Bronchogenic Carcinoma: Relation to Antecedent Pulmonary Infection*

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INTRODUCTION

It has long been established that proliferation and metaplasia of the bronchial epithelium may occur in the course of certain acute and chronic pulmonary infections. The similarities between the histologic findings due to infection and bronchogenic carcinoma have suggested a possible etiologic relationship to many observers. Emphasis was originally placed on changes secondary to bronchopneumonia, tuberculosis, and influenza, but recent studies have also involved viral diseases, bronchitis, and nonspecific pulmonary fibrosis.

HISTORIC REVIEW

Postpneumonic atypical proliferation of bronchial epithelium was described by Friedländer1 in 1876 and similar changes secondary to tuberculosis were noted by Wolf2 in 1895. These findings were confirmed by later observers3-6 and Moore7 in 1912 concluded that chronic epithelial proliferation resulting from bronchitis and bronchopneumonia constituted a significant causal factor in malignancy. Following the pandemic of influenza in 1918-1920, necropsy studies revealed a recurring pattern of squamous metaplasia, disorganized epithelial proliferation, and mitoses which bore a striking resemblance to invasive neoplasm.8-14 Winternitz and associates15 in 1920 made the prophetic prediction that later years would witness an increased incidence of lung cancer and Berblinger16 in 1925, attributed the increase in pulmonary malignancy in Germany specifically to the previous influenza epidemic. In a recent study of the bronchi in influenza, Type A, Walsh and co-workers17 found metaplastic changes of the epithelium and hyperchromatic pleomorphic nuclei.

During the past two decades, many observations have linked chronic pulmonary inflammation with neoplasia. Tuberculosis and lung cancer, formerly considered mutually exclusive by Rokitansky18 have been encountered in coexistence with increasing frequency.19-24 High percentages of antecedent pulmonary infection associated with lung cancer have been reported by Finke,25 Walzer,26 and Case and Lea.27 Reid and Fairbairn28 found a fourfold increase of lung cancer deaths in patients with bronchitis and these data have been corroborated by life insurance statistics.29

Peripheral lung tumors originating in areas of parenchymal fibrosis were reported by Beaver and Shapiro30 who reviewed the literature on alveolar carcinoma and found a 62 per cent incidence of previous inflammatory disease such as bronchiectasis or organized pneumonia. Balo, et al.31 postulated a sequence of changes in areas of pulmonary infarction starting with alveolar epithelial proliferation and terminating in malignancy. The striking similarity between an established viral disease in sheep, jaagsiekte, and alveolar carcinoma has been demonstrated by Bonné,32 Delarue and Graham,33 Bell,34 Drymalski and colleagues,35 and Ikeda.36

The histologic findings in sheep of pulmonary adenomatosis are virtually indistinguishable from the forms of alveolar carcinoma characterized by single layers of mucus-producing columnar epithelium lin-
ing the alveolar spaces. Metastases have also been found in sheep adenomatosi.

Duran-Reynals and associates\textsuperscript{27} considered adenomatosi as a complex with multiple gradations from inflammation to malignancy.

In 1961, Papanicolaou and co-workers,\textsuperscript{28} described specific degenerative changes (ciliocytophthoria) in bronchial epithelium occurring in certain acute and chronic pulmonary disease. Their studies showed that ciliocytophthoria occurred with greatest frequency in patients with viral infection and bronchogenic carcinoma suggesting an association with both disease.

**Materials and Methods**

There were 302 cases discharged from the Metropolitan Hospital during the ten-year period, January 1, 1951-December 31, 1960 with the diagnosis of bronchogenic carcinoma. In 24 instances, necropsy examination revealed that the diagnosis had been incorrect and that the malignancy had been of metastatic origin. The sites of primary origin were, respectively, gastrointestinal tract (seven cases), breast (six cases), kidney (three cases), prostate (two cases), uterus (two cases), and one case each from larynx, tongue, bladder and thyroid. It was of considerable interest that every case of metastatic carcinoma had clinical and roentgen findings compatible with the diagnosis of bronchogenic carcinoma and had positive laboratory confirmation such as lymph node biopsy, needle biopsy of the lung, or the finding of malignant cells in the sputum or pleural fluid. There was an additional group of 25 cases excluded from the study because of incomplete data. In the remaining 253 cases the diagnosis was established by bronchoscopic biopsy, thoracotomy or necropsy.

The series of cases studied consisted of 210 men and 43 women giving a sex ratio of 5:1. The age distribution was similar for both sexes with the vast majority of cases occurring in the sixth, seventh and eighth decades. Evidence of previous pulmonary infection was obtained from the history, roentgen examination, and necropsy examination. The problem of differentiating between primary and secondary infection was arbitrarily resolved by establishing a five-year interval between the history of infection and the diagnosis of lung cancer.

**Results**

A definite history of previous pulmonary infection was obtained in 102 cases (40 per cent) of which 83 were men and 19 were women. The percentages within each sex closely approximated that for the combined group.

The antecedent pulmonary infections are listed in Table 1. There were 12 cases (11.7 per cent) with a history of epidemic influenza during the period 1918-1921 followed by persistent or intermittent cough. The chronic bronchitis group of ten cases consisted of patients with histories of cough and wheezing of many years duration of insidious onset. Seven patients had a history of cough for more than 20 years. There were six cases (5.9 per cent) with a history of pleurisy without any associated or subsequent pulmonary involvement. When the history included pleurisy and tuberculosis or pleurisy and pneumonia, the cases were listed under the respective pulmonary disease. There were 52 instances of pneumonia (50.9 per cent). Lack of specific data made etiologic or anatomic differentiation of pneumonia impractical. The tuberculosis group consisted of 22 cases (21.7 per cent).

The 102 bronchogenic carcinoma cases associated with infection were classified according to central or peripheral origin of tumor. The central group included tumors arising from the major, secondary, or ter-
The peripheral group included tumors arising from the branches of the segmental bronchi or distal to them. Inasmuch as these data were obtained from routine necropsies, precise localization of site of origin was not available. There were 86 (84 per cent) tumors in the central group and 16 (16 per cent) in the peripheral group. A similar subdivision of the 151 cases without infection showed 121 (80 per cent) in the central group and 30 (20 per cent) in the peripheral.

Histologic classification was available in 176 carcinoma cases, 90 with previous infection and 86 without infection (Table 2). Correlation of cell type with infection history showed no striking differences except for the alveolar carcinoma cases. There were seven cases diagnosed in this category. Five occurred in the infection group with a history of antecedent pneumonia and two occurred in the non-infection group.

**D**iscussion

The statistical relationship of infection to carcinoma lends support to the concept that epithelial changes in chronic inflammatory disease may lead to malignancy. The frequent association of squamous metaplasia, carcinoma-in-situ, and invasive bronchogenic carcinoma has been commented on by Black and Ackerman,4 Prior and Jones,4 Williams,4 and Auerbach et al.4 and others. This sequence of pathologic events has also been observed in animal experimentation.44-46

Squamous metaplasia has been found in many chronic pathologic processes and its occurrence, *per se*, cannot be interpreted as a premonitory change leading to bronchogenic carcinoma. In the usual reparative changes, regeneration of injured bronchial epithelium is a result of basal cell activity leading to proliferation of cells toward the surface. The cells are densely packed at first and gradually become stratified to resemble squamous epithelium. If the activity of the basal cell layer should be intensified, normal cellular differentiation will not occur and the resulting pattern will be one of disorganization with variations in the nuclear-cytoplasmic ratio, hyperchromatism, increased and irregular mitoses and anisocytosis. Localization of the process with an intact basement membrane gives rise to carcinoma-in-situ which, in turn, leads to invasive carcinoma.

Evidence for this theory is circumstantial and consists largely of the finding of multiple pre-invasive (intra-epithelial) tumors in the vicinity of, or at a distance from, a frank malignant bronchial lesion. The concept has also been extended to include bronchiolo-alveolar carcinoma which is characterized by cuboidal or columnar epithelium lining the alveolar septa. It is claimed that chronic parenchymal inflammation results in hyperplasia and metaplasia of the bronchiolar and/or alveolar epithelium and that the metaplastic changes subsequently progress to produce alveolar cell carcinoma. These changes have been observed in organs other than the lung. In the cervix, serial biopsies have shown stages
of development from hyperactivity of the basal layer to epidermoid carcinoma-in-situ and finally to invasive epidermoid carcinoma."

**SUMMARY**

1. A study of 253 cases of bronchogenic carcinoma revealed that 102 cases (40 per cent) had a history of antecedent pulmonary infection.
2. The infections most commonly associated with bronchogenic carcinoma were pneumonia (50.9 per cent), tuberculosis (21.7 per cent) and influenza (11.7 per cent).
3. There were seven cases of alveolar carcinoma in the series of which five (70 per cent) had a history of pneumonia.
4. With the exception of the alveolar carcinoma cases, there were no striking differences between the 102 cases with infection and the 151 cases without infection with respect to anatomic distribution of tumors or histologic differentiation.
5. The histologic evidence for implicating chronic inflammatory disease with bronchogenic carcinoma was reviewed.

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**RESUMEN**

1. El estudio de 253 casos de carcinoma bronchogénico reveló que 102 (40 por ciento) tenían en sus antecedentes una infección pulmonar.
2. Las infecciones más comúnmente encontradas en esos antecedentes fueron: neumonía (50.9 por ciento), tuberculosis (21.7 por ciento) e influenza (11.7 por ciento).
3. Hubo siete casos de carcinoma alveolar en la serie, de los que 5 (70 por ciento) tenían antecedentes de neumonía.
4. Con excepción de los casos de carcinoma alveolar no hubo diferencias notables entre los 102 casos con infección y los 151 sin ella, respecto de la distribución anatómica de los tumores o de su diferenciación histológica.
5. Se revisa la evidencia histológica para implicar la enfermedad crónica inflamatoria con el carcinoma broncogénico.

**ZUSAMMENFASSUNG**

1. Eine Untersuchung von 253 Fällen von Bronchuskarzinom ergab, daß 102 Fälle (40%) eine Vorgeschichte vorausgegangener pulmonaler Infektion hatten.
2. Die häufigsten mit Bronchuskarzinom verküppften Infektionen waren Pneumonie (50,9%), Tuberkulose (21,7%) und Influenza (11,7%).
3. Es waren 7 Fälle von Alveolar-Karzinom in dieser Gruppe, von denen 5 (70%) eine Vorgeschichte mit Pneumonie hatten.
5. Der histologische Berveis für eine Verknüpfung chronischer entzündlicher Krankheitsformen mit Bronchuskarzinom wurde näher besprochen.

All references will appear in the reprints.

For reprints, please write Dr. Rosenblatt, 1040 Fifth Avenue, New York 28, New York.

**COLON INTERPOSITION FOR ESOPHAGEAL LESIONS**

Twelve cases of colon interposition for esophageal replacement are presented and the history and evolution of the interposition operation for esophageal substitution are outlined. The operative death rate, late results and complications are discussed. The advantage of left colon because of unlimited length, similar diameter to esophagus, and excellent blood supply is outlined. A relatively new approach to radical cancer therapy of the esophagus is proposed and has been carried out in a limited number of cases.