THE PATHOLOGY OF THE LUNGS IN FIVE NICKEL WORKERS

BY

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This investigation is to determine whether there are any characteristic pathological changes in the lungs of men employed in nickel refining. Five patients were available for study, four of whom had developed pulmonary carcinoma. All these men had worked at the same refinery. Previous pathological reports are scanty, but a few cases have been described by Amor (1939) and by Laken (1950).

Materials and Methods

Gough-Wentworth large sections were prepared in all cases except No. 2. These sections facilitated examination, especially in judging the extent of fibrosis and the presence of cystic change. Histological sections were prepared of representative areas of the lungs, about 14 in each case. The sections were stained with haematoxylin and eosin, Van Giesen, Lendrum reticulin, and Perl's stains; in addition all were examined under polarized light.

The age, type of tumour, and source of material are shown in Table 1. Details of the manufacturing process are not given and may be seen in the preceding paper by Morgan (1958). The dates of beginning and the total duration of employment, together with the detailed occupational histories of the five cases, are shown in Table 2.

Cases 3, 4, and 5 all had one mild, transient attack of acute nickel carbonyl poisoning one year, four years, and four months respectively before death; Cases 1 and 2 had no such history.

Results

The pathological findings are summarized in Table 3 and are arbitrarily classified into three grades.

A few general features may be considered before giving the details of individual cases. With the exception of Case 4 very little dust was found in these lungs on naked-eye and histological examination and in no instance did it constitute pneumoconiosis. It consisted of non-birefringent, mainly black, amorphous particles. There were also a few brown particles, 10% of which stained for iron and were thought to be haemosiderin as most of the lungs showed chronic venous congestion. None of the cases showed any evidence of silicosis. Signs of active tuberculosis were absent but Cases 1 and 4 showed healed tuberculosis in hilar glands and pleural scars. There were no demonstrable vascular changes.

Case 1.—This was a man aged 58 at death, and necropsy showed squamous carcinoma.

The right lung showed a carcinoma of the upper lobe bronchus. Both lungs showed basal bronchopneumonia, generalized oedema, and slight interstitial fibrosis. There was a slight degree of compensatory emphysema. The heart was normal. The patient died with multiple metastases.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>AGE, TYPE OF TUMOUR, AND SOURCE OF MATERIAL</th>
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<tbody>
<tr>
<td>Case No.</td>
<td>Age</td>
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<tr>
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<tr>
<td>2</td>
<td>54</td>
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<table>
<thead>
<tr>
<th>Table 2</th>
<th>DETAILS OF PATIENTS' OCCUPATIONS IN YEARS</th>
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<td>Case No.</td>
<td>Duration of Employment (years)</td>
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<td>11</td>
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<td>4</td>
<td>35</td>
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TABLE 3
HISTOLOGICAL DATA

<table>
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<tr>
<th>Case No.</th>
<th>Tumour</th>
<th>Squamous Bronchial Metaplasia</th>
<th>Atypical Alveolar Metaplasia</th>
<th>Bronchiectasis</th>
<th>Interstitial Fibrosis</th>
<th>Bronchopneumonia</th>
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<tr>
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<td>Squamous</td>
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<td>-</td>
<td>-</td>
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<td>++</td>
</tr>
<tr>
<td>2</td>
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<td>-</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Alveolar cell carcinoma</td>
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<td>Carcinoma</td>
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<td>++</td>
<td>+</td>
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<tr>
<td>4</td>
<td>Squamous</td>
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<td>Squamous</td>
<td>++</td>
<td>-</td>
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<td>+</td>
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</table>

Microscopy.—The right upper lobe bronchus was involved by a squamous carcinoma with spread into blood vessels (Fig. 1). There was a slight degree of interstitial fibrosis shown by increased amount of reticulin and little Van Giesen-positive collagen, but its nature was not specific. Bronchopneumonia was extensive. There was no evidence of bronchial metaplasia or atypical alveolar metaplasia.

Case 2.—On a man aged 34 at death necropsy showed no tumour.

The lungs showed prominent cystic change with spaces up to 3 cm. in diameter. The cysts were mainly in the posterior basal segment of both lower lobes and in the anterior and posterior segments of the right upper lobe. Bronchiectasis was also present (Fig. 2). There was a slight degree of generalized unspecific diffuse fibrosis and congestion. There was no evidence of tumour. The patient died of cor pulmonale with a hypertrophied right ventricle, probably the result of bronchiectasis.

Microscopy.—The lungs showed mild interstitial fibrosis, bronchiectasis, and broncholeoctasis producing well-marked cystic change (Fig. 3). Many alveoli were lined by single-layered epithelium with frequent multinucleated giant cells of foreign-body type (Fig. 4), designated atypical alveolar metaplasia (Jones Williams, 1957).

There was no evidence of bronchial metaplasia or recent bronchopneumonia.

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FIG. 1.—Epidermoid carcinoma with invasion of pulmonary artery. Haematoxylin and eosin, × 105.

FIG. 2.—Gough-Wentworth large section (¼ natural size) of right lung of Case 2 showing cystic change and bronchiectasis.
Case 3.—Necropsy on this case aged 58 at death showed alveolar cell carcinoma.
Both lungs showed widespread severe diffuse interstitial fibrosis with patchy areas of consolidation. Scattered throughout both lungs were areas of "cystic change", mainly towards the periphery, the cysts measuring up to 4 mm. diameter (Fig. 5). There was no obvious tumour of bronchi. The right ventricle was hypertrophied and the patient died with cor pulmonale with no evidence of extrapulmonary primary carcinoma.

Microscopy.—Interstitial fibrosis was severe and extensive, in many areas obliterating the air spaces. It was of recent origin, as evidenced by the presence of numerous thin-walled blood vessels. There was also intra-alveolar fibrosis resulting from organizing bronchopneumonia. The pattern of fibrosis was not specific with no tendency to nodule formation.

There was widespread bronchiolectasis and cystic change. Some cysts were lined by condensed fibrous tissue and devoid of epithelium, others were lined by bronchial epithelium. In many, the lining consisted of atypical squamoid epithelium up to 10 cells thick (Fig. 6), in some areas showing atypical mitosis (Fig. 7). The appearances favoured the diagnosis of the nodular form of alveolar cell carcinoma. The widespread epithelial metaplasia involved only peripheral air passages. Free intra-alveolar macrophages are also common, which, together with polymorphs, and intra-alveolar and interstitial fibrosis, constituted the features of an organizing bronchopneumonia.

Case 4.—A right pneumonectomy was performed on a man aged 60, and squamous carcinoma was diagnosed.
There was a 6 cm. diameter carcinoma arising at the origin of the right lower lobe bronchus and involving the hilar glands. There was a moderate degree of bronchopneumonia and basal bronchiectasis. All lobes showed moderate fibrosis. There was no evidence of emphysema or cystic change. There were a few scattered subpleural scars. The patient died nine months later with generalized carcinomatosis but no necropsy was performed.

Microscopy.—The carcinoma was of squamous type with a few keratinizing cell nests. Adjacent areas of bronchus showed squamous metaplasia (Fig. 8). The tumour was spreading outwards to adjacent fibrosed lung and also involved contiguous hilar lymph nodes.

Bronchopneumonia was widespread and most marked in the lower lobe distal to the tumour. In some areas organization was apparent (Fig. 9).

There was a moderate amount of interstitial fibrosis well marked beneath the pleura, at the margins of secondary lobules, and around bronchopulmonary trunks. It tended to be nodular with central dust-laden macrophages (Fig. 10). These features were, however, complicated by the organizing bronchopneumonia. There was no evidence of focal emphysema. The pleural scars consisted of dust-pigmented fibrous tissue, probably healed tuberculosis. There was no evidence of atypical alveolar metaplasia.
FIG. 5—Gough-Wentworth large section (1 natural size) of left lung of Case 3 showing cystic change.

FIG. 6—Alveolar cell carcinoma. Haematoxylin and eosin. × 150.

FIG. 7—Alveolar cell carcinoma, showing mitosis. Haematoxylin and eosin. × 630.
FIG. 8.—Squamous carcinoma with overlying bronchial squamous metaplasia. Haematoxylin and eosin, × 85.

FIG. 9.—Section from Case 4 showing organizing bronchopneumonia with lung fibrosis. Haematoxylin and eosin, × 100.

FIG. 10.—Section from Case 4 showing nodular interstitial fibrosis. Haematoxylin and eosin, × 88.
Case 5.—A man aged 57 was subjected to left pneumectomy when squamous carcinoma was diagnosed. There was a 2½ cm. diameter carcinoma involving the site of origin of the left upper lobe bronchus and extending to within 2 cm. of the pleura. The lung distal to this showed partial collapse and bronchopneumonia. Generalized interstitial fibrosis was minimal, “cystic change” and emphysema were absent. The patient is still alive and well 18 months after operation.

Microscopy.—The origin of the left upper lobe bronchus was partially occluded by poorly keratinizing (Grade III) squamous carcinoma. The tumour also involved the left apico-posterior bronchus. The left upper lobe showed early bronchopneumonia and partial collapse.

Squamous metaplasia was present in the left main bronchus and its divisions, both in continuity with the tumour (Fig. 11) and separate from it.

Interstitial fibrosis was slight. The alveolar lining cells were proliferating with the formation of dust-laden macrophages, but showed no indication of malignancy (Fig. 12).

**Tissue Analysis**

Material was available for chemical analysis in Cases 4 and 5 (Table 4). Control material consisted of pooled samples of non-industrial lungs and coal-workers’ lungs, 25 of each for nickel and 10 of each for arsenic and copper. Both cases showed measurable amounts of nickel, 90 and 120 p.p.m. in dried lung, the lower limit of detection being 5 p.p.m. No arsenic could be detected in the two cases analysed, the lower limit of detection being 0·2 p.p.m. of dried lung. Nickel and arsenic were not detected in the control specimens. Copper was also estimated, being 460 and 2,810 p.p.m. in dried lungs whereas the controls showed 29 and 31 p.p.m.

**Discussion**

These cases were the only ones available to the author and may not be representative; by chance four of the five showed pulmonary carcinoma. The case without carcinoma was included in order that

![Fig. 11.—Section from Case 5, showing squamous metaplasia in continuity with squamous carcinoma. Haematoxylin and eosin, × 250.](image1)

![Fig. 12.—Alveolar phagocytes. Haematoxylin and eosin, × 350.](image2)

**Table 4**

<table>
<thead>
<tr>
<th>Chemical Analysis</th>
<th>Ash (%)</th>
<th>Nickel in Dried Lung (p.p.m.)</th>
<th>Arsenic in Dried Lung (p.p.m.)</th>
<th>Copper in Dried Lung (p.p.m.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Controls</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coal-miners</td>
<td>14-95</td>
<td>&lt; 5</td>
<td>Nil</td>
<td>31</td>
</tr>
<tr>
<td>Non-miners</td>
<td>14-1</td>
<td>&lt; 5</td>
<td>Nil</td>
<td>29</td>
</tr>
<tr>
<td>Case 4</td>
<td>12</td>
<td>90</td>
<td>Nil</td>
<td>460</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>120</td>
<td>Nil</td>
<td>2,810</td>
</tr>
</tbody>
</table>

*Nickel controls were 25 coal-miners and 25 non-miners. Arsenic and copper controls were 10 coal-miners and 10 non-miners.*
as many as possible with and without carcinoma could be examined. It is only by documenting all available cases that one can evaluate the significance of the pathological findings.

In the present series, three of the four carcinomata were squamous. Løken (1950) described three squamous carcinoma and Amor (1939) found one squamous and three anaplastic. Thus seven of the 11 reported cases are squamous. These figures are in agreement with the general opinion that the squamous variety predominates in industrially induced carcinoma. Thus Holleb and Angrist (1942) found that 60% of asbestos cancers were squamous. This finding, if confirmed in more cases, might be used to substantiate the action of an external carcinogen in nickel workers. The finding of alveolar cell carcinoma in Case 3 does not suggest the action of a carcinogen as this rare tumour has seldom been reported in industrial workers, though Jones Williams (1957) has recently reported one in an asbestos worker.

The epithelium of non-respiratory and respiratory air passages was examined for any changes which might be specific or suggest a premalignant state. Bronchial squamous metaplasia was found in two cases, both with squamous carcinoma, but they also showed evidence of chronic inflammation. As Niskanen (1949) found squamous metaplasia in 50% of lungs with chronic infection and Weller (1953) in 70% of non-industrial lung cancers, it cannot be considered specific for nickel workers nor definitely premalignant. It is an interesting supposition, however, that chronic inflammation resulting in squamous metaplasia, together with an added carcinogenic agent, might produce carcinoma. As regards respiratory air passages, Case 2 showed atypical alveolar metaplasia, but Jones Williams (1957) in a survey of 287 cases of industrial lung fibrosis from occupation, with varying incidence of lung cancer, could not relate this to the development of malignant change. It is therefore concluded that in this small series of five cases there are no diagnostic or definite premalignant epithelial changes in non-respiratory or respiratory air passages.

Two of the five cases showed honeycomb or "cystic change" which was associated with, and is probably a manifestation of, bronchiectasis and bronchiolectasis. The cysts were thick-walled which distinguishes them from emphysema. Neither of the two cases showed carcinoma of major bronchi but one showed atypical alveolar metaplasia and the other alveolar cell carcinoma; the latter also showed extensive interstitial fibrosis. The presence of "cystic change" is not diagnostic of industrial lung disease, including nickel, and may be seen in diffuse lung fibrosis from many causes, including eosino-

philic granuloma (Spillane, 1952), scleroderma (Evans and Parker, 1954), and tuberculosis (Heppleston, 1956). In Case 2 it may have been congenital in origin.

Pulmonary fibrosis was present in all five cases. It involved predominantly the interstitial tissue and showed no specific localization or pattern, with the exception of Case 4 where there was a suggestion of nodularity. There was no resemblance to silicosis. Pleural thickening was inconspicuous. The fibrosis was indistinguishable from the diffuse interstitial fibrosis of industrial origin, such as asbestosis, and from that seen in non-industrial long-standing inflammation. In some cases it was associated with intra-alveolar organization, but affected primarily the alveolar walls and peribronchial tissue. There is some experimental evidence to incriminate nickel as a cause of interstitial fibrosis (Barnes and Denz, 1951), but in the present cases it is probable that the fibrosis is the result of chronic pulmonary inflammation, as four of the five showed evidence of inflammation. Only one of Løken's (1950) cases showed any fibrosis while Amor (1939) does not give any details apart from the histology of the tumours.

Carcinoma may have developed in these men irrespective of the occupation or it may have been the result of a carcinogenic agent. The statistical evidence (Doll, 1958), strongly suggests the presence of a carcinogen in this industry. He finds that lung cancer is approximately five times as frequent as in the general population, and further that the risk in men described on the death certificate as having worked directly on some part of the extraction process is about twice that for other employees. All five cases in this series can be considered as process workers. It is of interest that of the four men with carcinoma, one started work in 1922 and three after 1924. These dates are noted as the refinery underwent considerable reorganization between 1920 and 1924, which included the change from the use of crude to pure arsenic-free sulphuric acid, the wearing of masks, and general dust suppression.

There are two substances present to which these men were exposed which may be incriminated as carcinogenic agents, nickel and arsenic. Nickel is suspect both as the element and as the gas, nickel carbonyl. Hueper (1952) produced malignant tumours, predominantly sarcoma, in rats, by parenteral injection of pure nickel suspended in lanolin. Sunderman (1958) claims to have produced lung cancer in rats by nickel carbonyl inhalation. Three of the four men with carcinoma had mild attacks of acute nickel carbonyl poisoning but the interval between death is too short to agree with the long latent interval usually accepted for the induction of industrial carcinoma. This, however, does
not exclude long-continued subclinical exposure which may have been suffered by three of the four patients with carcinoma who had worked in the nickel plant for six, nine, and 17 years respectively (Table 2). Stringent precautions are, however, taken to avoid and detect gas leakages in the carbonyl process. All five cases were exposed to nickel (Table 2) which was present in the lungs of the two cases analysed (90 and 120 p.p.m. respectively) and was not detectable in 50 control cases (Table 4). This represents between twenty and a hundredfold increase, as the lower limit of detection was 5 p.p.m.

Arsenic must also be considered as it is an accepted skin carcinogen. There is no definite evidence, however, that it produces lung cancer (Saphe, 1930; Hill and Fanning, 1948; Snegireff and Lombard, 1951). Tissue for arsenic analysis was available in Cases 4 and 5, and none could be detected. It is therefore considered unlikely that arsenic was concerned with the development of carcinoma in these two cases.

In Cases 4 and 5 copper was present in amounts up to 100 times that of the controls (Table 4). While copper is not a recognized carcinogen, its presence proves the fact of metal inhalation. Together with nickel it is retained in the body, while arsenic if absorbed is probably completely excreted.

One particular carcinogen cannot be definitely incriminated and it may be that there is a combination of carcinogens. Another possibility is that the state of the patient allows a weak carcinogen or combination of carcinogens to become effectively carcinogenic. Pulmonary inflammation might fit this role as a predisposing factor, though Doll and Hill (1952) could not prove an association between previous respiratory infection and the development of carcinoma. Case and Lea (1955), from a study of war pensioners, suggest that chronic bronchitis may be associated with the development of lung cancer. There is evidence of long-standing inflammation in four of the five cases as shown by the presence of varying degrees of bronchiectasis and/or cystic change, together with interstitial fibrosis. It may be that men with chronic inflammatory changes may, in the presence of nickel, be more liable to the development of carcinoma.

The cause of death in two of the five cases was right heart failure and it is of interest that both these cases showed “cystic change” (honeycomb lung), together with interstitial fibrosis. Two patients died with multiple metastases and no evidence of cor pulmonale, while the fifth patient is alive and well 18 months after pneumonectomy.

Summary

Lungs from five men working at the same nickel refinery (nickel carbonyl process) were examined macroscopically and histologically. The length of employment ranged from 10 to 35 years. Four had developed carcinoma of the lung, three squamous and one alveolar cell. No diagnostic or premalignant epithelial changes were found.

Four cases showed evidence of long-standing inflammation, two of these showed honeycomb lung and died with cor pulmonale. All cases showed varying degrees of non-specific diffuse interstitial fibrosis, probably of infective rather than industrial origin.

Nickel and copper were present in excess in the two cases analysed, but no arsenic could be detected.

The aetiology is discussed, and, although the evidence is inconclusive, it is possible that nickel together with chronic inflammation may be the carcinogenic factor.

The material was made available to me in three cases by Dr. M. E. Sharp, and the other two by Drs. D. Davies and D. B. Richards, and to them I extend my sincere thanks. I am indebted to Prof. J. Gough for his criticisms, to Dr. J. G. Morgan for his comments, and to Dr. E. A. Danino for access to his clinical notes. The chemical analyses were kindly performed by Miss E. S. Nelson, Safety in Mines Research Establishment, Sheffield, and Dr. L. E. Coles, Public Analytical Laboratory, Cardiff.

REFERENCES


