Cancer of the Lung

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Preface

The past five years have produced an explosion in the knowledge, techniques, and clinical application of radiology in all of its specialties. New techniques in diagnostic radiology have contributed to a quality of medical care for the patient unparalleled in the United States. Among these techniques are the developments and applications in ultrasound, the development and implementation of computed tomography, and many exploratory studies using holographic techniques. The advances in nuclear medicine have allowed for a wider diversity of application of these techniques in clinical medicine and have involved not only major new developments in instrumentation, but also development of newer radiopharmaceuticals.

Advances in radiation therapy have significantly improved the cure rates for cancer. Radiation techniques in the treatment of cancer are now utilized in more than 50% of the patients with the established diagnosis of cancer.

It is the purpose of this series of monographs to bring together the various aspects of radiology and all its specialties so that the physician by continuanee of his education and rigid self-discipline may maintain high standards of professional knowledge.

LUTHER W. BRADY, M.D.

Contents

Chapter One

The History of Diagnosis and Treatment of Cancer of the Lung

The first issue of the *New Series of the Transactions of the College of Physicians* was published in 1850 and contained an article entitled "Cases of Cancer of the Lungs and Mediastinum" by Dr. William Pepper,[18] an outstanding physician of the Pennsylvania Hospital. He surveyed the data about lung cancer that had been gathered up to that time and stated: "Such cases were viewed as mere matters of medical curiosity not known to be in any degree influenced by medicine and too rare to be of much practical importance." He emphasized "the rarity of the affection and exceeding great difficulty which attends its diagnosis," and said that there was reason to believe this disease occurred much more frequently than was commonly supposed and might escape detection entirely in a great majority of cases. Of the 3 patients reported by Dr. Pepper 2 were women 20 and 27 years of age, the other was a 20-year-old man.

Probable cases of thoracic or pulmonary neoplasm were mentioned as early as 1761 by Morgagni;[14] however, the first commonly accepted case of primary lung cancer was reported by Bayle[2] in 1810. The author described his attendance at the autopsy of a 72-year-old man who died in 1805 and was found to have a mass "the interior of which resembled brain" at the root of the left lung and in the lung itself. The patient also had small tuberculous cavities in the remainder of the lung, numerous brainlike masses in the liver, and movable, subcutaneous bodies similar to the internal tumors.

To my knowledge, the first reported patient in the United States is mentioned in the *U. S. Medical and Surgical Journal* of August 1835 and later reported verbatim in the *Boston Medical and Surgical Journal* of December 1835. A Dr. Hall[6] of Newark, New Jersey described the clinical symptoms in this 40-year-old man: "He had been ill for many weeks, and on examination the following symptoms were manifest—emaciation, extreme pain on pressure in the region of the diaphragm, great debility, prostration, and difficult respiration. Tongue red at the edges, moist, with its papillae erect in the centre. No pain in the head, but at times complains of dizziness, with cramps in the arms, feet and legs. Pulse 120, full and quick, but in ten or fifteen minutes, intermitting, slow, and weak, becoming in a few minutes again full, with a flush on the cheek, and when the face was flushed the breathing was most difficult. When the pulse was weakest, the greater was the pain in the region of the diaphragm. Bilious and dark-colored discharges from the bowels, which we learned from the attending physicians were alternately constipated and relaxed through the whole of his illness."

The patient died the following day, and the autopsy is reported by Dr. Hall as follows: "On raising the sternum, we found it adhering firmly to the mediastinum by a preternatural enlargement, so as to require the use of the scalpel, to detach its whole length. At the superior extremity of the sternum, the tumor was small, compared with its magnitude at its termination—for as we approached the pericardium, the morbid appearances increased; the morbid mass was of a pyramidal shape, with its base resting on the pericardium, and its top running a small space above the superior portion of the sternum. The superior and anterior portion of the pericardium, and the inferior portion or base of the tumor, were so firmly attached, that it was not possible to detach them only by dissection. The tumor was, from its anterior to its posterior surface, two inches in thickness, at its base gradually tapering to its top, and from one lateral extremity to the other, between four and five inches, and running to its superior termination tapering, giving the mass a sort of cuneiform shape. When detached it weighed three pounds (avoir-dupois). It was of a pale red color generally, with interstices of a pale yellow, occasionally slightly vascular, heavier than water, and resembled in its general appearance the glands of the mammae; the left lobe of the lungs adhered extensively to the tumor, at its posterior and superior portion, and at the inferior extremity of the right and middle lobes they were both found strongly adhering to the tumor immediately above the right superior portion of the pericardium. The right lobe was also adhering to the pleura at the second rib near its centre, extending round from thence to the spinal column; in other respects the lungs were sound and manifested a healthy appearance. In the cavity of the thorax were effused seven pints of serous fluid, slightly tinged with blood; the pericardium contained a small quantity of effused fluid, not exceeding two ounces. The heart at its superior extremity was slightly inflamed; pleura costalis sound; diaphragm inflamed slightly; stomach and intestines were healthy, and no symptom of inflammation was discovered in either. Spleen, paler than usual; the vessels of the pancreas engorged with grumous blood; liver slightly enlarged; the gall-bladder flaccid and empty; the renal glands, ureters, urinary cyst, manifested no diseased appearance; the encephalon with its contents was not examined."

The symptoms of prostration, flushing, tachycardia, and diarrhea fit the clinical picture of a carcinoid tumor, although at the time of this report the histologic diagnosis of tumors had not been introduced into medical practice. As in other case descriptions in the earlier part of the nineteenth century, treatment was usually limited and unsuccessful, and the gross pathology is confusing. Cancer of the lung was clearly a necropsy diagnosis, as shown in a review of the nineteenth century literature by Onuigbo.[16] Cockle[3] reported that a Dr. Baron may have been the first to diagnose lung cancer during the

life of his patient, who was initially examined in 1819 but not reported in the literature until 1865. Differential diagnosis in the early nineteenth century was usually between aneurysm, tuberculosis, and lung cancer. Dr. Pepper[18] wrote: "In a vast majority of cases it [lung cancer] entirely escapes detection owing to the great difficulty which attends its diagnosis."

Metastatic disease as a presenting symptom was reported by Greene[5] in 1843 in a patient who had metastatic lung cancer deposits in the frontal brain lobes. The astute physician also noted that such deposits do not produce pain. Another extrathoracic finding was described in 1869 by the Swiss ophthalmologist Horner,[7] who reported the first patient with the syndrome which bears his name.

The scientific basis for the diagnosis of lung cancer was greatly enhanced by Virchow[21] in Germany, who applied the concept of cellular pathology to the histologic study of tumors. No longer was it permissible to grossly describe "encephaloid" lesions, and histologic examination became a routine feature of postmortem examination. In 1857, Quain[19] was one of the first to describe the microscopic appearance of malignant cells in lung cancer and the spread of these tumors along the bronchial tree and in pulmonary veins. A report on the first series of patients with histologically confirmed cancer of the trachea and bronchi was published by Langhans[12] in 1871. Thus, clinical diagnosis and histologic diagnosis on postmortem examination developed gradually following the introduction of the stethoscope by Laennec in 1834. The attempts at clinical diagnosis before death were frustrated by the difficulty of diagnosing lung cancer by auscultation and percussion.[1]

On November 8, 1895, Wilhelm Conrad Roentgen discovered roentgen or x-rays, and a few months later, in April 1896, F. H. Williams[24] of Boston demonstrated one of the first chest x-rays of a patient with pulmonary tuberculosis at a meeting of the Association of American Physicians. The exposure was made with a Crookes' tube and a Wimshurst electrostatic machine: "The lungs are easily penetrated, the ribs, clavicles and vertebrae are in marked contrast to other portions of the thorax. Against the lower part of the right lung the outline of the upper portion of the liver is distinctly seen, and the rise and fall with the respiration easily follows. Between extreme inspiration and expiration the liver moves vertically about three inches." The application of radiographic methods to the diagnosis of diseases of the thorax was the most

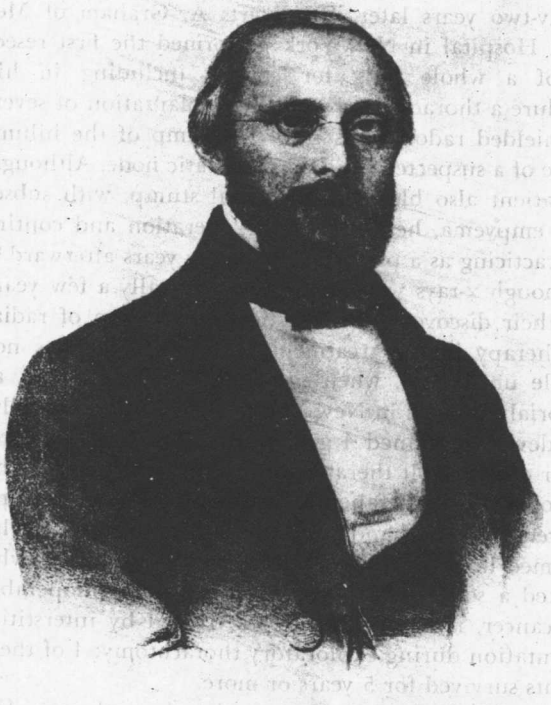

Fig. 1. Rudolf Virchow (1821–1902). (Used with permission of the library of the College of Physicians of Philadelphia.)

Fig. 2. Rene Theophile Laennec (1781–1826). (Used with permission of the library of the College of Physicians of Philadelphia.)

Fig. 3. Wilhelm Konrad Roentgen (1845–1923). (Used with the permission of the library of the College of Physicians of Philadelphia.)

important early development in diagnosing of bronchogenic carcinoma during the patient's lifetime.

Other technological advances occurred toward the end of the nineteenth century, and on April 23, 1895 Kirstein[10] first observed directly the vocal cords and the bifurcation of the trachea, thus marking the birthday of direct laryngoscopy and heralding the development of bronchoscopy, described by Killian[9] in 1898. Thoracoscopy followed in 1912, and bronchography in 1922.

Thus, the methods of clinical diagnosis, radiographic and histologic examination of specimens combined to allow a more accurate and earlier diagnosis of lung cancer in the twentieth century. Although Flint[4] prophesied as early as 1866, "It is possible that the microscopical characters of cancer may be discovered in the sputum," and although the first identified cancer cells were described in the sputum in 1875, it was not until after World War II that Dr. George N. Papanicolaou[17] developed cytologic examination of sputum specimens to its present technical perfection. His first examination of tumor cells in a patient with lung cancer was reported in 1945.

As expected, treatment in the early reports of necropsy material was entirely symptomatic and unsuccessful, and included the use of sal soda and senna, sulfate of quinine, wine whey, brandy toddy, and other tonics (Hall[6]). Small bleedings were believed to afford temporary relief but could not be repeated often.

The first intrathoracic operation, described in 1889, changed an attitude that was dramatized by Salter[20] in his lectures: "With regard to treatment, gentlemen, I need not tell you that I have nothing to tell you." In that year a simple thoracotomy was performed for a localized lung abscess. In 1895, Sir William Macewen, Regius Professor of Surgery at the University of Glasgow, actually removed a lung, a portion of the chest wall, and a lung tumor by repeated cauterization. The patient survived and was alive as late as 1940.[22] In 1911, Kümmell[11] reported the first successful total pneumonectomy for cancer. The patient subsequently blew out his bronchial stump and died of "septic suppuration." The surgeon reported that "the danger of a lung operation can be lessened; namely, by instituting a gradually increasing pneumothorax." X-Rays of the thorax accompanied this report, and an overpressure apparatus was not used. Twenty-two years later, Dr. Evarts A. Graham of Memorial Hospital in New York performed the first resection of a whole lung for cancer, including in his procedure a thoracoplasty and the implantation of seven gold-shielded radon seeds into the stump of the hilum, the site of a suspected residual metastatic node. Although this patient also blew his bronchial stump, with subsequent empyema, he survived the operation and continued practicing as a physician for many years afterward.[23]

Although x-rays were used therapeutically a few years after their discovery, the practical application of radiation therapy in the treatment of lung cancer was not possible until 1928, when the radium element pack at Memorial Hospital in New York was first used clinically. This device contained 4 g of radium and was the forerunner of megavolt therapy equipment, which forms the basis of modern therapeutic radiology. One of the first reported results of radiation therapy for histologically confirmed lung cancer was published by Ormerod,[15] who reported a series of 100 consecutive cases of inoperable lung cancer, most of which were treated by interstitial implantation during exploratory thoracotomy; 4 of these patients survived for 5 years or more.

The palliation of lung cancer by chemotherapy followed shortly after the introduction of nitrogen mustard in the treatment of malignant disease, and was reported by Levine and Weisberger[13] in 1955. More recently,

manipulation of the immune status of patients with lung cancer has been used in treating patients with bronchogenic carcinoma by Israel and Halpern[8] with some encouraging results.

"What is past is prologue" is as true in cancer of the lung as it is for the Archives of the United States of America. The survival rate among patients with lung cancer remains poor. The possible rate of cure has been raised from 0% 150 years ago to about 3 to 5% of all patients diagnosed as having bronchogenic carcinoma in 1973. On the other hand, although cancer of the lung used to be described as a rare disease, it has now become a major killer of men in the United States. Treatment remains unsatisfactory in spite of all the technical advances our modern age has achieved. Hopefully, the past will prove the prologue to successful elimination of the mortality rate from bronchogenic carcinoma, if not to its complete extinction.

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Chapter Two

The Incidence of Cancer of the Lung

Bronchogenic carcinoma was a medical curiosity 150 years ago. It has now achieved the dubious distinction of being the number one killer among malignancies in United States males. The statistics of the American Cancer Society[1] for 1975 indicate that 81,100 patients are expected to die of lung cancer, and 63,500 of these will be male. Of the 83,000 new cases that will be diagnosed, 67,000 will be male. For comparison, the next most frequent malignancy in the male, cancer of the prostate gland, killed 17,200 patients in 1971 of 35,000 newly diagnosed cases. In the United States, of the 69,600 female patients newly diagnosed as having breast cancer, there were 30,750 deaths approximately triple the female death rate from bronchogenic carcinoma in this country. United States vital statistics for 1967[9] reveal 310,983 deaths from cancer in that year, a record second only to heart disease, the cause of death in 720,892 patients. The percentage of cancer deaths expressed in relationship to the total number of deaths was 16.8%. Death from bronchogenic carcinoma accounts for nearly 20% of all cancer deaths in the United States; thus approximately 3.5% of all U.S. patients die of this disease. Disregarding the obvious differences in populations that might die from one disease or another, lung cancer causes death in as many patients as do highway accidents or influenza and pneumonia.

Although underreporting and early death from infectious disease were mainly responsible for the apparent rarity of lung cancer in the nineteenth century, the statistics of the U.S. Bureau of the Census[2] indicate a precipitous rise in the frequency of bronchogenic carcinoma in male patients since about 1935 (Fig. 1). This increase is greatest for the nonwhite male population.[4] Racial differences are also evident in national trends in bronchogenic carcinoma, with significant differences in the incidence of lung cancer in male and female Japanese and Chinese as compared to U.S. whites (Table 1).[7] The relatively uniform incidence of lung cancer among females of all races except Maori women, who are heavy cigarette smokers, is very evident.

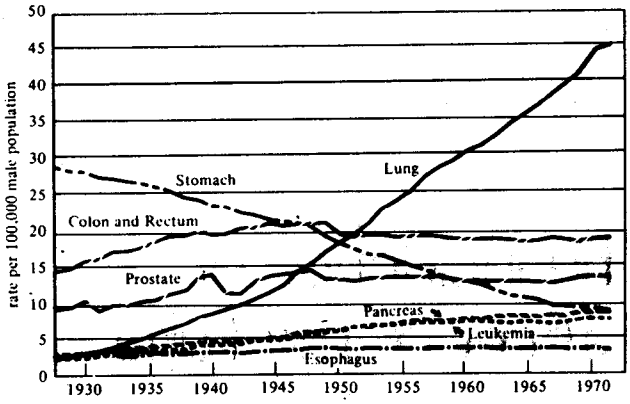

Fig. 1. Male cancer death rate by site, United States, 1930–1969. (Courtesy of American Cancer Society, Inc.)

If male lung cancer mortality had been eliminated, there would have been no increase in the U.S. male cancer rate over the past 10 to 20 years. At present lung cancer accounts for 32% of the male cancer rate in the United States and for 43% in England, Wales, and Scotland.

The increase in longevity in the U.S. population earlier in this century is not the only factor contributing to the frequency of lung cancer, although there is a

TABLE 1. AGE-ADJUSTED DEATH RATE PERCENTAGES BY SELECTED PRIMARY SITE AND SEX: JAPAN, TAIWAN AND U.S. WHITES, 1960–1961[7]

Primary Site	Japan		Taiwan		U.S. Whites	
	Males	Females	Males	Females	Males	Females
Buccal cavity and pharynx	1.32	0.59	4.73	2.10	4.58	1.26
Esophagus	6.95	2.26	6.97	1.58	3.26	0.78
Stomach	69.50	36.80	21.86	11.93	11.46	5.81
Intestines (except rectum)	2.79	2.88	3.02	3.34	13.24	13.31
Rectum	4.27	3.44	2.74	1.40	5.97	3.80
Liver and biliary passages	15.07	9.46	—	—	4.66	4.53
Pancreas	3.02	1.88	—	—	7.78	4.63
Lung, bronchus, and trachea	9.97	3.67	7.73	4.00	31.36	4.69
Breast	—	3.76	—	3.80	—	21.38
Uterus, all parts	—	15.51	—	16.32	—	11.52
Ovary, fallopian tube, and broad ligament	—	1.57	—	—	—	7.35
Prostate	1.43	—	0.59	—	12.84	—
Bladder and other urinary organs	2.05	1.03	—	—	5.18	1.80
Leukemia and aleukemia	3.35	2.56	—	—	7.84	5.05

higher incidence among older patients (Fig. 2).[6] Langston[5] reported that the increase in mortality from cancer of the lung has been less for patients 40 to 44 years old since about 1945, for those in the 45 to 49 age group since 1950, and for those 50 to 54 years since 1955. These statistics may indicate a prospect for slowing the rate of increase in male mortality from bronchogenic carcinoma, with the patients who were born around the turn of the century showing the highest rate. If this wave of high-risk patients passes through our patient population, a possible decrease may be forecast for the future It should be noted here that this study applies only to patients seen in a U.S. Veterans' Administration Hospital; similar studies are not available for other population groups.

Another significant factor in the incidence of lung cancer is the ratio of male to female patients in the United States. Between 1950 and 1967 this ratio increased from 6:1 to 5:1.[1] Since then, however, the rate of increase has been higher in the female population.

Although possible etiologic factors will be dealt with in the next chapter, major differences in incidence are noted among histologic subgroups of lung cancer. According to a study published by Vincent et al.,[8] 60% of the male patients with lung cancer had epidermoid carcinoma, whereas only 9% had adenocarcinomas. The data for female patients showed epidermoid carcinoma in 14% and adenocarcinoma in 49%. This suggests that the rapid increase in the incidence of lung cancer among female patients may be limited to epidermoid and oat cell carcinomas.[10]

The economic impact of lung cancer in this country can only be estimated, since accurate figures of the cost of treatment are not available. It is difficult, however, to underestimate this impact when one considers the relatively small change in survival rate and the rapid increase in incidence since earlier this century. A U.S. Public Health Service report[3] indicates that there were approximately 300,000 cancer deaths in the United States in 1963. The direct cost for hospitalization, nursing care, physicians, and other services and medications exceeded $1.5 billion in 1969. The indirect cost is even greater when one includes the loss of earnings during the illness and the loss of earnings during the balance of the normal life expectancy of these patients, many of whom had been stricken in a productive phase of their lives. Taking all these factors into consideration, the total cost of cancer to the U.S. economy is approximately $15 billion. Thus, each cancer death may represent an expenditure of about $5000 in direct services and $50,000 in loss to the economy as a whole. At current rates of inflation, the cost of cancer to our economy may amount to as much as 2% of the gross national product. Bronchogenic carcinoma accounts for a major portion of this loss of the most important resource of our country: the lives of our citizens.

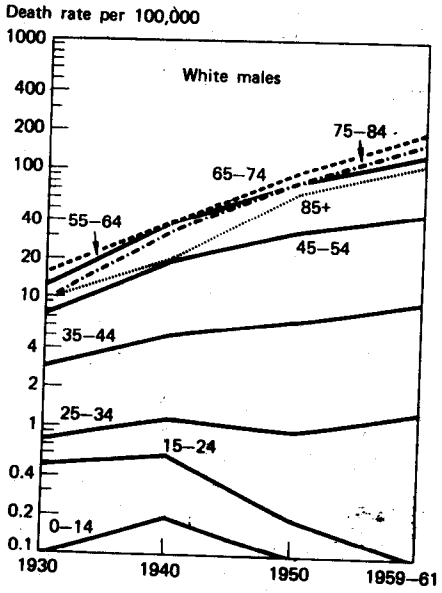

Fig. 2. Trends in death rate for malignant neoplasms of bronchus and lung in white males, United States, 1930–1961. (Copyright 1972 by the President and Fellows of Harvard College.)

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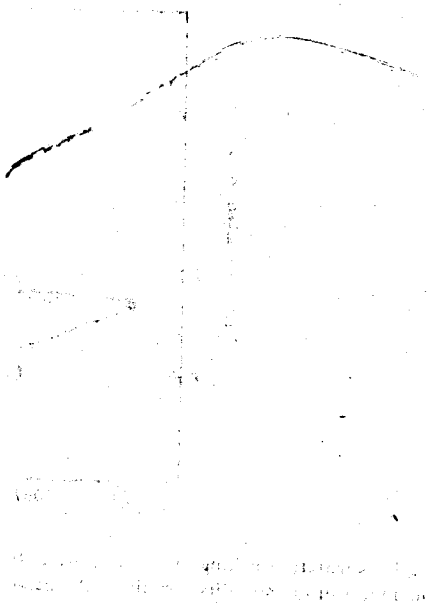
Chapter Three

The Etiology of Cancer of the Lung



Tobacco was introduced to Europe during the reign of James I of England (1603–1625), who was also James VI of Scotland (1567–1625). In a treatise entitled "A Counterblast to Tobacco," he described smoking as "a custom dangerous to the lungs, and in the black stinking fumes thereof nearest resembling the horrible Stygian smoke of the pit that is bottomless." Three and a half centuries later, in 1964, another counterblast to tobacco was published, a report by the U.S. Surgeon General[14] that summarized evidence implicating smoking as one of the major contributing factors in the development of lung cancer and other serious threats to health. Since then, additional information linking smoking to lung cancer has come to light. A study of major importance deals with the mortality rate in Swedish twins.[4] Death rates of cigarette smoking patients were compared with those of twins who did not smoke. There was no excess mortality among the smokers born between 1886 and 1905. Among twins born between 1906 and 1925, however, there was a higher death rate among the smokers.

This study forms one of the links between smoking and lung cancer, and other demographic studies support the thesis that cigarette smoking is a major factor in the development of lung cancer. The disease is rare among nonsmoking Seventh Day Adventists.[4] The incidence of lung cancer among British physicians who stopped smoking is decreasing, while an increase is evident among the male adult population in the United Kingdom[13] (Fig. 1). The correlation of decrease in cigarette smoking with a lower incidence of lung cancer is statistically significant. Another prospective study linking cigarette smoking to the development of lung cancer comes from Japan:[9] in a study of 265,118 adult males who were followed, the death rate of the cigarette smokers from lung cancer was four times higher than that of the nonsmokers.

Retrospective studies have shown a dose-response relationship between cigarette smoking and lung cancer[19] (Fig. 2) and prospective studies have confirmed this relationship. A study by Graham and Levin[8] indicates that lung cancer risk in smokers approaches that of nonsmokers after abstention from cigarette smoking for 10 years, and that the risk also declines in patients who have smoked for 30 or more years.

The likelihood of developing lung cancer is related to both the amount of smoking and the length of exposure. Evidence is also being accumulated that smoking not only causes cancer of the respiratory and upper digestive tracts, but that there is also an increase in cancers of the esophagus and bladder among tobacco smokers.[7] It has been estimated that in male patients who never smoked the total mortality rate from lung cancer may be reduced to 10% or 20% of its present rate, and female mortality may be cut to approximately 50%.[5]

Pre-malignant changes introduced into the bronchial mucosa of smokers who died of accidents and other causes not related to cancer have been described in detail by Auerbach et al.;[2] the resulting changes after cigarette

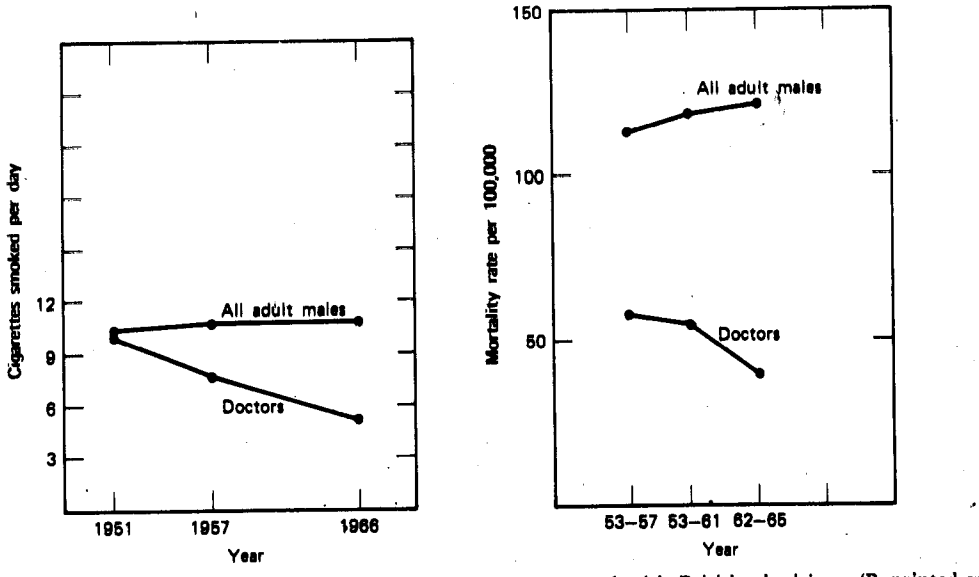


Fig. 1. Cigarette smoking and lung cancer: time trends of smoking and lung cancer mortality for all adult males in the United Kingdom compared with British physicians. (Reprinted with permission from reference 13.)