 years). In one case, this was not exactly known (No. 30).

These figures clearly show that lung cancer is the most common complication encountered in cases of asbestosis, with the exception of agonal pneumonia and cardiac insufficiency. Even tuberculosis, whose rate of incidence is generally far higher than that of cancer, is considerably lower than for lung cancer in these cases. This constitutes conclusive evidence of the close correlation between asbestosis and lung cancer. It is surprising to note that the current percentage values, based on large amounts of material, are in complete agreement with those of Nordmann performed

[redacted] small amount of working material.

As to the status of this question is as follows:

The English are the most experienced in this field. However, according to English documentation, this experience unfortunately does not lend itself to the study of individual observations. This is due to the fact that it is very complex, since some individual cases have been published more than once, and cannot be traced individually. For the time being, we shall have to accept the figures produced by Gloyne based on 99 autopsies of asbestosis carriers (according to Baader), during which he observed 6 cases of lung cancer (probably with pleural growth). This gives us a lung cancer incidence of 12% in asbestosis patients.

Very similar figures were obtained from the United States. I was able to collect 13 autopsy cases in U.S. literature up to 1939. This figure is probably not totally accurate, since there were a few works which I was unable to obtain. Among these autopsy cases of asbestosis, I encountered 2 cases of bronchial cancer, which we have already mentioned. This corresponds to a percentage figure of about 15%. There was no mention of any other types of organic cancer. Pneumonia was quite often reported (4 times) as the cause of death.

Absolutely no relevant data is available from France on this subject.

Other countries also reported little on the subject.

In Italy, where asbestosis is well-known, no cases of lung cancer have yet been reported (Vigliani et al.).

In world-wide literature, we therefore find 14 cases of malignant lung and pleural growths of epithelial origin out of 92 autopsies performed. The incidence of lung cancer in autopsied cases of asbestosis is therefore around 16%.

Of these 14 cases, only 11 have as yet been described in detail, so that additional statistical data still remains to be obtained (see Table 2).

A breakdown by sex gives us 7 males and 4 females.

The ages lie between 35 and 71 years of age.

Only 4 are between the relatively young ages of 35 and 41.

The period between employment and the development of cancer is always relatively long (between 12-42 years). Short term exposure to the dust is generally followed by a long dust-free interval, which would tend to indicate that the action of the dust, if there be such, gradually leads to the development of cancer.

Table 2 (continued)

Case #	Age(yrs)/ Sex	Dust ex-posure (years)	Dust-free interval (years)	Asbestosis stage	Type of growth	Locali-zation	Metas-tases	Author
9	40/F	10	?	III	pseudo-alveolar mesothelium	right pleura	peritoneum	Teutschla
10	60/M	42	1/2	I-II	adenomatous pleural cancer	left pleura	general-ized	Albert-Fischer-Vasels
11	59/M	21	?	--	non-differ-entiated carcinoma	left lower lobe	?	Gloyne

[illegible] of the patients who died [illegible]red from severe asbes-[illegible] usually have to be in this form.

There were 9 cases of pulmonary growth and 2 cases of pleural growth. [illegible] of lung cancer (as much as can be determined at this time) originated from the bronchial epithelium. No specific observation of alveolar [illegible] could be observed here.

From a histological point of view, there was a definite majority of cornified carcinomas of the pavement epithelium. Out of 8 histologically diagnosed cases of lung cancer, there were 5 cases of cornified carcinoma of the pavement epithelium; one additional case of cancer of the pavement epithelium was not cornified. One additional cancer case belonged to the group of non-differentiated growths, and the last case grew acinose.

The three pleural growths were described as "pseudo-alveolar mesothelium", "adenomatous pleural carcinoma" and "squamous carcinoma".

In 4 of the plumonary growth cases, in a strict sense of the word, there were no metastases to be found.

In 7 cases, the localization of the primary lung cancer was in the lower lobes, where the asbestosis is always most severe. In 4 cases, the growth is localized in the left lower lobe; in 3 cases in the right lower lobe. In contrast, there was only 1 case of growth in the right center lobe, and another in the right upper lobe.

The concordance between the localization of the growth and the most severe asbestosis-related tissue changes in the lower lung is evident.

The statistical incidence of lung cancer in asbestosis carrier autopsies is the first conclusive evidence obtained in our efforts to determine the corrrelation of these two diseases at their origin. The percentage figure of 16% for lung and pleural cnacer exceeds by far the incidence rate to be expected in other autopsies based on statistical data. Although the incidence of lung cancer has certainly increased considerably over the last decades, on the average, it has not increased by more than 2-6%, based on statistics of autopsies performed. Although, as we were able to show, the absolute asbestosis figures are still relatively low, they are nevertheless convincing, since approximately similar values were obtained from totally different countries (Germany, England, U.S.).

Based on the afore-mentioned conclusions, the purely statistical figures present an even more positive aspect, since such data had already been mentioned by Nordmann, although in smaller numbers.

We shall now mention the age groups of the cancer patients. Only four of the latter were between the ages of 35-41. Although younger people are sometimes afflicted by lung cancer, the highest incidence is found primarily in the age group 50-60. Within our study, 6 patients belonged to that age group.

breakdown concerned, the females here are at [illegible] 11 cases, we find 4 women. For lung cancer, large [illegible] otherwise offer a sex breakdown of 1:61 for males and [illegible] cases, we must keep in mind that in comparison to the U.S., the number of women employed in asbestos plants far exceeds the number of men employed, both in Germany and in England.

As we have already mentioned, one important consideration is the [illegible] of coincidence of growth localization with the most severe changes caused by asbestosis in the lower part of the lung.

Moreover, the histological nature of pulmonary growth is evident. Statistically, the incidence of mostly cornified carcinoma of the pavement epithelium is by far the highest. Out of 8 diagnosed cases of bronchial cancer, we found 6 such cases. The general lung cancer statistics for various types of growths thus become one-sided to the advantage of cancer of the pavement epithelium. If we perform a histological breakdown of lung cancer into three large groups, namely non-differentiated cells, carcinoma of the pavement epithelium and carcinoma of the columnar epithelium, the first will have the highest statistics with a total allotment of about 2/3 of all cases. Since cancer of the pavement epithelium has the lowest tendency towards metastasizing, it would be understandable that, of the above observations, four were found to be without metastases. The histological nature of lung cancer itself, as well as the above-mentioned highest incidence of cancer of the pavement epithelium, explains its classification under lung cancer.

Cancer was only observed following a relatively long period of latency following exposure to the dust. Could this be due to the fact that the period of employment under asbestos dust conditions was very long, or that a short period of employment with considerable exposure resulted in a longer interval during which the effect of the dust continued to progress? A series of thorough observations, which were partly performed by the author himself, showed that, particularly in the case of asbestosis patients, dust intoxication often appeared during this first interval, and often led to progressive fibrosis. Among all the lung cancer cases observed in asbestosis patients, there is not one single case in which a long period of action of asbestos particles was not reported. This agrees very well with other observations made of other types of occupational cancer.

Other histological findings in the lungs of asbestosis carriers allow us to better understand the above-mentioned correlations. In the small bronchi of lungs affected by asbestos particles, we mostly find generalized epithelial metaplasia, considered as a per-cancerous stage. It is very probable that the carcinomatous regeneration originates here. In one case, Nordmann even made the observation that, in a severe case of carcinoma in the left lower lobe, a smaller cancer was beginning to develop on the other side, which was not to be considered as metastasis, but rather as a cell-developing cancer originating from the metaplastic bronchial epithelium. For that reason, he considers the multilocular development of cancer in asbestosis patients to be particularly significant. Here we find parallels to the Schneeberger lung cancer.

[illegible] asbestosis, it appears as though other histological [illegible] will contribute to the development of cancer. One [illegible] the increased tendency toward growth in the tissues. To name a few, we can speak of extensive epithelial desquamation with alteration of the shapes of epithelial cells, formation of numerous macrophages and giant foreign body cells, as well as proliferation of the connective tissue. Thereupon, as mentioned by Linzbach, the various tissues are released from their normal condition without the injury to the tissue being extensive enough for the cell to collapse. This increased tendency toward regeneration and the disorder of normal tissue conditions can probably be considered as promoting factors in the development of cancer.

These theories also apply to pleural growth. The pleura is involved in the decomposition process. Here we find epithelial desquamation, fibrin deposits, regeneration of the connective tissue, cornification and accumulation of asbestos crystals and asbestos particles (Gloyne, et al.).

All these theories are based on statistical figures and constitute valid arguments in support of the inner correlation between asbestosis and lung cancer.

In addition to the increased incidence of cancer in asbestosis patients, we also require proof of the reproducibility of the conditions through animal experimentation. As yet, this point could not be proven in the case of asbestosis. This, however, is not based on negative results of experiments performed, but rather simply due to the fact that this question has not as yet been addressed to any significant degree. The first experiments were performed by Nordmann and Sorge, who obtained astoundingly similar results. These were already mentioned in the previous paragraphs. For more certainty, however, it will be necessary to obtain further confirmation and recognition of this complex correlation from other specialists.

Nevertheless, all the observations made up to now tend to indicate with all probability that Nordmann's theory on occupational cancer in asbestos workers is a valid one. Other authors such as Gloyne, Lynch and Smith, Egbert and Geiger, as well as Linzbach, also tend to take a correlation of the cause into consideration. No attempt has yet been made from any side to deny this assumption.

If we now attempt to determine the origin of the carcinogenic effect of asbestos particles, we must differentiate between general and local promoting factors. We can generally assume that the occurrence of cancer is usually due to an inclination (predisposition) toward this disease. Just where we should look for the answer for this is difficult to say. We know from general human experimental pathology that predisposition toward cancer is dependent upon systemic factors. This is particularly evident by the fact that under identical experimental conditions and fairly similar exposure to carcinogenic hazards, only a number of the endangered persons do actually suffer from cancer. The available asbestosis-related observation material is not sufficient to allow us to perform an analysis of familial carcinogenic conditions.

[illegible] of the [illegible] in which scle[illegible] fiber particle injuries can [illegible] a general predisposition to cancer is not known. Our theory [illegible] is regarded [illegible] still only a hypothesis. However, it would seem that [illegible] general predisposition is not strong enough to promote cancer in [illegible] organs. Two of the afore-mentioned figures would tend to indicate this. The varying localization would seem to be of primary importance [illegible]. Its morphological effects on the modified tissue reactions of the [illegible] have already been mentioned. Since the chemical definition of asbestos is fairly simple, the conditions in this case are easily understood. Right from the start, we can state that noe of the elements from the group of well-known carcinogenic agents can be taken into consideration here. The effects of asbestos particles on the lungs are probably the result of chemical and mechanical injuries. The chemical effects can probably be traced to silicic acid released from the somewhat vulnerable serpentine asbestos. Based on experience in the field of human pathology and numerous animal experiments, it is very impractical and unlikely that the latter would have any carcinogenic effects. We must keep in mind that the tissue changes which it causes, and which are different in their localization and extent in the case of asbestosis, would therefore present different conditions than silicosis. This different type and form of tissue regeneration can thus cause different biological reactions in the tissue. In addition to this, however, the mechanical repercussions of the many tips of asbestos needles and particles, most likely are characteristic of hornblende asbestos with its solid and hardly soluble properties. These probably play a significant role in the typical tissue reactions resulting from constant mechanical irritation.

We must finally remember that, particularly in the bronchi, there can be inflammatory reactions in severe cases of asbestosis. These are partly accompanied by the formation of bronchiectases, which can also be promoting factors for the development of cancer.

Based on our current knowledge of the subject, it is in these general, and, more particularly, regional, factors that we shall have to look for an explanation of cancer development in asbestosis patients. By definition, many of the injuries do not come under the group of chronic irritations. The fact that we are still far from completely understanding the finer factors involved here also applies to cancer development in asbestosis patients.

Let us now turn to the clinical diagnosing of cancer in lungs affected by asbestos particles: basically, all diagnostic aspects taken into consideration in the case of cancer detection in the lungs and the pleura can be used and are valid here. However, since this type of cancer originates from another primary disease, we shall have to take special characteristics of the clinical image as well as known elements with regard to the symptomatology of asbestosis into consideration.

For the past history, it is important to first do an occupational anamnesis, and keep in mind the fact that lung cancer in asbestosis patients generally appears only following year-long exposure to the particles, but

[illegible] particularly for [illegible] intensities. There is only one case in which the duration of [illegible] conditions was only 1 1/2 years; in all other cases, [illegible] at least 7 years or more. In the case of short-term, intensive [illegible] to the particles, it appears that there is always a longer dust-[illegible] interval before the appearance of cancer.' As yet there has been no case in which the period of time from the date of employment in dust-filled environment up to the confirmation of the presence of cancer was less than 12 [illegible] ars. Generally, we can expect that cancer only occurs in particularly pronounced, if not always the most severe, forms of asbestosis. The above examples are support of this.

The first symptoms of developing lung cancer, which are mostly not characteristic or pathopneumonic, will not be as evident as they might be in a previously healthy person, since shortness of breath, coughing, expectoration and certain discomforts in the thoracic area are already experienced by persons suffering from asbestosis. A certain loss of general strength, which is sometimes not present at all in the early stages of cancer, loss of weight and loss of appetite, are also frequent symptoms of severe forms of asbestosis. Acute worsening of the general condition, including local lung disorders, often indicates accompanying infections which are more difficult to overcome. In general, the rule in the case of cases of pure asbestosis is that the development of the disease occurs very gradually over the years, sometimes over decades. If there is evident local and general worsening of the condition during the course of such development, the possible occurrence of cancer must then be taken into consideration. In addition to cancer, infections which are most frequently non-specific are also encountered with bronchitis, pneumonia or abscesses. According to our experience, complex tuberculosis only played a minor role here. It is also much too often diagnosed. Of course, it is normal that it should be considered within the realm of possibilities. Nothing has yet been published on possible accompanying pulmonary lues or fungus diseases.

Of the general symptoms, quick loss of weight can be an indication, but it is not a conclusive factor. This, as we previously said, also applies to the lack of appetite, unhealthy appearance of the skin, and night sweats. If all of these are related to the progress of asbestosis, they will generally be accompanied by increased shortness of breath, cyanosis, possibly drumstick fingers and other local lung discomforts; however, we must keep in mind that a lung tumor would also promote an increase of such disorders. Generally, however, the status of the disease cannot be determined based on the case history alone.

There is little additional information that can be obtained from local disorders. Since severe asbestosis generally causes considerable irritation through coughing, little can be achieved from this symptom of the disease. This also applies to shortness of breath. Sputum observations would appear to be more important, as far as I am concerned. In the case of non-complicated asbestosis, the latter is mostly sparse and glutinous; in the case of more acute bronchitis and bronchiectasis, it is more considerable and purulent. It rarely contains blood. More frequent

[illegible] also [illegible] [illegible] case, [illegible] used in [illegible] [illegible] of [illegible] [illegible] in one [illegible] [illegible] tumors. [illegible] enumeration, [illegible] [illegible] [illegible] even for [illegible] simple asbestosis. [illegible] cells [illegible] [illegible] sediment in the sputum. Hornig mentions having seen considerable amounts of epithelial cells in the sputum of one asbestosis patient with tumor. If there is collapse of the lung tissue, this can easily be identified through the alteration of the sputum. This was a very significant factor in my observation. The patient suddenly began to throw up large quantities of core-shaped necrotic masses. Perhaps we can find here the "asbestosis bodies in clumps" symptom as mentioned by the English. These are rosette-shaped accumulations of asbestos particles which always appear in the sputum whenever lung tissues collapse (abcess, tuberculosis, tumor). Their diagnostic value is similar to that of flexible fibers observed in the sputum. We have already mentioned the significance of shortness of breath. In widespread tumors or bronchial obstructions, this is directly related to the latter. On the other hand, I find chest pains to be highly significant. For patients suffering from asbestosis alone, these are generally minimal and non-specific. In our tumor case, these progressed parallel to the development of the tumor; they were characteristically neuralgic. The documentation contains similar observations. These are due to an attack by the growth on the parietal pleura and possibly the intercostal nerves, if not actually on metastases.

These indications of the general and local disorders which can mostly be obtained from the case history should be sufficient.

As far as other objective findings are concerned, please note the following: asbestosis affects the lungs bilaterally. Exclusive unilateral processes, which generally indicate a tumor, do not occur here. The alterations which occur are generally very symmetrical. However, it must be noted that fibrosis can normally affect the right lung to a higher degree. General suppressions are never found above the upper part of the lungs. The respiratory sounds here are mostly hoarse, but rarely weak. The sounds of related pulmonary parts are mostly slightly to moderately weakened, and if not totally symmetrical, at least always bilateral. Only induration or specific as well as non-specific complications can cause exceptions here. The respiratory sounds are weaker in the lower part than in the upper part. The opposite is rarely the case. Accompanying sounds are more considerable and frequent in the bottom part than in the upper part; lateral differences are not significant. If definite symptoms of atelectasis are observed unilaterally, this could indicate the highest degree of tumor. Of course, this symptom is not always present in the case of lung tumor. Effusions, particularly hemorrhagic effusions, are hardly ever observed in normal cases of asbestosis. The tumor can show signs of fusion with the abcess and tuberculosis. Bronchiectasis in the form of cylindrical tracheal expansion is frequent in severe cases of asbestosis. Their differentiation with fusions can sometimes cause problems during the clinical examination.

An uneven asymmetry of the thorax, as well as distortion of the mediastinal organs and diaphragm, requires special analysis.

...uld result in ... important consideration ... presence of a tumor. It must be remembered here ... of asbestosis do not always result in a purely symmetri... ...ation of the lung tissues (as claimed in the documentation). In addition to certain asymmetries, there can also be superficial descriptive ... in the lower fields, particularly in the medial area. These ... shadows, however, are usually not so compact and tumorous, but rather are in the form of somewhat hazy stripes. Solid or tomographic ... often show the bronchial system as being open and sometimes even ...ded. Bronchial stenosis, which sometimes follows infection, has not ...t been observed in cases of asbestosis. Compact, unilateral and superficial opacities in the lungs, possibly with bronchial obstruction, are practically almost indicative of a tumor. This also includes mediastinal displacements which are either constant or vary with the respiration, with paralysis of the diaphragm and recurrence with upper lobe processes, mostly accompanied by a Horner syndrome. Circumscribing opacities in the upper fields never indicate asbestosis. These conditions, in this case, are much clearer and simpler than in the case of silicosis. In the case of asbestosis, coarse shadow formations primarily indicate non-specific infections. Tuberculosis is far from being as frequent as is generally assumed. Based on previous observations, its appearance rarely originates in the lower fields of patients suffering from asbestosis. For purposes of completeness, we must add here that, within the scope of useful diagnostic methods, tomography and bronchography can give different results as far as tumor detection is concerned, and are to be interpreted according to the standard rules that apply. The same applies to bronchoscopy. Other than for a few experiments, there is little knowledge available on diagnostic lung punctures performed to detect asbestos particles in the lung fluids. With primary pleural tumors or metastases, the detection of tumorous cells in the punctate greatly elucidates the situation. This was also observed by Alwen.

In the case of metastases, the diagnosis can always be made quickly.

The fact that persistent tumors can create fever is diagnostically non-significant, since infections also cause this symptom.

As far as blood count and the erythrocytic sedimentation rate are concerned, please note that anemia is not a symptom of asbestosis. On the contrary, high color and cellular values are signs of compensation. Accompanying infections could cause exceptions to this rule. Increasing anemia, with the exclusion of complicating causes, could be indicative of a tumor. A differential blood count should also not be considered as diagnostic evidence of the presence of a tumor. In cases of uncomplicated asbestosis, the blood sedimentation rate does not increase in itself. Nevertheless, it is often found to be significantly higher in group examinations of a large number of asbestosis patients. This is probably due to the fact that infections of the bronchial system are more often encountered in these patients. A higher and increasing sedimentation rate must always be observed and evaluated according to the standard clinical standards.

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