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Pulmonary Actinomycosis Simulating Bronchogenic Carcinoma

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ABSTRACT

During a 2½-year period, in a 360-bed general hospital, three cases of pulmonary actinomycosis were encountered in men aged 38, 47 and 49 years. In each instance the symptoms, signs and radiological and laboratory findings were such as to warrant a presumptive clinical diagnosis of bronchogenic carcinoma. Thoracotomy was performed in each case. This experience suggests that a definitive clinical diagnosis of bronchogenic carcinoma should not be made without histological evidence. Furthermore, such individuals should have the benefit of exploratory thoracotomy on the off-chance that the pulmonary lesion may be benign and amenable to treatment. Above all it should be remembered that pulmonary actinomycosis can simulate bronchogenic carcinoma to a marked degree.

BECAUSE of the increasing incidence of bronchogenic carcinoma the good clinician today has a high "index of suspicion" with respect to this particular malignancy, whenever he encounters a patient with chest symptoms. Where histological confirmation of a neoplasm is lacking, such as sputum containing malignant cells, the diagnosis of bronchogenic carcinoma is made after thorough sifting and evaluation of history, physical examination, laboratory data and, most important, radiographic studies of the chest. It is common knowledge that one of the great pitfalls in a diagnosis so made is the possibility that a benign pulmonary lesion is present rather than a malignant one. This benign lesion may so closely mimic a neoplastic one that it is well nigh impossible to differentiate one from the other clinically. In this report three cases of pulmonary actinomycosis will be described, which, for good and substantial reasons, were diagnosed as bronchogenic carcinoma on clinical grounds.

Case Reports

Case 1.—In the course of a complete physical examination, G.F., a 47-year-old executive, was found to have a suspicious-looking radiograph of his chest. Two weeks later, on September 26, 1959, he was admitted to hospital for further investigation of this chest lesion. This patient had no complaints referable to the respiratory system. He had smoked three to five cigars daily for about 10 years and before that had smoked "a few" cigarettes daily. His past history revealed nothing which contributed to the explanation of his chest lesion.

Chest radiographs taken in the hospital revealed a parenchymal density extending from the left root area somewhat towards the periphery, which appeared to be localized mostly in the anterior segment of the left upper lobe (Fig. 1.) A left bronchogram was reported as essentially normal. The radiographic appearance of the lung was considered to be non-specific. However, in view of both the negative bronchogram and the negative bronchoscopic examination, an inflammatory or granulomatous lesion was considered on the basis of the radiological findings, as well as a neoplasm.

Examination of the sputum for acid-fast bacilli and malignant cells was negative. A scalene node biopsy showed no evidence of neoplasm. The hemoglobin was 88%; the leukocyte count 7400 cells per c.mm., and the sedimentation rate 34 mm. in one hour. The final preoperative diagnosis was bronchogenic carcinoma of the left lung.

Operative findings and clinical course.—After evaluating all features of the case, an exploratory thoracotomy was performed. A mass was felt in the anterior segment of the upper lobe of the left lung. Since this was covered with a fibrinous exudate, it was thought to be inflammatory. The left upper lobe was then resected. After a stormy postoperative course, the patient was discharged well and remains well at the present writing.

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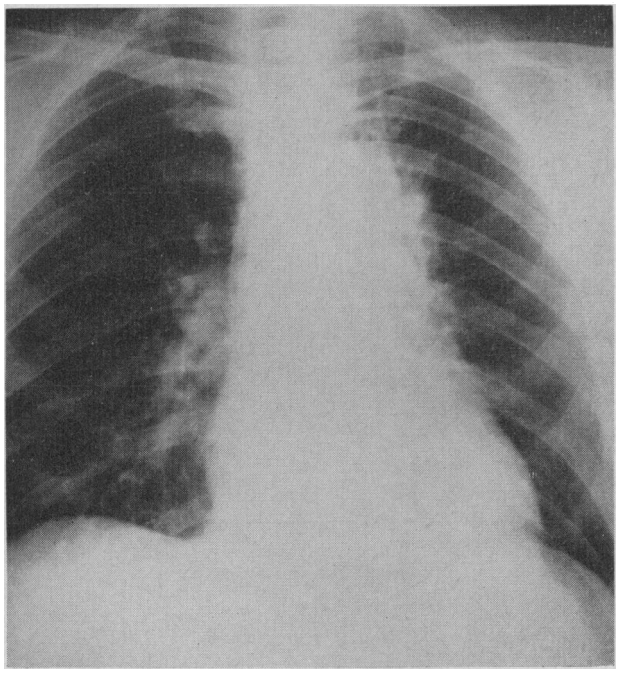

Fig. 1.—Case 1. Posteroanterior view of chest. Note the parenchymal density extending from right root area towards the periphery.

Pathological findings.—The specimen received in the pathology laboratory consisted of the upper lobe of the left lung and two moderately enlarged black lymph nodes from the hilar region. Along the anterior surface of the upper lobe in the mid-portion, a firm indurated area was seen measuring 6 cm. in maximum diameter. This extended into the parenchyma of the lung for a distance of approximately 4 cm. The cut surface showed that the indurated area was made up of firm tissue with grey streakings; distributed throughout this tissue were yellowish areas which did not appear to be necrotic or liquified. The lesion was not encapsulated or even well demarcated from the adjacent lung tissue. A smaller similar nodular yellowish area was seen in the adjacent lung parenchyma. The pleura overlying the lesion was thickened and hemorrhagic, and showed some fibrinous adhesions. Microscopically, sections taken from representative areas from the lesion varied in appearance. In some places there was a predominance of suppuration, while in others the alveoli were distended with granular lipoid-laden macrophages. The alveoli containing these macrophages showed occasional epithelial transformation. In the parenchyma, marked chronic inflammatory cellular reaction with occasional multinucleated giant cells of the foreign-body type could be seen. Dense bands of fibrous connective tissue containing chronic inflammatory cells were also present. Some lymphoid follicles were noted. In a few areas the lumina of the bronchioles were collapsed, with hyperplasia of their lining epithelial cells.

In the purulent areas, small abscesses were formed. In a few of these abscesses, colonies of morphologically typical Actinomyces were observed (Figs. 2 and 3).

The final pathological diagnosis was actinomycosis of lung.

CASE 2.—G.U., a 49-year-old married musician, was admitted to New Mount Sinai Hospital, Toronto, on May 7, 1960, complaining of cough, chest pain and

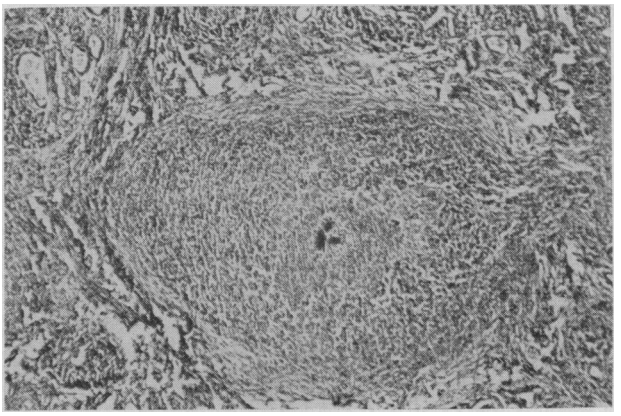

Fig. 2.—Case 1. Section of left upper lobe (× 42). The chronic purulent area is "walled-off" by a band of fibrous connective tissue. In the centre of this area may be seen three colonies of Actinomyces.

hemoptysis. Approximately one year before admission to hospital, the patient had been treated at home for "pneumonia". Subsequently he had numerous attacks of "colds" and "bronchitis"; with these episodes he had considerable cough and raised much sputum. During the month before his admission he had pain in the right chest on coughing. He had noticed flecks of blood in his sputum. He stated that he had lost 15 lb. in weight during the previous three months.

The positive findings on physical examination were decreased movement of the right side of the thorax with breathing, some wasting of the muscles over the anterior chest walls and a flattening of the percussion note in the same area. Bronchial breathing and rales were heard over both upper lung fields.

Radiographs of the chest showed a soft tissue mass within the anterior segment of the right upper lobe (Fig. 4). Associated with this finding was some degree of atelectasis and a shift of the trachea to the right.

Bronchoscopic examination and scalene node biopsy did not show any malignant cells. Skin tests were negative for tuberculosis and coccidioidomycosis and slightly positive for histoplasmosis. Sputum culture was negative for acid-fast bacilli. The hemoglobin was 88%, the sedimentation rate 34 mm. in one hour, and the leukocyte count 7400 cells per c.mm. with an essentially normal differential count. A provisional diagnosis of bronchogenic carcinoma was made.

Operative findings and clinical course.—At thoracotomy on May 12, 1960, firm pleural adhesions were noted about the upper lobe of the right lung. After dissecting through these with some difficulty, the upper lobe of the right lung was exposed and was noted to be firm. The frozen section diagnosis and a biopsy of this upper lobe was "granulomatous inflammatory tissue". The upper and middle lobes of the right lung were then excised without incident. The postoperative and subsequent course of this patient were uneventful. He is well at the present writing.

Pathological findings.—The specimen submitted consisted of the upper and middle lobes of the right lung, together measuring 22 x 9 x 9 cm. The pleural surfaces were covered with dense hemorrhagic fibrous-like adhesions, particularly over the anterior border. In the hilus the bronchi were narrowed and surrounded by dense fibrous connective tissue. Within the lung surrounding the hilum there was a diffuse indurated mass approximately 11 cm. in greatest diameter. This ex-

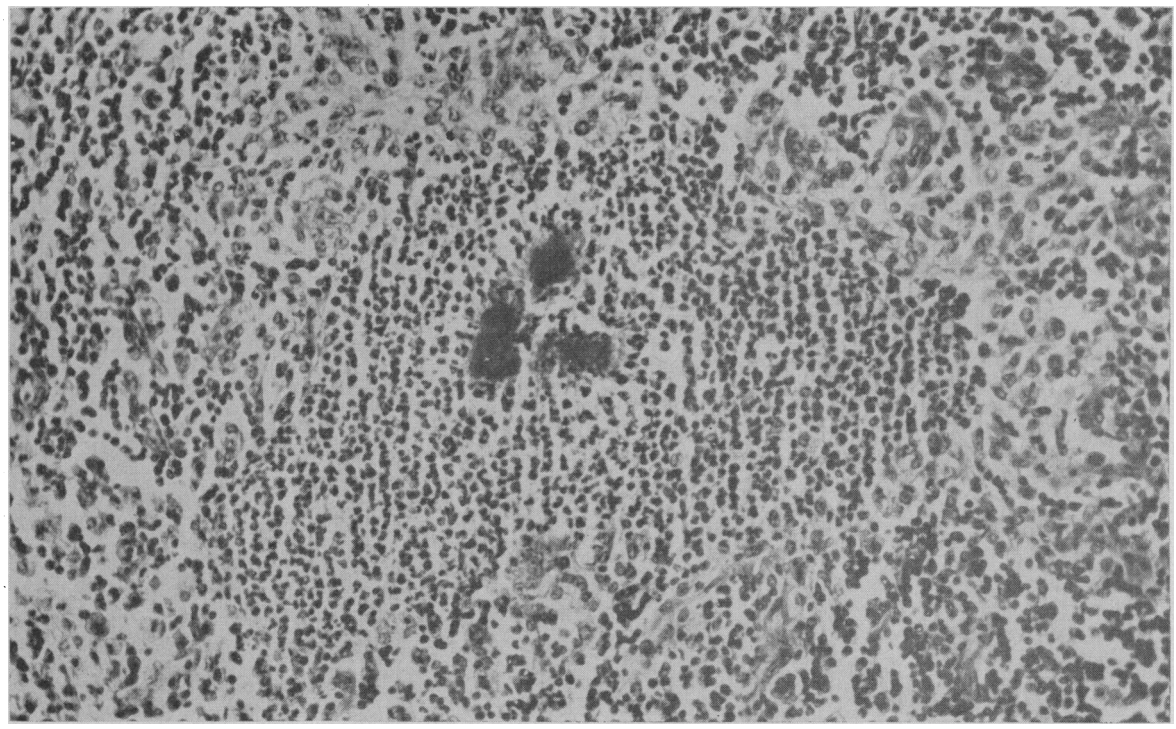

Fig. 3.—Case 1. Section of left upper lobe (× 120). A higher power view of Fig. 2 showing the three colonies of Actinomyces. These are surrounded by lymphocytes and polymorphonuclear leukocytes; immediately around this focus are a number of histiocytes.

tended through the full thickness of the lung parenchyma. The cut surface of the indurated zone was a mottled bluish-grey colour interspersed with a paler grey-to-white area. It was divided into ill-defined nodules with bands of dense white tissue.

The mass was fairly well demarcated from the adjacent lung tissue, although isolated diseased areas adjacent to the main mass could be seen lying within grossly normal lung parenchyma. The surrounding lung was edematous and boggy and showed much anthracotic pigmentation. In the lower part of the mass a single small cystic area, 1 cm. in diameter, was found; this was lined by a smooth-walled membrane and contained a dirty grey and red fluid. The tracheobronchial lymph nodes were small and anthracotic. No frank pus could be obtained from any of the cut surfaces of the specimen.

The microscopic appearance of the lesion in different areas was fairly constant. In the main it consisted of a diffuse inflammatory process, partially limited by bands of connective tissue, showing some hyalinization and limiting the process into ill-defined lobules. Purulent foci were seen in several areas consisting of dense aggregates of polymorphonuclear leukocytes with some extravasated red blood cells. In the centre of several of these minute abscesses, colonies of Actinomyces could be seen. These consisted of irregular masses, purple in the centre with pink-staining peripheral projections (Figs. 5 and 6). With Gram

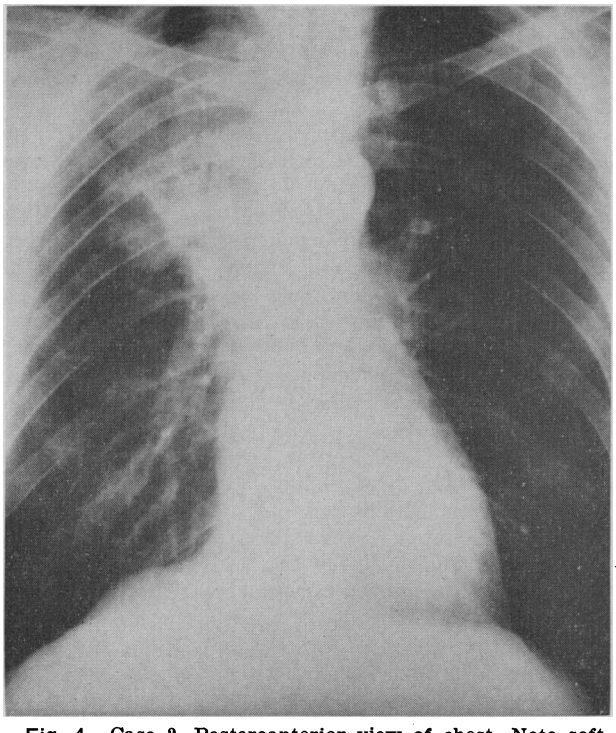

Fig. 4.—Case 2. Posteroanterior view of chest. Note soft-tissue mass in the right upper lobe and the shift of the trachea to the right.

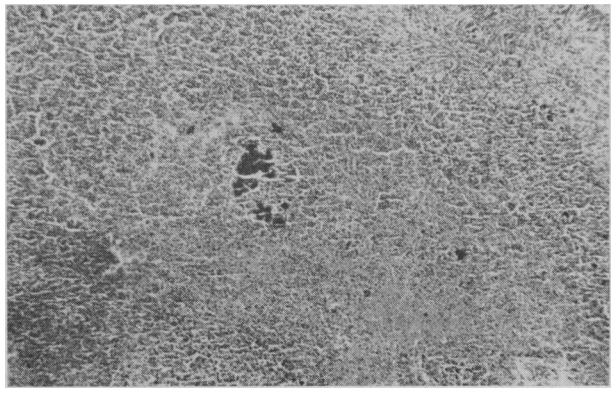

Fig. 5.—Case 2. Section of right lung (× 42). Colonies of Actinomyces in a purulent area.

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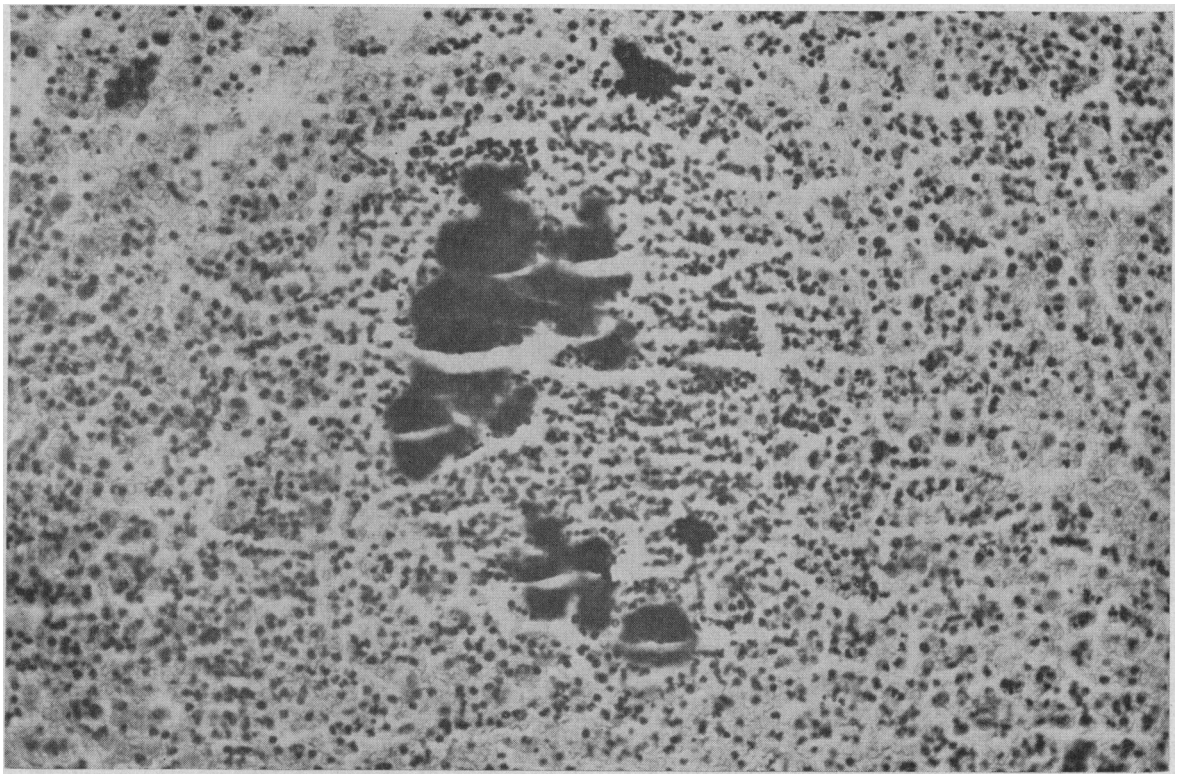

Fig. 6.—Case 2. Section of right lung (× 120). Higher power of Fig. 5 showing more detail of actinomycotic colonies and infiltrate consisting chiefly of polymorphonuclear leukocytes.

staining, these structures were seen to consist of numerous interlacing threads with tiny granules distributed along their course. The purulent foci were irregular in shape and surrounded by fibroblastic tissue.

In the adjacent areas of the lung the outlines of alveoli could be seen. All their lining cells were frequently irregular in size and poorly orientated. The alveolar septa were greatly thickened and infiltrated by macrophages in addition to the polymorphonuclear leukocytes and lymphocytes.

Beyond the inflammatory area described in the previous paragraph, there was an additional area in which the alveoli were distended and packed with macrophages and numerous polymorphonuclear leukocytes. Occasional binucleated and multinucleated histiocytic giant cells were observed as well as some foci of lymphocytes. Many of the bronchi showed a folding of their lining mucosa, some epithelial proliferation and an intense inflammatory infiltration of their walls. Microscopically, as in the gross, there was fairly sharp demarcation between the diseased and relatively healthy parenchymal tissue. The lymph nodes present showed an intense non-specific inflammatory reaction with sinusoidal dilatation and destruction of the follicular pattern.

The final diagnosis was actinomycosis of lung with chronic lipoid pneumonia.

CASE 3.—J.S., a 38-year-old "speculator", was admitted to hospital on February 18, 1961, complaining of fatigue for one month, and cough and pain in the chest for about four months.

The present illness began four months before admission when the patient developed a sharp pain in the right chest which was aggravated by cough. A diagnosis of "pleurisy" was made and he was kept in bed for one month. During this time he perspired profusely. In the three-month period before admission the chest pain was less but he lost 14 lb. in weight, tired easily and became progressively weaker.

This patient had smoked 40 to 50 cigarettes daily for many years. He had a chronic cough for 20 years, but only lately had raised any blood-tinged sputum.

Physical examination on admission revealed increased tactile fremitus over the upper lobe of the right lung posteriorly. Fine rales were also heard over this area. Except for a possible enlargement of the liver, the rest of the physical examination was essentially negative.

Radiological examination of the chest revealed an ill-defined area of increased density in the right root area behind the hilus with ill-defined margins merging into the surrounding normal lung tissue (Fig. 7). This finding appeared to be associated with a slight thickening of the minor interlobar fissure. The remainder of the lung fields were unremarkable and the radiological impression at that time was bronchogenic carcinoma involving the superior segment of the right lower lobe.

Bronchoscopic and scalene node examinations were both negative for malignancy. Sputum culture was repeatedly negative for acid-fast bacilli, fungi and pathogenic bacteria. The Mantoux test using old tuberculin was positive. The hemoglobin was 91% and the leukocyte count was 12,800 cells per c.mm. with a normal differential count.

Operative findings.—On the basis of a preoperative diagnosis of bronchogenic carcinoma of the right lung, thoracotomy was performed on February 21, 1961. At this operation a large mass was felt in the middle of the right lung involving the bronchi to the lower and upper lobes. A right pneumonectomy was carried out without difficulty. Phrenicectomy was performed at the same time. The patient's immediate postoperative

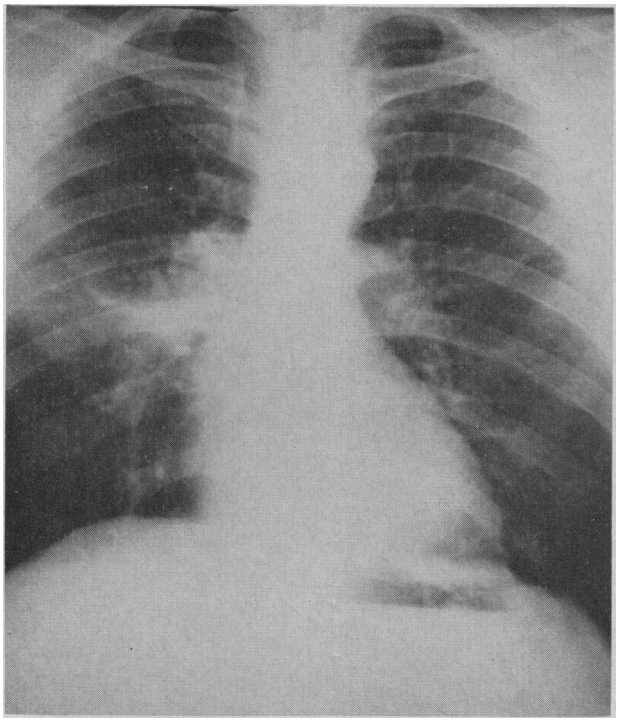

Fig. 7.—Case 3. Posteroanterior view of chest. Note ill-defined area of increased density in the right root area with ill-defined margins. There is also slight thickening of the minor interlobar fissure.

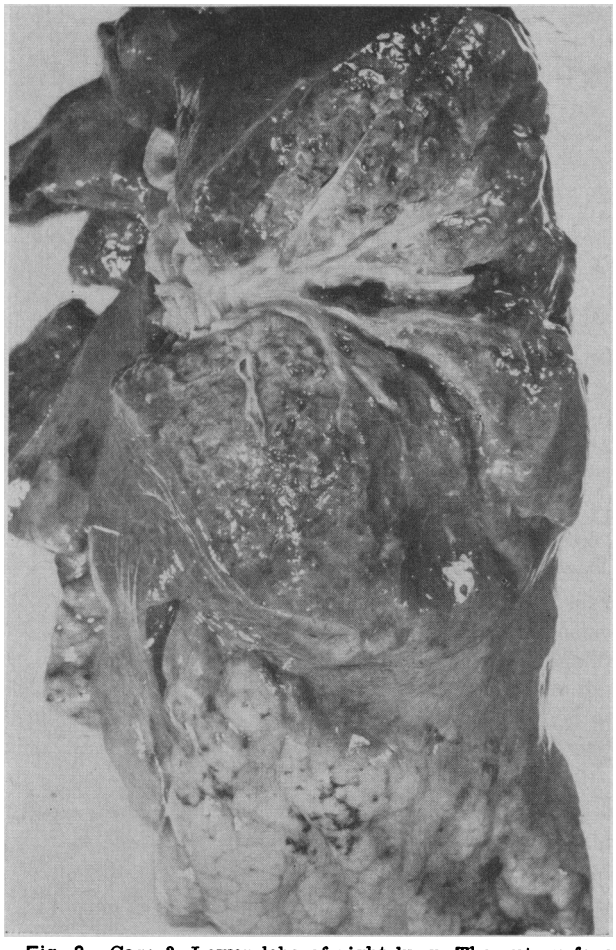

Fig. 8.—Case 3. Lower lobe of right lung. The cut surface shows the right lower bronchus surrounded by firm but friable tissues which appear grey and granular in the photograph.

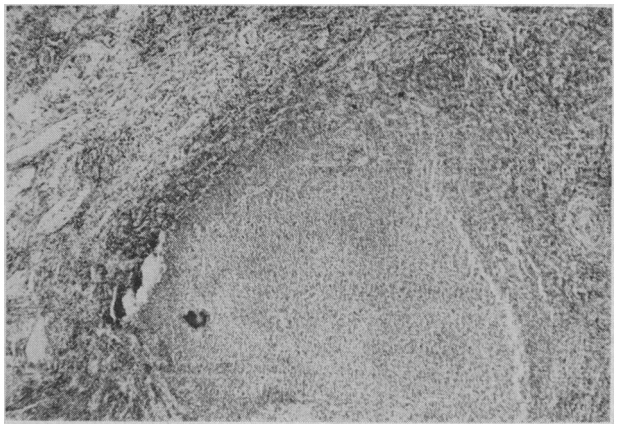

Fig. 9.—Case 3. Section of right lower lobe (× 42). The colony of Actinomyces can be seen to one side of the rather discrete area of purulent material. About this area there is a rampart of histiocytes (see Fig. 11).

course was uneventful and he was discharged on the twelfth postoperative day.

A few days after discharge from the hospital the patient began to develop progressively increasing hemoptysis. He was advised to enter the hospital immediately. He suddenly died at home while entering the ambulance. Permission for autopsy was not obtained but death was thought to have been due to a pulmonary embolus.

Pathological findings.—The right lung submitted for examination weighed 650 g. Several areas of hemorrhage and some fibrous tags were present over the external surface. In the upper portion of the lower lobe close to the hilus were two rounded hard masses, the larger of which measured 4.5 cm. in greatest diameter on palpation. Around these masses the lung was atelectatic. At the periphery of the lung some emphysema was observed. The cut surface of the lung (Fig. 8) showed a large, firm but friable area of lung parenchyma surrounding one of the branches of the lower bronchus. In this region there were necrotic foci exuding purulent material.

Microscopically, numerous foci of dense inflammatory cell infiltration were observed. In some of these circumscribed regions colonies of Actinomyces could be seen (Figs. 9 and 10). Surrounding these inflammatory areas were zones of granulomatous inflammatory tissue. The latter were comprised of fibroblasts and many lipoid-filled histiocytes (Fig. 11).

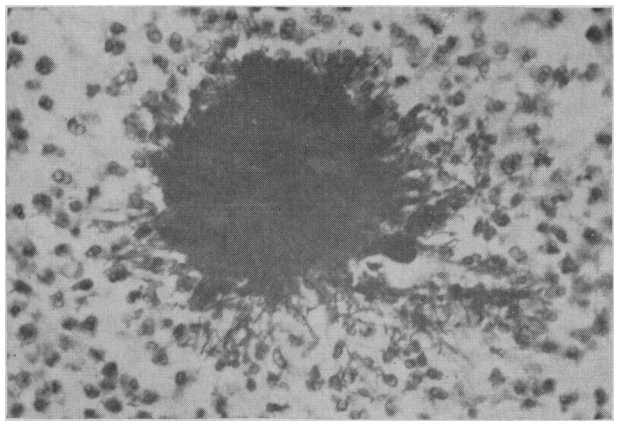

Fig. 10.—Case 3. Section of right lower lobe (× 480). High-power view of the colony of Actinomyces showing hyphae.

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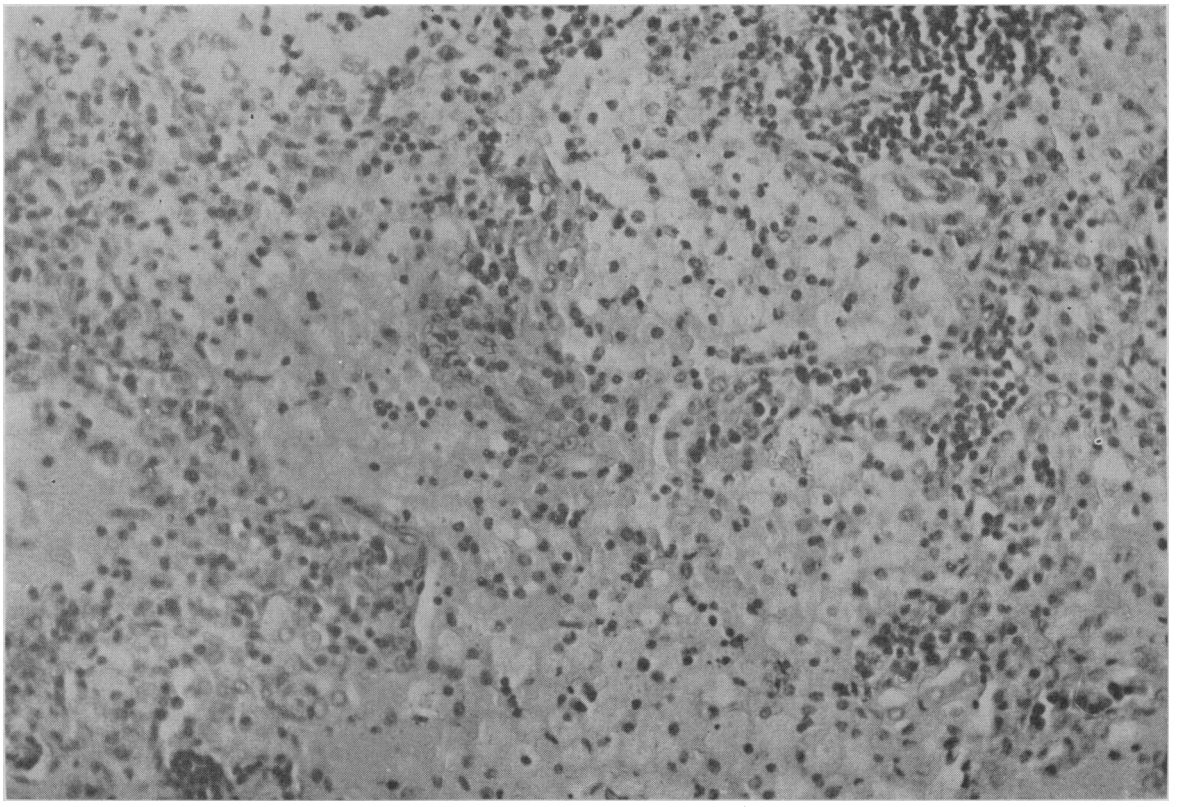

Fig. 11.—Case 3. Section of the right lower lobe (× 120). Medium-power view of histiocytes about the purulent focus shown in Fig. 9. In essence this is typical of endogenous lipoid pneumonia.

The pathological diagnoses were actinomycosis of right lung and lipoid pneumonia of right lung.

DISCUSSION

All three cases involved males of sedentary occupation who were between 38 and 49 years of age. All three were city dwellers and were never associated with farming. In the first patient there were no chest symptoms and the lesion was discovered on a routine chest radiograph. The second patient presented with cough, hemoptysis and chest pain associated with a 15-lb. weight loss. From the history it was apparent that this man had had chest disease of some nature for at least a year. The third patient, whose chief complaint was fatigue, had pleuritic pain, cough and later hemoptysis with a loss of 14 lb. in weight. The total duration of his illness was about 14 months.

The clinical picture in these cases was one of insidious onset with either no symptoms or those of cough, hemoptysis, chest pain, fatigue and weight loss. The radiological features were more suggestive of neoplasm than anything else. The laboratory investigations were not specific—an elevated sedimentation rate in two cases, and an elevated white blood cell count in one case. The similarity of signs and symptoms to many other chest diseases, particularly tuberculosis and carcinoma, is obvious.

Pathologically in the lungs removed from each patient there were purulent granulomatous foci containing occasional Actinomyces. About these foci there were areas of endogenous lipoid pneumonia.

ETIOLOGICAL FEATURES OF ACTINOMYCOSIS

Actinomycosis is the most common fungal disease of man.[1] It is world-wide in distribution. The causative organism, *Actinomyces bovis,* is an anaerobic fungus commonly occurring as a normal inhabitant of the mouth. The exact taxonomy of *A. bovis* has not been finally established in that it possesses certain features more characteristic of bacteria than fungi. For example, it grows at 37° C. but not at room temperature. It thrives on bacteriological media but not on Sabouraud's medium. Moreover, its growth is inhibited by penicillin. Traditionally, however, it has been grouped with the fungi on a morphological basis.

This organism has not been isolated from soil or plants and although it may infect cattle, the general opinion is that the human disease is produced by endogenous organisms rather than by transmission from animals or human cases.

Actinomycosis has been reported in patients of all ages but occurs most commonly in young adults, and twice as frequently in men as in women. It has been stated that it is more common in farmers and others working in agriculture than in urban dwellers.

Histologically the diagnosis is confirmed by observing a granulomatous lesion containing

typical branching Gram-positive filaments less than 1 micron in diameter. In its most typical form the colony shows clubbing of the radially disposed peripheral filaments. If possible, it is desirable that this observation be confirmed by anaerobic culture of *A. bovis* from a specimen of pus or infected tissue.

To date no skin tests or serological techniques are available for the diagnosis of actinomycosis. This is in part due to the presence of Actinomyces and related organisms in the mouth and skin of healthy persons, so that reactivity to a prepared antigen would not be restricted to persons with an actual infection.

PULMONARY ACTINOMYCOSIS

Thoracic actinomycosis accounts for some 15% of all forms of actinomycosis, the other forms being abdominal and cervicofacial ("lumpy jaw"). The last is the most common form. Cope[2] classified thoracic actinomycosis into three sub-types, namely, bronchial, mediastinal and parenchymal. Presumably the bronchial variety is manifested by bronchitis. The mediastinal form involves the mediastinum with invasion of the chest wall and of the vertebrae. The parenchymal form is said by Cope to spread directly to the ribs and pleura, resulting in a characteristic "radiological picture". Our three cases were examples of the parenchymal form but it must be said that the chest radiographs were not "characteristic".

Cope's classification was discussed in a case report by Jepson, Rose and Tonkin,[4] who in the same article listed a number of references dealing with the etiology of actinomycotic infection, particularly with regard to the importance of associated organisms. They pointed out that the Actinobacillus described by Klinger in 1912 as *Bacillus actinomycetum comitans* is the organism usually found in association with closed thoracic actinomycotic lesions. In the case described by Jepson, Rose and Tonkin,[4] weight loss, elevated white blood cell count, and pleuritis or shoulder pain were the principal findings. In only one of our cases was there an elevation of the white blood cell count.

The cases of primary thoracic actinomycosis reported in the literature were manifested by fever, cough and sputum.[3] The latter was occasionally purulent and sometimes sanguineous. Other findings included loss of weight, weakness, night sweats and even dyspnea. The physical signs were non-specific and the roentgenographic findings were variable. In most of the cases the findings, however, were bilateral and had a tendency to occur at the base. The resemblance of these symptoms to many of the findings of tuberculosis and advanced bronchogenic carcinoma were striking.

The significance of *A. bovis* as a cause of chronic chest infection was also discussed by Kay,[5] who suggested that the presence of this organism is of less importance to the patient than are the associated bronchial occlusion, tissue destruction, avascularity and fibrosis.

It is suggested that these factors may produce an anaerobic state conducive to the growth of *A. bovis* which in turn predisposes to chronicity. It is further stated that *A. bovis* is commonly found in mixed chronic pulmonary infections and can be isolated from sputum and/or bronchoscopic aspirations. It is frequently difficult to evaluate the extent to which this fungus has been responsible for initiating the infectious process.

Usually cervicofacial actinomycosis will be suspected very early by the attending physician. However, this is not true of the pulmonary variety. While anaerobic sputum culture offers considerable help in diagnosis in cases of pulmonary actinomycosis, it should be remembered that as a rule sufficient time is not available for anaerobic culture of every specimen of sputum. Nevertheless, when a clinician strongly suspects that a patient has pulmonary actinomycosis he should specifically ask for an anaerobic sputum culture for Actinomyces. Simple sputum culture will not reveal these organisms.

SUMMARY

During a period of 2½ years, in the New Mount Sinai Hospital, Toronto, three cases of pulmonary actinomycosis were encountered.

All three patients presented in a manner indistinguishable from that of carcinoma of the lung, and thoracotomy was necessary to establish the final diagnosis. The lesion in each instance was restricted to one lung.

These observations suggest that pulmonary actinomycosis should be considered as a chest disease of uncertain etiology, and multiple sputum specimens should be sent to the laboratory in such instances with a specific request for anaerobic fungus culture.

A review of these cases suggests that even in those intances of suspected bronchogenic carcinoma with negative scalene and bronchoscopic biopsies, exploratory thoracotomy is necessary to establish the diagnosis conclusively. Without such exploration, patients with pulmonary actinomycosis misdiagnosed as carcinoma would be denied the necessary treatment of their disease and their chance of survival would thus be seriously prejudiced.

The authors wish to extend their thanks to Dr. D. Bohnen, Chief of Surgery, and Dr. M. M. Reingold, Attending Surgeon, New Mount Sinai Hospital, Toronto, for permission to report these cases.

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