The Etiology of Bronchogenic Carcinoma*

ALTON OCHSNER, M.D., F.C.C.P.

New Orleans, Louisiana

Bronchogenic carcinoma has become one of the most important and most lethal lesions to which civilized man is heir—a disease which, until about 25 years ago, was of little significance. However, it has become one of the most frequently encountered of all visceral carcinomas, and its incidence is increasing more rapidly than that of any other cancerous lesion. In Massachusetts, where vital statistics have been extremely valid since 1955, the incidence of cancer of the lung supersedes that of cancer of the breast and female genital tract. The rate increased from 3.08 per 100,000 population in 1930 to 42.16 in 1955, during which time the rate of cancer of the breast increased from 29 to only 36 per 100,000 population. In 1930, there were 2,500 deaths from bronchogenic carcinoma, as contrasted with 40,000 in 1962. In 1930, cancer of the lung represented 2.2 per cent of all malignant disease, as contrasted with 15 per cent in 1960, and it is conservatively estimated that, unless something is done to prevent it, in 1975 it will represent 40 per cent of all cancerous lesions. This is indeed conservative, because on the Isle of Jersey, a small island off the coast of England, where more cigarettes per capita are smoked than anywhere else in the world because of no tax, cancer of the lung now represents 40 per cent of all malignant lesions.

The reason for the unprecedented increase in the mid-30's is that at the beginning of World War I, men began to smoke cigarettes heavily, and the 20-year lag between 1914 and the mid-30's is just about the length of time necessary for the cancer producing effect of cigarettes to become evident. In New York State from 1931 to 1950, the incidence of the disease increased 385 per cent in men, during which time that of all other types of cancer increased only 2 per cent. The increase in incidence of bronchogenic cancer in women during the same period was 68 per cent, during which time the incidence of all other cancers decreased 15 per cent. In England from 1920 to 1954, the incidence increased 38-fold. In Denmark from 1931 to 1960, the death rate from cancer of the lung increased from 4.5 per 100,000 population to 86.7 per 100,000 population, and in Holland from 1924 to 1951, the incidence increased 24-fold in men and ten-fold in women.

Because the incidence of bronchogenic cancer began to increase sharply around 1935, many suggested that the changes in the bronchial mucosa resulting from antecedent influenza were precancerous, and this accounted for the tremendous increased incidence at that time. However, even earlier many disputed this relationship. In a series of 249 cases of carcinoma of the lung observed at necropsy, Kikuth found a history of influenza in only 21. In more recent years, the increase in occurrence of bronchogenic cancer has been even more rapid, and the number of patients who had antecedent influenza is infinitesimally small. It is thus obvious that antecedent influenza plays no etiologic role in cancer of the lung.

In a consideration of the cause of bronchogenic carcinoma, it is essential to differentiate between the histologic types. It is generally agreed that adenocarcinoma, which is becoming relatively less common, has an entirely different etiology from the other types of primary bronchogenic cancer. Graham believed that adenocarcinomas originate in embryonic rests. This explains why they are encountered in younger
persons than the other types of bronchogenic carcinomas, as has been our experience. In 1959, we\textsuperscript{14} reported that of our patients younger than 50 years of age with bronchogenic carcinoma, 44.1 per cent had epidermoid carcinoma and 20.5 per cent, adenocarcinoma. Of those between 50 and 59 years, 52 per cent had epidermoid and 20 per cent adenocarcinoma, and of those older than 70 years, 75 per cent had epidermoid and only 11 per cent adenocarcinoma. Moreover, there is considerable variation in the histologic types that affect the two sexes. In our series of cases of bronchogenic carcinoma in men, 54 per cent had epidermoid carcinoma, 29 per cent, undifferentiated, and only 16 per cent adenocarcinoma. In women, these respective incidences were 33 per cent, 26 per cent, and 41 per cent.\textsuperscript{15}

Auerbach,\textsuperscript{18} who with his associates, has had more experience in the histopathologic study of human bronchi than anyone else in the world, has repeatedly stated that he has never seen a non-smoker with primary epidermoid carcinoma of the lung. These investigators also demonstrated that the bronchial mucous membrane in non-smokers is usually normal, but in persons who smoke as little as one-half package of cigarettes a day, the incidence of abnormal cells in the bronchial mucosa increases tremendously.\textsuperscript{4} They observed that in non-smokers, only 3.8 per cent of bronchial cells were atypical; in occasional smokers this figure was 10.9 per cent; in those who smoked as little as one-half package a day this increased to 90.6 per cent; in those who smoked from one-half to one package, 97 per cent; from one to two packages, 99.3 per cent; and more than two packages, 99.6 per cent! The incidence of carcinoma \textit{in situ} in the bronchi also varied according to the smoking habits: non-smokers, 0; occasional smokers, 0; less than one-half package a day, 0.3 per cent; one-half to one package, 0.8 per cent; one to two packages, 4.3 per cent; and more than two packages, 11.4 per cent.

After considerable experience with bronchogenic neoplasms, we are convinced that the history of smoking is the most important diagnostic criterion in carcinoma of the lung, and that a lesion of the lung which might be a neoplasm in a non-smoker is almost without exception either adenocarcinoma or is not malignant. The original contention of a causal relationship between smoking and cancer of the lung was based on the fact that few, if any, patients with carcinoma of the lung (exclusive of adenocarcinoma) were non-smokers. Bio-statisticians criticized this retrospective type of statistical analysis because they said it was based on a pre-selected group, namely, those with bronchogenic cancer. As a result, a number of prospective studies were undertaken, originally by Doll and Hill\textsuperscript{16-17} in England among the medical profession and by the American Cancer Society in the United States.\textsuperscript{19} There have been seven such studies, and slightly less than two million normal individuals have been interrogated and followed for a number of years. All these studies have consistently shown that the incidence of bronchogenic carcinoma is lowest in non-smokers, next in cigar smokers exclusively, next in pipe-smokers exclusively, the highest in cigarette smokers. These respective figures for the study by the American Cancer Society were 3.4, 11.4, 28.9, and 78.6 per 100,000 population, respectively. The incidence also varied according to the amount smoked. In the study by the American Cancer Society, these figures were as follows: non-smoker, 3.4; less than one-half package a day, 51.4; one-half to one package, 59.3; one to two packages, 143.9; and more than two packages, 217.3. Additional evidence that cigarette smoking is a factor in the production of bronchogenic cancer is that the chances of developing the disease decrease when a person discontinues smoking. The longer the time that has elapsed since discontinuance, the less the chance of getting cancer of the lung.

The Royal College of Physicians made an extremely significant report recently.
After a three-year, intensive study, they reported a definite relationship between cigarette smoking and cancer of the lung. The report stated “The strong statistical association between smoking, especially of cigarettes, and lung cancer is most simply explained on a causal basis ... The conclusion that smoking is an important cause of cancer of the lung implies that if the habit ceased, the death rate from lung cancer would eventually fall to a fraction, perhaps one-fifth or even, among men, to one-tenth of the present level.” The study also showed that the risk of developing cancer of the lung in the United Kingdom was thirty times greater in those who smoked forty cigarettes a day than in those who did not smoke.

Wynder and associates and Bock and co-workers have offered further evidence of the causal relationship between smoking and bronchogenic cancer. They found carcinogens in the tarred residue from cigarette smoke. Application of cigarette tar to the skin of animals over a period of time resulted in true carcinoma, which metastasized and killed the animals.

Although these investigations prove conclusively the carcinogenicity of cigarette smoke, the criticism has been made that the cancers produced are not in the lung. Sir Robert Platt, the president of the Royal College of Physicians, succinctly stated that there is ample experimental evidence that cancer of the lung is caused by cigarette smoking in self-induced experimentation by smokers, in whom the incidence was found to increase with the increasing amounts smoked. Lombard showed that the incidence of cancer of the lung in individuals beginning to smoke after the age of 20 years was approximately 24 per 100,000 population; in those who had begun between 15 and 19 years, it was 44; in those who had begun between 10 and 15 years, it was 80; and in those who had begun before the age of 10, it was approximately 140.

It has been frequently suggested that the increasing incidence of bronchogenic carcinoma is due to smog, and one of the reasons for the high incidence of cancer in London has been said to be the prevalence of smog. This might be acceptable if, for the fact that immediately across the English Channel in Copenhagen, where the incidence of cancer of the lung is almost identical with that in London, and where the smoking habits are approximately the same, there is no smog whatsoever. Moreover, in the United States the highest incidence of cancer of the lung is not in Pittsburgh or Los Angeles, but in New Orleans, where there is no smog whatsoever. Wynder and associates showed that the incidence of cancer of the lung in Venice, Italy, which is free of smog but where cigarette smoking is common, is higher than that of any other kind of cancer. The final reason against a relationship between smog and cancer of the lung is that if smog were a factor, the disease should affect men and women with equal frequency, because although women may have cleaner minds than men, they certainly breathe the same putrid air.

There are still a few physicians (although the number is decreasing) who deny a causal relationship between smoking and cancer, but these, without exception, are either employees of the tobacco industry or addicted themselves. The number of cigarette-smoking physicians is definitely decreasing.

It has been pointed out by some that cancer may not develop in heavy smokers for many years. In fact, I have seen cancer of the lung develop in a patient only after he had smoked a package of cigarettes a day for more than 65 years, but conversely I have also seen cancer of the lung develop in a person after he had smoked a package of cigarettes a day for only three years. This is because of the individual variance in susceptibility to cancer. Some people are extremely susceptible, and the same carcinogens in such an individual will produce cancer within a relatively short period of time, whereas, those who are extremely resistant may require application of the
carcinogen for a long time before cancer develops, or conceivably a person may be so resistant that he will never get cancer.

The governments of Great Britain, Norway, Sweden, Denmark, the Netherlands, and Italy have taken official cognizance of the overwhelming evidence that the increasing incidence of bronchogenic cancer is due to cigarette smoking by instituting measures to decrease the incidence of cigarette smoking. Since bronchogenic carcinoma (with the exception of adenocarcinoma) is preventable by refraining from smoking and since the results and treatment of this disease are so uniformly poor (only about 5 to 6 per cent of persons in whom the diagnosis is made survive five years), it is obvious that prevention is the only logical therapy. The precancerous changes that occur in the tracheobronchial tree as the result of smoking are, up to a certain time, reversible by total abstinence from smoking. Unfortunately, there is a time when these changes become irreversible and it is equally unfortunate that it is impossible for the physician to say when that time will or has occurred. The studies of the American Cancer Society and Doll and Hill have shown, however, that with abstinence from smoking the incidence of bronchogenic cancer becomes progressively lower the longer the time has elapsed since one has discontinued smoking.

**Summary**

1. Bronchogenic carcinoma, an extremely rare disease 25 years ago, has become the most common of all visceral carcinomas, exceeding in frequency cancer of the breast and female genital tract.

2. The unprecedented increase in the incidence of bronchogenic cancer began in the United States approximately 20 years after the first World War, when men began to smoke cigarettes excessively. The increased incidence of bronchogenic cancer definitely parallels the increased sale of cigarettes.

3. Prospective studies involving slightly less than 2,000,000 people show that the more cigarettes smoked the greater the incidence of cancer of the lung.

4. Although influenzal infection was once thought to be the cause of bronchogenic carcinoma, this has been disproved.

5. Studies have shown that air pollution is of no etiologic significance in bronchogenic carcinoma.

6. Next year in the United States more people will die of bronchogenic cancer than will be killed in automobile accidents.

7. Bronchogenic cancer is a preventable disease. The only hope at present is prevention because the curability rate is extremely low—approximately 5 per cent.

**Resumen**

1. El carcinoma bronquiogénico que era una enfermedad extremadamente rara hace 25 años, se ha hecho el más común de los carcinomas viscerales, excediendo por su frecuencia al cáncer mamario y al genital.

2. El aumento sin precedente en los Estados Unidos del cáncer bronquiogéneo empezó aproximadamente 20 años después de la Primera Guerra Mundial, cuando los hombres empezaron a fumar en exceso. Definitivamente hay paralelismo entre el aumento de ese cáncer y el aumento en las ventas de cigarrillos.

3. Los estudios que comprenden algo menos de 2 millones de personas muestran a mayor fumar de cigarrillos mayor frecuencia del cáncer pulmonar.

4. Aunque alguna vez se pensó que las infecciones de influenza podían ser causa del cáncer bronquiogénico, esto fue descartado.

5. Los estudios han demostrado que la polución atmosférica no tiene significación en el cáncer broncogénico.

6. En el año próximo se espera en los Estados Unidos que fallezcan más personas de cáncer pulmonar que por accidente de automóvil.

7. El carcinoma bronquiogénico es una enfermedad que puede evitarse. La única esperanza al presente es la prevención porque la curabilidad es extremadamente baja, aproximadamente de 5 por ciento.

**Résumé**

1. Le cancer bronchique, affection extrêmement rare il y a 25 ans, est devenu le plus commun de tous les cancers viscéraux, dépassant en fréquence le cancer du sein et de l'appareil génital féminin.

2. L'augmentation sans précédent de la fréquence du cancer bronchique commence aux États-Unis approximativement 20 ans après la


3. Prospektive Untersuchungen, die etwas weniger als 2.000.000 Menschen betreffen, zeigen, daß je mehr Zigaretten geraucht werden, je größer die Häufigkeit an Lungenkrebs ist.

4. Obleich man von Influenza-Infectionen vorderhand anmahnt, daß sie die Ursache des Bronchuscarzinoms seien, ist dies inzwischen widerlegt.

5. Untersuchungen haben nachgewiesen, daß eine Luftverschmutzung von keiner ätiologischen Bedeutung für das Bronchuscarzinom ist.

6. Im nächsten Jahr werden in den Vereinigten Staaten mehr Menschen an Bronchuscarzinom sterben, als durch Kraftfahrzeugunfälle getötet werden.

7. Das Bronchuscarzinom ist eine verhältnisweise Erkrankung. Die einzige Hoffnung besteht gegenwärtig in der Verhütung, weil die Heilungsrate extrem niedrig ist, etwa 30%.

ZUSAMMENFASSUNG

1. Das Bronchuscarzinom, eine extrem seltene Krankheit vor 25 Jahren, ist zu dem häufigsten aller Eingeweidecarzinome geworden und übersteigt hinsichtlich seiner Häufigkeit den Krebs der Brust und des weiblichen Genitaltraktes.


3. Prospektive Untersuchungen, die etwas weniger als 2.000.000 Menschen betreffen, zeigen, daß je mehr Zigaretten geraucht werden, je größer die Häufigkeit an Lungenkrebs ist.

4. Obleich man von Influenza-Infectionen vorderhand anmahnt, daß sie die Ursache des Bronchuscarzinoms seien, ist dies inzwischen widerlegt.

5. Untersuchungen haben nachgewiesen, daß eine Luftverschmutzung von keiner ätiologischen Bedeutung für das Bronchuscarzinom ist.

6. Im nächsten Jahr werden in den Vereinigten Staaten mehr Menschen an Bronchuscarzinom sterben, als durch Kraftfahrzeugunfälle getötet werden.

7. Das Bronchuscarzinom ist eine verhältnisweise Erkrankung. Die einzige Hoffnung besteht gegenwärtig in der Verhütung, weil die Heilungsrate extrem niedrig ist, etwa 30%.

References

1 Lombard, H. L.: Personal communication.
13 Auerbach, O.: Personal communication.

For reprints, please write Dr. Ochser, 1514 Jefferson Highway, New Orleans 12.