tumour and urine extracts, vascular studies of resected lungs, and autonomic block are all possible keys to the solution of this fascinating problem.

Summary

Bronchial carcinoma may now be regarded as the chief cause of generalized hypertrophic pulmonary osteoarthropathy. A review of 24 patients with this syndrome encountered during the past seven years is presented.

The pathogenesis of osteoarthropathy has been reviewed in the light of our clinical studies, past experimental work, and the dramatic and invariable "cure" effected by tumour removal.

Such patients are often treated for rheumatism or rheumatoid arthritis for many months, and may become bedridden cripples before the presence of a silent lung tumour is suspected.

Fifteen of the patients were submitted to lung resection. Only four are alive. Operative results in this type of tumour might be expected to improve when the significance of such joint symptoms becomes more generally appreciated.

We wish to thank Mr. Bruce Dick for his ever-helpful co-operation and stimulation; Dr. Angus Scott (Cases 3, 4, and 15) and Professor Sir John McNee (Case 16) for permission to record their respective patients; Mr. R. S. Barclay and Mr. Kenneth Fraser for surgical assistance and advice; and Dr. Ian Anderson for biochemical determinations. For the photographic reproduction we are indebted to Mr. H. C. Gray, of the clinical photographic department, Victoria Infirmary, Glasgow.

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CARCINOMA OF BRONCHUS IN ASSOCIATION WITH ACTIVE PULMONARY TUBERCULOSIS

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Both pulmonary tuberculosis and carcinoma of the bronchus are common diseases, and it is not a matter of surprise that the two conditions should at times be encountered together. It is generally accepted that there has been, in recent years, an absolute increase in the incidence of bronchial carcinoma, a disease more common in middle-aged and elderly males. With modern methods of treatment, the mortality from pulmonary tuberculosis has shown a dramatic fall, and this implies that more tuberculous patients are surviving into the cancer age. In addition, more cases of active pulmonary tuberculosis are being found in the older men. It is to be expected, therefore, that the two diseases will be encountered more and more in association. For this reason it is of interest to describe the following six cases with the dual pathology. They were all seen during the past three years, the diagnosis being made during life and confirmed at necropsy. They demonstrate the various problems which arise in the diagnosis of these conditions when associated, and their possible interrelationship.

Case 1

A plasterer aged 50 was found, in 1935, to be suffering from bilateral fibrocavernous tuberculosis, the left upper lobe being chiefly affected. He spent two years in a sanatorium, at the end of which time his sputum still contained tubercle bacilli, but his condition was improved. He remained well and at work for the next 10 years in a stable chronic condition. When seen in 1950 he was bothered by a wheezy bronchitis, but for two years there had been no change in the radiological appearances of his lungs, which showed many calcified foci on the right side, while on the left there was some fibrotic disease of the upper lobe.

In October, 1951, he began to deteriorate. There was some staining of the phlegm, he became easily fatigued, but there was little loss of weight. He was forced to give up his work. Radiologically there was a coalescence of the opacities present in the left upper lobe. In February, 1952, streptomycin and P.A.S. were administered to him at home, with little benefit, and in May it was necessary to admit him to hospital. Tomograms of the left upper lung showed a number of large cavities, those lying posteriorly having a fairly regular outline, but there was one anteriorly which had a very irregular wall. This appearance suggested the possibility of a carcinoma having supervened on his chronic pulmonary tuberculosis. He was too ill for bronchoscopy. Despite the administration of further streptomycin, together with isoniazid, his condition deteriorated. In October the sputum still contained tubercle bacilli, but thereafter all sputa were reported as negative for tubercle bacilli on direct smear. Radiologically there was the gradual development of a large dense opacity in the left upper lung, and the left hemidiaphragm became paralysed. No radical therapy was possible, and in March, 1953, he died.

Necropsy revealed the presence of chronic fibrosis and cavity formation of a tuberculous nature in the apices of both lungs, but in the left lung there was also a round necrotic mass (7.5 cm. in diameter), macroscopically a carcinoma, lying mainly in the upper lobe, against the hilum and the aorta.

Histology showed the carcinoma to be of the epidermoid type, arranged in solid masses, with a little differentiation

into squamous cells. The cell type was relatively polymorphic, and the mitotic frequency relatively high. Tubercles were seen in sections from the adjacent portions of the lung.

Case 2

A railway clerk aged 60 was discovered by mass radiography in 1946 to have quiescent tuberculous lesions in both upper lobes. In 1949, however, he developed a cough, and radiographs showed some slight apical fibrosis on the right side, but on the left side there was infiltration in the upper and mid-zones not previously present in 1946. Examinations of the sputum were negative, but Löwenstein culture of one laryngeal swab in October, 1949, revealed a scanty growth of tubercle bacilli. In 1950 tomograms demonstrated a small thick-walled cavity in the left upper lobe. Apart from three months of bed rest, he did not receive any specific treatment, but continued at work feeling fairly well, although he did complain of undue fatigue. In April, 1952, radiographs showed his condition to be stable.

In July he developed a bad "cold," which was followed by stabbing pains in the right axilla, spreading towards the back of the right chest. At this time he had already retired from his work, but he still was very fatigued. He was bothered by considerable dyspepsia, and was losing weight. Radiologically he was found to have developed a new circumscribed homogeneous opacity in the right upper zone. Tomograms showed a well-defined opacity, but there was no central excavation. Sputum tests were negative for tubercle bacilli.

Bronchoscopy was performed, but with negative result. Nevertheless, the presence of a carcinoma was strongly suspected on radiological grounds, but treatment, either by surgery or radiotherapy, was not thought advisable. In January, 1953, he had considerable pain in the right chest and arm and he developed severe headache and vomiting. It was thought that he now had a cerebral metastasis. In April he had to be admitted to hospital. Radiologically the opacity in the right upper lobe had steadily increased in size, but sputum examinations for tubercle bacilli were negative. Later his liver enlarged, he became jaundiced, and he died in August, 1953.

Necropsy revealed an extensive lesion of the right upper lobe, consisting of areas of carcinoma round one division of the right upper lobe bronchus, and a firm plaque of similar appearance under the pleura, both layers of which were firmly adherent. The rest of the right upper lobe was necrotic, with areas suggestive of tuberculosis. The left upper lobe contained fibrocasseous tuberculous disease, with cavitation. There were also scattered firm nodules in both lungs, due to metastases. The liver was enlarged and showed fatty infiltration but no metastases, and examination of the brain failed to show any evidence of secondary deposits.

Histology showed the carcinoma to be of undifferentiated anaplastic type, and there were some foci of tuberculosis adjacent.

Case 3

A painter aged 53 developed in October, 1951, a cough with sputum, associated with fever and loss of weight. When seen in January, 1952, he was found to be in very poor condition, 1½ st. (10 kg.) underweight, with a marked kyphosis and an emphysematous chest. A chest radiograph revealed evidence of tuberculous infiltration and fibrosis in the left upper zone, the right lung being quite clear. Sputum tests were negative for tubercle bacilli. It was significant that a chest radiograph in 1948 had been normal. He spent six weeks in a sanatorium, which he left prematurely at his own request. He was then treated at home with rest and P.A.S. for four months, but with little benefit.

In May, 1952, a new small opacity appeared in the peripheral portion of the right first intercostal space. During the course of the next two years his general condition and the radiological appearance of the lesions in the left apex did not seem to alter, but the opacity in the right upper

zone showed a steady increase in size, becoming a large, rounded mass. Sputum tests were negative for tubercle bacilli. The blood Wassermann reaction was negative. His haemoglobin was 87%, and white blood count 13,100 (87% polymorphs).

In June, 1954, his clinical condition deteriorated, and he became more easily dyspnoeic. Bronchoscopy was not attempted, as it was not thought likely that any abnormality would be visible, since the growth, if present, was peripheral. Nevertheless, on clinical and radiological grounds, he was believed to have a carcinoma of the right lung in addition to the quiescent pulmonary tuberculosis in the left lung. Radical therapy was not regarded as being indicated.

In August he developed severe headaches and became mentally confused. He was admitted to hospital, where he was found to have papilloedema, and a cerebral metastasis was suspected. There were now also some subcutaneous nodules under the skin of the right forearm which had not been previously present. He became comatose, and soon died.

Necropsy revealed fibrotic tuberculous lesions in the left apex, adherent to the chest wall, while in the right upper lobe there was a large rounded solid mass of carcinoma (10 cm. in diameter) replacing most of the lobe. The nodules under the skin of the right forearm were confirmed to be secondary deposits. The right cerebellum contained one large metastasis (5 cm. in diameter).

Histology revealed the carcinoma to be of the undifferentiated, polymorphic, large-celled variety. Sections of the left apex showed evidence of fibroid tuberculosis.

Case 4

An unskilled labourer aged 64 developed in January, 1953, a cough associated with undue dyspnoea on effort. He also lost his appetite, had considerable abdominal pain after meals, and was losing weight. In March, 1953, his doctor referred him for a barium-meal examination, but no abnormality was discovered in his alimentary tract. One month later the cough was worse, there was a great deal of offensive yellow sputum, and his voice became husky. He was referred for a chest radiograph, and this revealed a dense opacity in the base of the left upper lobe with central excavation. There was pleural thickening over the left chest wall laterally. In the left lower lobe were miliary changes suggestive of tuberculous disease. He was then admitted to hospital, and the following facts were ascertained regarding his previous history. His mother had died of pulmonary tuberculosis. He himself had had three attacks of "pneumonia" before the age of 35. He had been a regular smoker of 10 cigarettes daily for most of his life.

Examination revealed him to be a very ill wasted man, with marked clubbing of the fingers. There were dullness and bronchial breath sounds, with many rales and rhonchi, on the left side of his chest, and the liver was enlarged. His haemoglobin was 72% and white blood count 16,800 (82% polymorphs). Sputum examinations revealed the presence of tubercle bacilli on direct smear. Pulmonary tuberculosis was diagnosed, but the dense opacity in the base of the left upper lobe made one suspicious of the presence of a carcinoma in addition. Any radical therapy for a carcinoma was, however, quite out of the question. Streptomycin and P.A.S. were administered, but his condition rapidly deteriorated, and he died a fortnight after admission to hospital.

Necropsy revealed the left upper lobe to be a solid mass of carcinoma and cavitation. There was one small focus of carcinoma in the right upper lobe near a bronchus. The left lower lobe presented the appearance of a localized miliary tuberculosis. The liver contained four large metastases (5-7.5 cm. in diameter). On the left side of the neck there was a large mass of glands, and smaller masses were in the anterior mediastinum and around the tail of the pancreas. There was a subcutaneous nodule at the

umbilicus, and scattered enlarged glands in the mesentery, the para-aortic area, and the pelvis.

Histology showed the carcinoma to be small-celled, poorly differentiated to an epithelial character. The cell type was moderately polymorphic, and the mitotic frequency relatively moderate. There were also tubercles distributed throughout the left lower lobe.

Case 5

A bookmaker's clerk aged 45 was seen in January, 1953, with a history of cough and sputum of six months' duration. He had regularly smoked 20 cigarettes daily. For three months he had been feeling increasingly fatigued, and had been running an evening pyrexia—to 99.4° F. (37.4° C.)—and had lost 1½ st. (10 kg.) in weight. His father had died of pulmonary tuberculosis.

On examination he was seen to be very ill, and was mentally confused. There was early clubbing of the fingers, and numerous crepitations could be heard in the left upper lung. A chest radiograph revealed a large cavity in the left upper zone, with infiltration in the left upper and mid-zones. The right lung was normal. It was of interest that a chest radiograph, taken when he was demobilized from the Royal Navy in 1944, was normal. Examination of the sputum revealed tubercle bacilli on direct smear. A diagnosis of active pulmonary tuberculosis was made, and he was admitted to hospital. Treatment with streptomycin and P.A.S. was begun at once, but despite this his condition deteriorated. In May he was bronchoscoped, but, owing to gross upward displacement, the orifice of the left upper lobe bronchus could not be seen. A biopsy was carried out on an enlarged gland in the neck, and histological examination showed the gland to be extensively replaced by an undifferentiated carcinoma, probably squamous-celled. It was now realized that a carcinoma of the lung was present, complicated by pulmonary tuberculosis, but no radical therapy for the carcinoma was feasible.

His condition deteriorated rapidly. He soon became cachectic, and clubbing was more pronounced. Radiologically there was now a larger dense mass in the left upper lung, in which there was a cavity (with fluid levels), the walls of which were very irregular, and in which one could distinguish several nodules of growth. His haemoglobin was 58%, and white blood count 15,200 (87% polymorphs). A right hemiplegia developed, and several epileptiform fits occurred, followed by marked impairment of speech. A skull x-ray film showed a small area of thinning of bone in the left frontal area, and it was thought that a cerebral metastasis was present. In July, 1953, he died.

Necropsy revealed a bronchial carcinoma involving and surrounding the left upper and lower bronchi. Distal to this in the lung was a large pus-filled abscess cavity (5 cm. in diameter). There were secondary involved glands in the mediastinum and both sides of the neck, as well as one plaque on the anterior surface of the liver and an enlarged para-aortic gland on the left side. In the brain there was a large cystic area in the left parietal region, the pathology of which was obscure.

Histology showed the lung substance to be infiltrated by cells of a poorly differentiated carcinoma of the bronchus. There were also tuberculous giant cells and endothelial cells.

Case 6

A retired welfare officer aged 69 was seen for the first time in January, 1953. He had suffered from bronchitis for many years, and in 1950 had had a brief attack of left-sided "pleurisy." He had smoked 20 cigarettes daily for most of his life. He had lost weight during the previous three months, and for one month had been having pains in the left chest associated with undue shortness of breath. His cough had become worse, and the phlegm was streaked with blood.

On examination his general condition was very poor and he was markedly dyspnoeic at rest. There was no clubbing of the fingers, but wheezy rhonchi could be heard in both lungs. A chest radiograph revealed some scattered opacities

in the right lung, and on the left side there was a dense opacity arising from the hilum and radiating upwards and outwards into the left upper lobe. Examination of the sputum was negative for tubercle bacilli, and the E.S.R. was 56 mm. in the first hour (Westergren). A diagnosis of carcinoma of the bronchus was made, but further investigation by bronchoscopy was not carried out, in view of his age and very poor condition.

In March he was admitted to hospital. He was cachectic, with an irregular pyrexia—to 102° F. (38.9° C.)—and had now developed clubbing of the fingers. Examination of the chest revealed diminished movement and air entry on the left side, and the coin test was positive. A radiograph revealed that a spontaneous pyopneumothorax had taken place on the left side. The sputum contained scanty tubercle bacilli on direct smear. The haemoglobin was 70%, and the white blood count 17,300 (81% polymorphs). The left chest was aspirated and turbid yellowish-green fluid withdrawn. This was lymphocytic and no tubercle bacilli were seen on direct smear, but Löwenstein culture proved positive. It was realized that the carcinoma was now accompanied by a tuberculous pyopneumothorax, but no radical therapy would avail. He deteriorated rapidly, and died in May, 1953.

Necropsy revealed the left lung to be a solid mass of cancer and abscesses, and perhaps tubercle, too. The left hilar glands were replaced by cancer. The neoplastic left lung had spread over the mediastinum, but the glands themselves were not obviously invaded, apart from the hilar ones. The left pleural cavity contained some purulent fluid, and the right upper lobe showed miliary tuberculosis.

Histology showed a bronchogenic carcinoma with solid epithelial alveoli but no further epidermoid differentiation. The cell type was fairly regular and the mitotic frequency relatively low. There were also scanty tuberculous follicles.

Discussion

It is now nearly 150 years since Bayle (1810), the great teacher of Laennec, described the "phthisis cancéreuses," but he used the term "phthisis" to include the wasting which might ensue from any pulmonary disease, and it is doubtful whether he was in fact describing tuberculosis and carcinoma occurring together in the lungs. Credit for the first description of the two diseases coexisting must be given to Penard (1846). In recent years it has become increasingly recognized that carcinoma and tuberculosis may occur together in the lungs, and reports have been published on the subject (Fried, 1935; Cohen, 1949; Blasi, 1950; Shefts and Hentel, 1950; Coutts, 1951; Helm and Moon, 1952; Nuessle, 1953).

Incidence

The incidence of the association of the two diseases at necropsy has varied greatly in the large series published by different authorities, and is shown in Tables I and II. Among live patients, Källquist (1952) has described a series of 5,527 cases of pulmonary tuberculosis, of which 11 (0.2%) had carcinoma of the bronchus as well; and Seyfarth (1952), in a series of 1,103 cases of carcinoma of the lung, found 11.42% to have evidence of tuberculosis also.

The discrepancies between these different series may partly be explained by the varied interpretations adopted

TABLE I

Authority	Necropsies on Pulmonary Tuberculosis	Coincident Carcinoma
Gerstl <i>et al.</i> (1946)	1,600	0.44%
Drymalski and Sweany (1948)	2,000	0.75%

TABLE II

Authority	Necropsies on Carcinoma of Lung	Coincident Active Tuberculosis
Farber <i>et al.</i> (1949)	266	3.8%
Bryson and Spencer (1951)	866	1.8%
Gloyne (1951)	648	5.5%

by the different workers regarding what constituted tuberculous disease. Thus Bryson and Spencer's (1951) low figures included only those with chronic active pulmonary tuberculosis, as distinct from mere microscopical evidence of old chronic tuberculous lesions.

It may be concluded that the incidence of active tuberculous changes in patients suffering from cancer of the lung (as exemplified in Cases 4, 5, and 6) are not rare, while patients with pulmonary tuberculosis developing a new growth (as in Cases 1, 2, and 3) are less common.

Problems of Diagnosis

When a carcinoma of the bronchus develops insidiously in a known case of chronic pulmonary tuberculosis (as in Cases 1, 2, and 3), the diagnosis of the dual pathology is likely to be more difficult than when a diagnosed case of carcinoma of the bronchus is complicated by the finding of tubercle bacilli in the sputum (as in Cases 4, 5, and 6).

Clinically, carcinoma of the bronchus should be suspected in a man over the age of 40, usually a smoker, and known to have chronic pulmonary tuberculosis, who appears to be more ill than his tuberculous condition alone warrants, or if he is unusually dyspnoeic or has a pain in the chest which is persistent. It is of interest that in the six cases described above, haemoptysis was not a conspicuous feature. Another suspicious feature is the failure to respond to specific antituberculous chemotherapy. There may, of course, be many reasons for this, but one of them may be the complication of a carcinoma of the bronchus. Similarly, excessive anaemia and a polymorphonuclear leucocytosis (as in Cases 3, 4, 5, and 6) may indicate the presence of a carcinoma superimposed on the tubercle.

The radiological features suggestive of carcinoma are the superimposition on the tuberculous changes of a dense opacity, especially near the hilum. Enlargement of hilar glands, paralysis of a hemidiaphragm, and erosion of a rib are also helpful diagnostic signs. Where there is a thick-walled cavity with a very coarse irregular lining (often best seen in tomograms), it may merely mean a breaking-down neoplasm, but it may also indicate a cancerous development in a tuberculous cavity (as in Case 1).

Bronchoscopy (which was possible only in Cases 2 and 5) did not prove at all helpful. The diagnosis of a cerebral secondary deposit, or the biopsy of an enlarged gland (as in Case 5) or of a subcutaneous nodule (as in Case 3), may be conclusive, but it indicates that such a metastasis precludes any hope of a radical cure.

So long as it is remembered that carcinoma and tubercle in the lung do not exclude one another, it is very unlikely that the diagnosis of the two conditions occurring together will prove difficult or be unduly delayed. In a known case of pulmonary tuberculosis the early diagnosis of a superimposed carcinoma is of great importance, since otherwise it may prove too late to treat. Although the six cases described here were diagnosed correctly during life, the carcinoma was too advanced in all of them to allow any radical therapy to be considered. It should be remembered that the finding of tubercle bacilli in a case of carcinoma of the bronchus may be of minor importance so far as the practical management of the case is concerned. The treatment of the cancer takes precedence.

Relationship of the Two Diseases

The association of tuberculosis and carcinoma of the lung may be considered in various ways.

1. *The Two Diseases Exert a Mutual Antagonism.*—Rokitansky (1854), as a result of his famous morbid anatomical studies, first propounded the theory that there was an antagonism between cancer and tuberculosis, and this was supported by Raymond Pearl (1929) in his statistical studies based on the records of the Johns Hopkins Hospital. Cooper (1932), however, in his comprehensive study of the association of the two diseases, showed conclusively that the two diseases were not antagonistic.

2. *Tuberculosis (active or healed) is a Factor in the Production of Carcinoma.*—Cherry (1931), as a result of experiments on mice and his statistical studies, believed that cancer was predisposed to by previous tuberculous disease. Woodruff and Nahas (1951), analysing 23 cases of carcinoma of the bronchus, found 12 which were squamous-celled, and these were associated with large calcified foci in the same lobe or adjacent tracheo-bronchial lymph node, but not with active tuberculous disease. They suggested that it was healed tuberculosis which, leading to calcification and bronchiectasis (usually saccular, in the upper lobes), predisposed to the development of cancer, since smoking tended to produce an accumulation of tobacco products in the saccules. It has been thought by many that chronic irritation and atypical regeneration of epithelial tissues in old tuberculous cavities may lead to neoplastic changes. Bryson and Spencer (1951), however, found in the 866 cases of cancer of the lung they studied *post mortem* only four examples where the cancer arose in the wall of a bronchiectatic cavity.

3. *Cancer Activates Pre-existing Tuberculous Disease.*—When one considers the frequency of healed tuberculous foci in the lungs it is not surprising that carcinomatous infiltration into the lung, as well as the debility produced by the cancer, should lead to erosion of the tuberculous foci, with proliferation of the tubercle bacilli and reactivation of the tuberculous disease. Thus Pagel (1934) showed that a cancer nodule in the lung may be seen to be encircled by recent macroscopic tuberculous foci. Even if a very small lesion is eroded by growth, some tubercle bacilli may be found in the sputum, but this may be of minor importance (Gloyne, 1951).

It is very likely that either of the points of view described in (2) and (3) above may operate in different circumstances. It is also true, however, that in many cases the two diseases arise quite independently, running their separate courses with little effect on each other.

Summary

Six cases in which carcinoma of the bronchus and active pulmonary tuberculosis were associated in male patients over the age of 40 are described. In three a carcinoma developed insidiously in known cases of chronic pulmonary tuberculosis. In the other three, carcinoma of the bronchus was complicated by the presence of active pulmonary tuberculosis.

The interrelationship of the two diseases and the problems of their diagnosis are discussed.

The incidence of the two diseases occurring together is presented, and it is suggested that possibly this association will now be encountered more frequently.

I should like to thank Dr. C. O. Edwards for allowing me to quote Case 2, and Dr. J. C. Lees for giving me access to his necropsy records.

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