PREVENTIVE MEDICINE 2, 611–614 (1973)

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Corner of History

My First Recognition of the Relationship of Smoking and Lung Cancer

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One of the early leaders in lung cancer surgery reflects on his early contacts with this disease particularly as it relates to the role of tobacco consumption and the progress in surgical techniques.

My interest in cancer of the lung and its relationship to tobacco use began serendipitously. During my junior year in medical school at Washington University in St. Louis, a patient with cancer of the lung was admitted to Barnes Hospital, the teaching hospital of Washington University, and, as usual, the patient died. Dr. George Dock, who was an eminent clinician and pathologist, asked the two senior classes to witness the autopsy because, as he succinctly said, the condition was so rare he thought we might never see another case as long as we lived. Being very young at the time and enamored by the clinical knowledge and judgment of our eminent professor of medicine, I was greatly impressed by this extremely rare condition. Seventeen years elapsed before I saw another case of lung cancer, at the Charity Hospital in New Orleans after having come to Tulane University as Professor of Surgery in 1927. There was nothing particularly unusual about seeing a rare case in 17 years, but eight other additional cases were seen in a period of six months which was extremely unusual. Having been impressed with the extreme rarity of the condition 17 years previously, the sudden increase in incidence represented an epidemic, and there had to be some reason for it. All the patients involved were men, they all smoked cigarettes heavily and had begun smoking in the First World War. I then ascertained that very few cigarettes were consumed before the First World War but during the war and afterward there had been a tremendous increase. Since there was a parallel in the rise in sale of cigarettes and the appearance of the new disease with a lag of approximately 20 years for 1914 to 1936, I considered that this might be the necessary length of time for a possible carcinogenic agent in tobacco smoke to become evident. The evidence was admittedly very nebulous, but it seemed as if this was the most likely cause. Furthermore, there had been some previous experimental evidence (1,8–11,13–15,17) indicating that tobacco did act as a carcinogen. Most

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of this consisted of the application of tobacco itself on the surfaces of animal which produced malignant tumors.

The observation that cancer of the lung was increasing rapidly has been substantiated, and it now has become the most frequent systemic cancer in the body and is one of the most lethal. Because cancer of the lung is a new disease which has developed during my lifetime and because of my interest in thoracic surgery, I have seen a large number of cases. Early in my experience I felt that the poor results obtained from the surgical treatment of lung cancer were due to the fact that we saw and treated only advanced cases. I mistakenly thought that if we could make earlier diagnoses our results would be better. At that time we did not understand the mechanism and time of extension beyond the lung. It is extremely difficult to diagnose bronchogenic carcinoma while the lesion is still limited to the lung because the lesion is early angioinvasive as demonstrated by Collier *et al.* (3–5). I thought if we could make earlier diagnosis and treat the patients by radical extirpation of the involved lung with en bloc excision of the regional lymph nodes more cases could be cured. Early in my experience I advocated this procedure in all cases of bronchogenic carcinoma in which it was considered that a pneumonectomy could be tolerated. At that time preoperative pulmonary function studies were not done, but, because we routinely employed preoperative pneumothorax, we were able to observe quite accurately the pulmonary reserve in the sound uninvolved lung. The decision to do radical excision in malignant disease of the lung was based on the general experience that excisable malignant lesions are best treated by early wide removal with en bloc excision of the regional lymph nodes. In 1956 Overholt (12) and in 1958 Churchill *et al.* (2) and Johnson *et al.* (7) questioned the advisability of pneumonectomy in all cases. I was reluctant to accept this philosophy for some time because I believed that radical excision was necessary in order to obtain more cures.

Shimkin and co-workers (16) asked Overholt and us to submit our respective cases to them for study and analysis. The two groups were similar in many respects. Both concerned private patients operated on by competent surgeons. The one difference was that many of the cases in the Overholt series had had conservative operative procedures, lobectomy or even segmental resection, whereas, in our series most had had a pneumonectomy. The mortality rates in the two series were comparable, and I was astonished by the fact that the long-term survivals were comparable—not better in the radically treated cases. Moreover, the morbidity was less in the Overholt series because the patients had more functioning lung tissue. Although our original premise regarding the desirability of radical removal of early malignant lesions was valid regarding most cancers, it was invalid in bronchogenic cancer because we did not appreciate its angioinvasive propensity as demonstrated by Collier *et al.* (3–5) and subsequently verified by us. Dr. Hurst Hatch, our chest internist in charge of the pulmonary function laboratory, several years ago reasoned that since blood in a vein draining a viscus containing a malignant disease contains more tumor cells than systemic blood contains (portal vein blood in carcinomas of the colon contains more tumor cells than the systemic circulation),

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there should be more tumor cells in the peripheral arterial blood of a patient with cancer of the lung. The blood from the lung traverses the short pulmonary vein to the left heart and out into the systemic circulation without passing through any capillaries. Dr. Hatch and Dr. G. M. Carrera of our Department of Pathology did cytologic examinations on the peripheral arterial blood of all patients examined in the pulmonary function laboratory. Some had nonneoplastic chest lesions but many of them had carcinoma. Tumor cells were not in the peripheral arterial blood of any patient with nonneoplastic disease. In other words, there were no false positives, but in 30% of those with proved malignant disease of the lung, tumor cells were found in the peripheral arterial blood, demonstrating that there is early invasion of the vascular system which permits the transportation of tumor cells to distant foci. Finding the tumor cells has not altered our treatment because the presence of tumor cells in the peripheral arterial blood does not necessarily indicate that metastases will develop because the blood has tumoricidal activity. It must be remembered, however, that the potentiality is present.

Treatment of carcinoma of the lung has been dismally unsuccessful; only about 5–10% of patients in whom a diagnosis of carcinoma is made survive five or more years. This poor result from the treatment of the most rapidly increasing cancer is particularly tragic because most bronchogenic cancers are caused by cigarette smoking and thus by the individuals themselves. There are few cancers in which the etiologic factor has been so well substantiated as in bronchogenic cancer. Its incidence is increasing more than any other visceral cancer and the results from therapy are dismal which is tragic, but even worse is that it was preventable in most of the cases and that the individual himself was entirely responsible. It is the one cancer which is almost entirely preventable, and if there could be complete cessation of tobacco use, the incidence of cancer of the lung would be as rare as it was when I was a student and would become of no clinical significance.

Dr. Evarts Graham, who performed the first successful pneumonectomy in 1933 for cancer of the lung on a physician (6) was my professor of surgery my senior year, when he was a young man so there was not much difference in our ages. When I first postulated that the increase in cancer of the lung was due to cigarette smoking because of the parallel between the sale of cigarettes and the increasing incidence of cancer of the lung, I was chided by Dr. Graham, who was a very heavy cigarette smoker. He said, "Yes, there is a parallel between the sale of cigarettes and the incidence of cancer of the lung, but there is also a parallel between the sale of nylon stockings and the incidence of cancer of the lung," which I could not refute. A few years later Dr. Graham wrote to me and reminded me that he had chided me and said that he would have to "eat crow" because a young man, a sophomore student at Washington University, had taken his (Dr. Graham's) cases of cancer of the lung and studied them and the results of this study convinced Dr. Graham that there was a relationship between cigarette smoking and cancer of the lung. This young sophomore student was Ernest Wynder, a man who has done much to demonstrate the relationship between tobacco use and cancer.

Following this observation Dr. Graham decreased his smoking to six a day,

two after each meal, until 1953 when he and Dr. Wynder (18) were able to prove that the tar from cigarette smoke when applied to the surface of animals produced skin cancer. Dr. Graham then completely refrained from smoking but, unfortunately, too late. The saddest letter I ever got from anyone was from Evarts Graham two weeks before he died. In it he stated, "Because of our long friendship, you will be interested in knowing that they found that I have cancer in both my lungs. As you know, I stopped smoking several years ago but after having smoked as much as I did for so many years, too much damage had been done." In two weeks he was dead, a tragic loss of a great individual and an eminent scientist.

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