TOBACCO: A MEDICAL HISTORY

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Editor's Note: Sir Richard Doll is at present an Honorary Member of the Imperial Cancer Research Fund's Cancer Studies Unit in Oxford, England. He qualified in medicine at St. Thomas's Hospital Medical School, University of London, in 1937, receiving his MB and BS degrees, and worked for 2 years as a hospital intern and for 6 years in the Royal Army Medical Corps before turning to research. He subsequently was awarded the degrees of medical doctor (MD, London, 1945; DM, Oxford, 1969) and doctor of science (London, 1958). In 1969, Sir Richard became Regius Professor of Medicine at Oxford, and in 1979, he became the first Warden of Green College, Oxford. Since his retirement in 1983, he has continued to work in his honorary capacity, with Professor Richard Peto.

Sir Richard was elected a Fellow of the Royal College of Physicians in 1957 and a Fellow of the Royal Society in 1966. He was knighted in 1971 and was made a Companion of Honour in 1996. He received the UN Award for Cancer Research in 1962, the British Medical Association's Gold Medal in 1983, the Royal Society's Royal Medal in 1986, and awards from Canada, France, Germany, Italy, Thailand, and the US. He has received honorary degrees from 13 universities.

From 1948 to 1969, Sir Richard worked in England's Medical Research Council's Statistical Research Unit, at first under Sir Austin Bradford Hill and then as the unit's director. With Professor Bradford Hill, he carried out a study of the causes of lung cancer; in 1950, this study established the relationship of lung cancer to smoking. He also initiated a study of the mortality of doctors in relation to their smoking habits, which demonstrated that smoking was related to many other diseases, including heart disease. Other work has included the first clear demonstration (in 1955) that asbestos caused lung cancer; that ionizing radiation causes a risk of leukemia proportional to dose; and that oral contraceptives are associated with a small risk of venous and arterial thrombosis. In recent years, he has written reviews of the avoidable causes of cancer and the trends in cancer incidence and mortality. His recent work includes studies of the effect of radon in homes and of exposure to electromagnetic fields.

In this paper, Sir Richard describes the often-turbulent medical history of tobacco. From tobacco's original introduction into Europe at the close of the 15th century as a treatment of disease, to its success as a recreational drug, and finally its identification as a causal

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factor for many diseases, Sir Richard creates an exciting panorama of the way medicine viewed, used, and then warned against tobacco. The work of this internationally renowned epidemiologist was salient in establishing a relationship between smoking and lung cancer. The *Journal of Urban Health* is indeed honored to share his address with its readership.

INTRODUCTION

In the preface to his history of smoking, Corti wrote that it would afford him the liveliest pleasure if, after finishing the book, a reader was unable to decide whether the author was a smoker or not.[1,2] Admirable though that sentiment is for a serious historian, I cannot hope to make a similar claim, so let me say now that I smoked both pipes and cigarettes from 1930 to 1949 and subsequently smoked an occasional cigar until 1972, when I learned that a friend, who smoked many cigars and had died of a disease closely related to smoking, used to say that it was safe to smoke cigars because I did. Since then, I have not smoked at all. I can say, however, that I was not antagonistic to tobacco when, in 1947, I began to study its effects. These are multitudinous, but I shall say little about most of them here as they are well known. I shall concentrate rather on the way knowledge developed before the early 1960s, when smoking was generally recognized to be seriously harmful to health.

To begin at the beginning, we have to go back some 2500 years, when the custom of burning tobacco leaves and inhaling the smoke was adopted by the Mayans in Central America. At first, the leaves were burned in religious ceremonies, and the priests, who were also physicians, credited the plant with powers of healing. Later, tobacco came to be burned, and the resulting smoke was inhaled for pleasure. Its use spread north and south and to the Caribbean Islands, where leaves were presented to the Spaniards when they landed at the end of the 15th century. Within a few decades, leaves were brought to Spain and Portugal, but whether they were said to be brought by Spaniards, Portuguese, or Dutch varies with the nationality of the historian.

The use of tobacco for medical purposes spread through Europe, where tobacco was chewed, taken nasally as a powder, or applied locally in the treatment of cough, asthma, headaches, stomach cramps, gout, diseases of women, intestinal worms, open wounds, and malignant tumours. Although the plant is now named after Jean Nicot, he did not encounter it until 1559 in Lisbon, where he had been sent on a diplomatic mission. While there, he became enthused by reports of its healing powers and gave some seeds to a visiting dignitary from the French Court.[2]

Smoking tobacco in pipes became common only in the last quarter of the 16th century, initially in England. It was introduced by Thomas Harriot on his return

from Virginia, where he had been assigned the task of investigating anything noteworthy in the new colony, and it was popularized by his friend Sir Walter Raleigh. Many, however, thought it a disgusting habit, and the use of tobacco in this way was attacked violently. The opposition was led by James VI of Scotland when he succeeded to the throne of the United Kingdom (as James I) in 1603, and he published a pamphlet in Latin against it in the same year[3] and a year later anonymously in English[4] under the title, "A Counterblaste to Tobacco." The pamphlet was read widely, praised dutifully, and generally ignored. He tried to persuade Parliament to increase taxation on tobacco, but failed; the main effect of his opposition was to diminish imports from Virginia and to increase the amount grown at home. By this time, Harriot had died of lip cancer,[5] and Raleigh might have done so, too, had he not lost his head for other reasons in 1618.

Pipe smoking subsequently spread to the Netherlands, where it was recorded in many paintings by the old masters, at the beginning of the 17th century; in the succeeding two centuries, it spread throughout Europe and the East. Attempts were made to ban it in Japan, Russia, Switzerland, and parts of Austria and Germany, but the prohibition invariably was flouted, and control by taxation or the granting of monopoly rights came to be preferred. Eventually, the revenue obtained in this way became so attractive to governments that in 1851 Cardinal Antonelli made the discouragement of the use of tobacco in the Papal States an offence punishable by imprisonment.

Over the years, the way tobacco was used changed gradually. By the end of the 17th century, it was taken commonly as snuff; a century later, cigars, which had long been smoked in a primitive form in Spain and Portugal, began to replace snuff. By then, cigarettes were being made in South America, and their use had spread to Spain; it was not until the Crimean War that they were adopted widely. Officers returning from that war made their use fashionable in Britain, and by the end of the 19th century, cigarettes began to replace cigars. Their use increased rapidly in the World War I, particularly in Britain, and by the end of the World War II, cigarettes had largely replaced all other tobacco products in most developed countries. By this time, smoking had become so much the norm that 80% of middle-aged men in Britain were regular smokers, and some doctors were accustomed to offer cigarettes to their patients to put them at ease. Women took up smoking in large numbers only later, at first in the Maori population of New Zealand at the end of the 19th century and then in the US and Britain in the 1920s, facilitated in Britain during the World War II by the fact that many women began to work outside the home and had an independent income. In

some other developed countries, such as France and Spain, only in the last two or three decades have women begun smoking.

ATTITUDE TO SMOKING IN THE FIRST HALF OF THE 20TH CENTURY

Antitobacco Movements

By the beginning of the 20th century, the idea that tobacco might be beneficial largely had been abandoned, except insofar as it was thought that nicotine might improve some aspects of cerebral function. Opposition to tobacco, in contrast, had been formalised in the activities of societies that sought to discourage smoking on the grounds that nicotine was addictive. Tobacco was classed consequently with alcohol, and the antitobacco societies were associated closely with the temperance movement.

These societies had little impact in the United Kingdom, but the idea that smoking stunted the growth of children impressed the Interdepartmental Committee on Physical Deterioration, which had been appointed to enquire into the reasons for the poor health of recruits at the time of the Boer War. The committee's findings contributed to the introduction of a law in 1908 prohibiting the sale of tobacco to children under 16 years old and empowering the police to seize cigarettes from any child seen smoking in public.[6] The societies were most successful in the US; early this century, they got the sale of tobacco prohibited in 12 states, while the temperance movement got the sale of alcohol prohibited nationally. The law prohibiting the sale of alcohol, however, was not respected, and the antitobacco movement lost credibility as a result of the backlash against the temperance movement. Prohibition of the sale of tobacco consequently was short-lived, and in 1927, Kansas was the last state to rescind it.

In Germany, the Association Against Tobacco for the Protection of Non-smokers (Deutscher Tabakgegnerverein zum Schutze für Nichtraucher) was formed in 1904, but the movement had a chequered career until the rise of the National Socialist party in the 1930s.[7,8] Hitler strongly opposed the use of tobacco and alcohol, which he thought weakened the national will and harmed the national "germ plasm." When the party came to power in 1933, elementary schools were required to discuss the dangers of tobacco; government pamphlets were published warning people against it; and Nazi medical leaders addressed mass meetings, attacking tobacco and alcohol as reproductive poisons and drains on the economy. The Reich Institute for Tobacco Research developed tobacco with very low levels of nicotine, but it never captured more than a small percentage of the market. Beginning in 1938, smoking was forbidden in more and more situa-

tions: by uniformed police and SS officers on duty; by soldiers in the streets; by young people under 18 years old in public; and by anyone in air-raid shelters, city trains, and buses. In 1941, a special institute was established for the investigation of the hazards of smoking (Wissenschaftliches Institut zur Erforschung der Tabakgefahren); the institute was under the direction of Karl Astel, rector of the University of Jena and president of Thuringia's Office of Racial Affairs, which received an initial grant of 100,000 RM from Hitler's personal office. However, the campaign against tobacco did not have much impact on the public, and the *per caput* consumption increased annually after the party came to power and became 18% higher before supplies were reduced at the outbreak of war.[9]

Evidence of Harmful Effects

The antitobacco movements, in general, were not acting on sound medical evidence of harm, for little such evidence was available to them. Some evidence, however, had been accumulating from the end of the 18th century. It was of four types: clinical observations of patients, comparisons of national trends, studies of the smoking habits of people with and without different diseases, and laboratory experiments.

Cancer Most of the evidence was related to cancer. Clinical observations led Hill in 1761 to ascribe to the use of snuff the nasal lesions that he clearly thought were malignant[10] and led Sömmering to write the following in a prize treatise in Germany 34 years later: "Carcinoma of the lip is most frequent when people indulge in tobacco pipes. For the lower lip is particularly attacked by carcinoma because it is compressed between the pipe and the teeth."[11] In the next 100 years, pipe smoking, especially the smoking of clay pipes, came to be accepted widely as contributing to the development of cancers of the lip and tongue and other parts of the mouth.[12–14] In the first half of this century, the same cancers were also found to be associated characteristically with "heavy" smoking, without reference to method, in cancer clinics in the US.[15–17] Comparisons were made between patients with different types of cancer or, in one instance, with life insurance policyholders,[16] but without allowing for differences in age (Table I). The associations observed, however, were not taken very seriously, and insofar as pipe smoking was thought to be a cause of cancers of the lip and mouth, the risk was attributed commonly to the heat of the pipe stem rather than to the smoke.

The possibility of an association between smoking and cancer of the respiratory tract had been considered periodically since 1898, when Rottmann[18] suggested that a small cluster of cases of lung cancer in tobacco workers in Leipzig might

TABLE I Proportion of Heavy Smokers in US Populations in the Late 1920s

Population	Proportion*	(%)*	Proportion†	(%)†
Patients attending cancer clinics with				
Cancers supposedly affected by smoking	34/35	(97)	8/17	(53)
Lung cancer‡	5/5	(100)	17/38	(45)
Other cancer	106/144	(74)		
16,662 life insurance policyholders	—	—	—	(33)

*From Hoffman.[15]
†From Lombard and Doering.[16]
‡Included with other cancers in original analysis.

point to an occupational hazard, possibly from tobacco dust. At that time, lung cancer was a rare disease, but it came to be diagnosed progressively more often over the next five decades, and several clinicians and statisticians in Britain,[19] Germany,[20,21] and the US[22-25] suggested that cigarette smoking might be a cause, basing their suggestion on the smoking habits of affected patients and the crude correlation between the increase in the incidence of the disease and the consumption of cigarettes. An association with moderate and excessive smoking, without reference to method of smoking, was also noted in patients attending Massachusetts cancer clinics by Potter and Tulley in 1945 (Table II).[17]

Pathologists, meanwhile, argued about the reality of the increase. Some, however, were impressed sufficiently to try to produce cancer with tobacco tar on the skin of laboratory animals. Roffo succeeded in doing so in the Argentine in 1931,[26] using rabbits, but his results generally were dismissed in the United Kingdom and the US on the grounds that the tobacco had been burned at unrealistically high temperatures. Experiments in Britain were negative,[27,28] apart

TABLE II Percentage of Men Attending Massachusetts Cancer Clinics with Different Cancers, by Smoking Habit

	Cancer of			
Use of Tobacco (No. of Men)	Buccal Cavity	Respiratory Tract	Other Sites	Other Conditions
None (655)	3.7	0.5	22.4	73.4
Slight (357)	8.1	1.1	25.1	65.7
Moderate (1155)	11.5	2.0	26.0	60.5
Excessive (760)	17.9	1.7	23.4	57.0

Source: From Potter and Tulley.[17]

from one that produced one cancer in 50 animals and led Cooper et al.[29] to conclude that "tobacco tar is relatively unimportant in the causation of cancers."

Müller is credited with the first case-control study of lung cancer and smoking, which was carried out in Cologne in 1939,[30] but the technique he employed was crude. Questionnaires were sent to the relatives of people diagnosed with lung cancer at autopsy; the questionnaires asked about the subjects' smoking habits and previous exposure to respiratory irritants. Replies were received relating to 86 men and 10 women, but the proportion of questionnaires returned is unknown. Not all the respondents gave quantitative details of the amounts smoked, and smokers were classed in categories based on either quantitative or qualitative descriptions. The findings for the 86 men are shown in Table III, in which they are compared with findings obtained from "the same number of healthy men of the same ages," but how the healthy men were selected and how the information was obtained from them again are not described. The findings, in combination with the knowledge that the use of tobacco had increased five-fold since 1907 and the results of Roffo's[31] experiments, led Müller to conclude that tobacco was an important cause of lung cancer and the single most important cause of the rising incidence of the disease. The weakness of the epidemiological method is evident, and the conclusion hardly is justified, but the results certainly should have stimulated research and might have done so in Britain (which, at that time, had the highest lung cancer rates in the world) had the war not intervened.

TABLE III Use of Tobacco by Disease Category: 86 Men with and 86 Men without Lung Cancer

	No. of Men	
Type of Smoker	With Lung Cancer	Healthy Controls
Extreme smoker*	25	4
Very heavy smoker†	18	5
Heavy smoker‡	13	22
Moderate smoker§	27	41
Nonsmoker	3	14

Source: From Müller.[30]

*10–15 cigars, >35 cigarettes, or >50 g pipe tobacco/day.

†7–9 cigars, >26–35 cigarettes, or >36–50 g pipe tobacco/day.

‡4–6 cigars, >16–25 cigarettes, or >21–35 g pipe tobacco/day.

§1–3 cigars, >1–15 cigarettes, or >1–20 g pipe tobacco/day.

Further research, however, was carried out in Germany and in the Netherlands. Schairer and Schöniger reported a case-control study from Astel's Institute in 1943,[32] and Wassink reported the results of a Dutch study in 1948.[33] Their findings are summarized with Müller's in Table IV. The similarity of the findings is impressive. The work of Schairer and Schöniger was more convincing than that of Müller because they gave more details of their methodology and had an additional control group of men who had died from stomach cancer. They thought that bias was an unlikely explanation, that other common explanations for the increase in lung cancer could be excluded, and that smoking was very likely to be a cause of the disease.

Vascular disease The idea that smoking might be a cause of vascular disease dates from the end of the last century, when Huchard[34] wrote:

> The [unfavourable] influences of nicotinism on the development of arteriosclerosis appears to have been demonstrated, and this is not surprising since nicotine produces most often arterial hypertension by vasoconstriction, as the experiments of Claude Bernard proved.

Eleven years later, Erb[35] found that 25 of 45 patients with intermittent claudication were heavy smokers, and shortly after that, Buerger[36] noted that the rare form of peripheral vascular disease named after him seldom occurred in nonsmokers. Buerger's findings were confirmed repeatedly in the US,[37-39] and Silbert, who reported a large series of cases from New York in 1935, stated that he had never seen a case in a nonsmoker.[40] Others,[31] however, said that they had; this, I was told when a medical student, showed that smoking was not the cause.

Coronary thrombosis was not diagnosed in life until Herrick diagnosed it in 1912.[42] Subsequently, it was reported progressively more often every year. The correlation between the increasing number of reports and the increasing consumption of cigarettes led Hoffman,[43] an American statistician, to suggest, as early as 1926, that smoking might be responsible for many cases. Several clinical studies of the relationship with smoking were published, but the findings were confused, and no substantial evidence was obtained until 1940, when English

TABLE IV Smoking and Lung Cancer Case-Control Studies Before 1950

	No. of Men		Nonsmokers, %		Heavy Smokers, %	
Author	Lung Cancer	Controls	Lung Cancer	Controls	Lung Cancer	Controls
Müller[30]	86	86	3.5	16.3	65	36
Schairer and Schöniger[32]	93	270	3.2	15.9	52	27
Wassink[33]	134	100	4.5	19.0	55	19

TABLE V Tobacco Use and Coronary Disease in Men

Age (Years)	Smokers, %*		P†
	Coronary Disease	Others	
40–49	79.7 (149/187)	61.9 (187/302)	<.001
50–59	71.7 (274/382)	73.9 (274/371)	—
60+	63.8 (275/431)	61.8 (202/327)	.28
Total	69.8 (698/1,000)	66.3 (663/1,000)	.05

Source: From English et al.[44]
*Number of smokers/all men in age group in parentheses.
†*P*, one sided.

and coworkers[44] reported finding an association in the records of the Mayo clinic. They compared the recorded habits of 1,000 patients with the disease with those of 1,000 other patients matched in three broad groups for sex and for age (Table V) and subsequently compared the frequency of the diagnosis of coronary disease in 1,000 smokers seen consecutively with that in 1,000 similarly matched nonsmokers (Table VI). The results led them to conclude that the smoking of tobacco probably had "a more profound effect on younger individuals owing to the existence of relatively normal cardiovascular systems, influencing perhaps the earlier development of coronary disease." They eschewed reference to causation because the subject would be controversial: "Physicians are not yet ready to agree on this important subject."[45]

Other conditions Other conditions related to smoking included tobacco amblyopia, a characteristic type of blindness, which was described by Beer in 1817.[46] It occurred principally in those who smoked a pipe heavily and in association with

TABLE VI Tobacco and Coronary Disease Frequency in Men

Age (Years)	Coronary Disease, %*		P†
	Smokers	Nonsmokers	
40–49	4.8 (10/208)	1.0 (2/208)	.01
50–59	6.2 (24/388)	2.6 (10/388)	.01
60+	5.0 (20/404)	6.4 (26/404)	—
Total	5.4 (54/1,000)	3.8 (38/1,000)	.04

Source: From English et al.[44]
*Number of men with coronary disease/number of men with all diseases in age group in parentheses.
†*P*, one sided.

malnutrition and probably was caused by the cyanide in smoke, when the ability to detoxify it was reduced by deficiency of vitamin B_{12}.[47,48] The disease has been much less common in cigarette smokers and is now extremely rare.

Peptic ulcers commonly were thought to be aggravated by smoking, possibly as a result of the action of nicotine on gastric motility, but the physiological evidence was inconsistent and never wholly convincing.

Extraordinarily, there was seldom reference to smoking as a cause of respiratory disease, except by Lickint in Germany.[49] In Britain, the cough that was so prevalent in smokers was dismissed as a benign "smokers' cough."

In retrospect, the most important evidence of the harmful effects of smoking was Pearl's observation in 1938[50] from a study of family history records collected at the Johns Hopkins School of Hygiene and Public Health: "The smoking of tobacco was statistically associated with the impairment of life duration and the amount or degree of this impairment increased as the habitual amount of smoking increased." Pearl's unwelcome finding was either ignored or dismissed as due to confounding with some hypothetical other feature.

Medical Teaching

Despite the accumulating evidence, academic departments in general paid little or no attention to smoking, and references to it in medical and surgical textbooks before 1950 were scarce and brief. In the United Kingdom and the US, most textbooks mentioned smoking in relation to Buerger's disease and cancers of the lip and tongue. A few mentioned tobacco amblyopia, and some said that excessive smoking aggravated peptic ulcers and should be stopped in the treatment of angina. None mentioned it in relation to coronary thrombosis or cancer of the lung.

More attention was paid to smoking in Germany, which had been the leading country for medical research. The misuse of tobacco was sometimes said to cause chronic nicotine poisoning, with effects in nearly every system in the body.[51,52] It was thought to aggravate peptic ulcers and to cause hypertension in susceptible people,[51] angina, and atherosclerosis.[52,53] It was mentioned as contributing to cancers of the mouth,[54] tongue, and larynx,[55] but not in relation to cancer of the lung, except by Bauer[56] in his textbook on cancer, who thought that tobacco might cause a precancerous condition in the bronchi that other agents converted into cancer.

THE 1950 WATERSHED

In 1950, the situation was changed radically by the report of the five case-control studies of cancer of the lung. They differed from the early German studies in

that many more patients were included, the possibility of substantial bias due to low response rates was avoided, and much more information was obtained about past smoking habits, including the method and amount of smoking and the ages at which smoking had been started and stopped. Outline results, similar to those shown for the three pre-1950 studies, are shown in Table VII. All showed a close association with smoking.

Two studies stood out because of their size, the precision with which lifelong nonsmokers were defined, and the argument that led to their conclusion. One was initiated by Wynder[62] in 1948, while he was a summer student at New York University, on the basis of knowledge that, "The burning of tobacco in pipes or as cigars or cigarettes, would lead to the formation of cancer-causing chemical compounds." The results he obtained from interviewing 20 patients so impressed Evarts Graham, the Chief of Surgery at Washington University School of Medicine, that the study was continued in Graham's surgical service, and a grant for expansion was obtained from the American Cancer Society in spring 1949. Analysis led to the conclusion that: "Excessive and prolonged use of tobacco, especially of cigarettes, seems to be an important factor in the induction of bronchogenic cancer."[60]

The other study was initiated by the British Medical Research Council following a 1947 conference to discuss the reasons for the dramatic increase in the mortality attributed to the disease. Neither of the two German papers was referred to, and the Dutch paper had not been published then. The idea that the increase might be due to the increased consumption of cigarettes was supported by Kennaway, the leading cancer researcher of his day, because of the probability that the combustion of tobacco would produce carcinogens; this appealed to Mellanby, then Secretary of the Medical Research Council, because the mortality from lung cancer in men was substantially higher in Nottingham, a centre of the

TABLE VII Smoking and Lung Cancer Case-Control Studies Published in 1950

	No. of Men		Nonsmokers, %		Heavy Smokers, %	
Author	Lung Cancer	Controls	Lung Cancer	Controls	Lung Cancer	Controls
Schrek et al.[57]	82	522	14.6	23.9	18	9
Levin et al.[58]	236	481	15.3	21.7	—	—
Mills and Porter[59]	444	430	7	31	—	—
Wynder and Graham[60]	605	780	1.3*	14.6*	51	19
Doll and Hill[61]	649	649	0.3*	4.2*	26	13

*Lifelong nonsmokers, with ex-smokers excluded.

British tobacco industry, than in nearby Leicester.[63] Bradford Hill was asked consequently to carry out a case-control study to test the various hypotheses that had been put forward to explain an increased incidence. Within 2 years, the study had been completed. After detailed consideration of the possibility of confounding, the consistency of the findings in different studies, the biological relationships with the amount and duration of smoking, the size of the estimated relative risk, and the relationships over time and place and for each sex, the authors concluded that: "Cigarette smoking is a factor, and an important factor, in the production of carcinoma of the lung."[61]

This conclusion was accepted by Sir Harold Himsworth, who had succeeded Mellanby as Secretary of the Medical Research Council, but it was not accepted generally by medical or statistical scientists and certainly not by the British Department of Health's Standing Advisory Committee on Cancer and Radiotherapy.[6] Most accepted that an association had been shown, but not that it implied cause and effect. Some, however, were even more sceptical, including Berkson,[64] coauthor of the 1940 study of coronary heart disease and the leading American medical statistician, who suggested that the findings were an artifact due to the combination of lung cancer and smoking leading to a greater chance of a patient's admission to hospital than the occurrence of the disease in a nonsmoker. Other sceptics included the representatives of the tobacco industry; in Britain, they sought an interview with the Medical Research Council and were referred to Professor Hill and myself. The conclusion that cigarette smoking was a cause of the disease, they argued, was unsustainable for three reasons: The international correlation between cigarette consumption and the mortality from lung cancer of about 0.5 was too low; smoking histories were too unreliable to use as a basis for an association with disease; and lung cancer, in any case, obviously was due to atmospheric pollution. To this, Hill replied that a correlation of the size observed with crude international statistics was, in his experience, unusually high and supported a causal relationship rather than the reverse: If smoking histories were unreliable, this would have weakened a true association rather than have created a false one; and if they thought that atmospheric pollution was the main cause of lung cancer, they should go away and prove it, for he and I couldn't.

WIDE ACCEPTANCE OF MAJOR HARM FROM SMOKING

Early Cohort Studies

Consequently, if reactions were to be changed, evidence of a different type clearly was needed, such as that obtained by recording the smoking habits of large

numbers of people and following them to see if the risk of lung cancer could be predicted from the information about the individual's level of smoking. According to Wynne Griffith (personal communication, 1952), the idea that doctors would make a suitable population to study came to Bradford Hill one Sunday morning when playing golf, and Griffith added: "I don't know what kind of a golfer he (is) but that was a stroke of genius." It was indeed, for when we wrote to all the doctors on the British Medical Register in October 1951, over 40,000 (two-thirds) gave details of their smoking habits; they proved so easy to trace that nearly all the men who were not known to have died could be traced 40 years later.[65] The story is, however, apocryphal for Sir Austin told me that the idea came to him, in the classical manner, in his bath.

The evidence from the cohort study of British doctors mounted quickly, and within 2.5 years, the findings with regard to lung cancer had confirmed those predicted from the case-control studies. This is shown in Table VIII, which gives the relative mortality rates for different levels of smoking as estimated from the final results of the British case-control study based on 1,357 deaths from lung cancer in men[66] and the first results of the cohort study based on only 36 such deaths.[67] With so few deaths in the second study, the confidence limits of the mortality rates were wide, but even so, the trend in mortality with smoking was significant ($P < .01$).

Altogether, however, 789 deaths had been recorded, and it was possible to examine the relationship between smoking and several other diseases. With 235 deaths attributed to coronary thrombosis, the mortality (standardized for age) increased progressively from that in lifelong nonsmokers to that in men who smoked an average of 25 g or more of tobacco per day. The increase was small (about a third), but the trend was significant statistically; it was concluded that there was a subgroup of cases in which "tobacco has a significant adjuvant effect."

In 1956, the main results were confirmed with larger numbers.[68] More impor-

TABLE VIII Relative Death Rates from Lung Cancer Standardized for Age by Amount Smoked: Case-Control and Cohort Studies, Men Aged 45–74 Years

	Rate as Percentage of Rate for All Men			
		Amount Smoked, Per Day		
Study	Nonsmokers	1–14 g	15–24 g	25 g or More
Case-control[66]	6	79	112	201
Cohort[67]	0	68	133	199

tant, they were also confirmed in the much larger study that the American Cancer Society had started in 1952 specifically, as the principal investigator told me that same year, to disprove the relationship between smoking and lung cancer observed in the case-control studies (E. C. Hammond, personal communication, 1952). The results, based on nearly 5,000 deaths in 190,000 American men followed for 2 years, are shown in Table IX for lung cancer and, in four age groups, for coronary disease.[69] The investigators were impressed by the correlations between cigarette smoking and the mortality from coronary thrombosis in men and women, in urban and rural areas, and over time and also by the previous reports that cigarette smoking caused vasoconstriction and increased heart rate and blood pressure. They concluded that: "Regular cigarette smoking causes an increase in death rates from these two diseases" (that is, from coronary thrombosis and cancer of the lung). In relation to the former, they added: "Probably nicotine is at least partially responsible for the findings."

Proof of Causation

The conclusion that cigarette smoking was a major cause of disease had not been easy to accept as the evidence was observational and unconfirmed by experiment. Two leading statisticians, moreover, remained unconvinced. In the US, Berkson was disturbed that the relationship with smoking held to some extent across the board with a variety of conditions.[70] In Berkson's opinion, this raised the suspicion that there must be something wrong with the method of enquiry, and he suggested that the findings were the result of the interplay of various subtle and complicated biases or that they had a constitutional basis, involving people who were nonsmokers or relatively light smokers, being the kind who were

TABLE IX Mortality by Amount Smoked Relative to Mortality in Nonsmokers

Age (Years)	No. of Deaths	Cigarettes Smoked, Per Day			Cause of Death
		<10	10–19	20 or More	
50–69	167		4.2	8.8	Lung cancer
50–54	377	1.7	2.1	2.5	Coronary heart disease
55–59	571	1.1	1.9	2.1	
60–64	594	1.5	2.2	2.0	
65–69	605	1.0	1.3	1.1	

Source: After Hammond and Horn.[69]

biologically self-protective and that this "correlated with robustness in meeting mortal stress from disease generally."

In making this criticism, Berkson[70] took no account of the great difference in the relative risks of different diseases among heavy cigarette smokers compared to nonsmokers, varying in Doll and Hill's study[68] from 24 to 1 for lung cancer to 1.01 to 1, or of the fact that tobacco smoke was not a pure chemical entity, but a mixture of many chemicals, subsequently shown to number more than 4,000. It was, as Hill pointed out,[71] as if he had said that milk could not be a cause of any disease because it spread tuberculosis, diphtheria, scarlet fever, undulant fever, dysentery, and typhoid, and, he might have added, contributed to the production of vascular disease and prevented osteoporosis.

In the United Kingdom, Fisher,[72] the most eminent theoretical statistician worldwide, was disturbed by Doll and Hill's original finding[61] that smokers with lung cancer reported inhaling less often than smokers without the disease (62% against 67%). Fisher thought this weighed against causation, unless it were also concluded that: "Inhaling cigarette smoke was a practice of considerable prophylactic value in preventing the disease.[72] He argued that secular changes in smoking habits could not be related to the increase in lung cancer since "lung cancer has been increasing more rapidly in men relatively to women," while "it is notorious, and conspicuous in the memory of most of us, that over the last 50 years the increase of smoking among women has been great, and that among men (even if positive) certainly small."[73]

Neither objection was valid. The effect of inhaling was impossible to predict without knowing where the smoke droplets were deposited, and this was uncertain because tobacco aerosols swell under warm and moist conditions and, if inhaled deeply, might deposit in the alveoli rather than on the bronchi.[74] Doll and Hill, moreover, found that, while reported inhaling was associated with a diminished risk of cancer in the large bronchi, it was associated with an increased risk of developing cancer in the periphery of the lung, which made biological sense.[66] As for the evidence of secular changes, Fisher[73] was just wrong for he had ignored the cohort effects by which the risks among successive cohorts are determined not only by their recent smoking history, but also by their smoking habits in the distant past. When comparisons are made at appropriate ages and times, the trends in the sex ratio of the disease mimic the trends in cigarette consumption by sex over the relevant periods.[75]

Difficulty in reaching a conclusion about causality also arose because different

people gave different meanings to "cause." In saying that a factor is a cause of disease, epidemiologists have in mind a situation in which, for example, prolonged cigarette smoking results in a rare disease becoming 10 times as common as it would have been in the absence of smoking. Cigarette smoking is not then a necessary cause or a sufficient cause, but it can be an important cause (as relatively few people would have developed the disease if they had not smoked), and this is not contingent on the absence of other causes. What was claimed was that, for several diseases, causation in this sense was proved beyond reasonable doubt. The detailed evidence that led to this claim has been reviewed many times, and I note here only the extraordinary strength of the association with lung cancer, with increased risks of more than 20-fold in heavy cigarette smokers (which alone made the alternative explanation of confounding virtually impossible), the diminution of risk with cessation of smoking, and the consistency of the findings with different methods of investigation, in different countries, and in different cultures.

During the 1950s, this epidemiological evidence was extended by case-control studies in many other countries[76] and was supplemented by the experimental demonstration that tobacco tars were carcinogenic when applied regularly for a long time to the skin of laboratory animals[77-82] and by the identification of known carcinogens in tobacco smoke.[83,84] Expert committees were able consequently to reach positive conclusions. Between 1956 and 1959, the Netherlands Ministry of Social Affairs and Public Health[85]; the British Medical Research Council[86]; a study group appointed jointly by the US National Cancer Institute, the National Heart Institute, and the American Cancer Society[87]; the Swedish Medical Research Council[88]; and the US Public Health Service[89] all reported that cigarette smoking was a cause of lung cancer. A year later, an expert committee of the World Health Organization did so, too.[90]

Public Acceptance of Causality

Despite their provenance, these reports had little lasting impact on the general public, and the situation did not change materially until after the reports by the Royal College of Physicians of London in 1962[91] and the Advisory Committee to the US Surgeon General in 1964.[92] The first was short and aimed at interested laypeople. The second was long and detailed and was particularly newsworthy because the tobacco industry had been privileged to veto any member of the committee who had expressed any views publicly about the subject. Both reports, nevertheless, agreed that smoking was a major cause of lung cancer. The Surgeon General's committee was also clear that it was a major cause of chronic bronchitis.

Both, however, were cautious about the meaning of the relationship of smoking to the many other diseases associated with it.

Following these reports, the idea that smoking was a major cause of lung cancer ceased to be challenged seriously. On the advice of Geoffrey Todd, their senior statistician, even the tobacco industry in the United Kingdom agreed not to deny the causal relationship. Todd had been a representative of the industry who had visited Doll and Hill in 1952 and had sought to persuade them that their conclusion was wrong, but he became convinced that it was right. In the US, however, the industry continued to maintain that all that had been shown was a statistical association and that causality had not been proven scientifically; this pertained until recently, when the smallest manufacturer broke ranks and accepted that smoking was a cause of the disease.

CURRENT KNOWLEDGE OF EFFECTS

In the three subsequent decades, cigarette smoking has been found to be associated positively with nearly 50 causes of death or morbidity and to be associated negatively with 8 or 9. Some of the associations are due to confounding with other factors, but the majority arise because tobacco smoke is a contributory cause. *Pace* Berkson, this is not surprising, not only because of the complexity of tobacco smoke, but also because many of the diseases are different clinical manifestations of common processes, such as DNA damage, vascular occlusion, and damage to small airways. Most of the associations have been demonstrated in cohort studies, which have now also been carried out in Canada,[93] China,[94] Japan,[95] Norway,[96] and Sweden,[97] as well as in Britain and the US; these studies have been extended to cover the last two decades, when most smokers have been smoking cigarettes nearly all their smoking lives.[65,98] Others have been demonstrated in case-control studies.

Harmful Effects

The morbid effects caused in part by cigarette smoking are listed in Tables X–XII. Those that are five or more times more common in cigarette smokers than in nonsmokers are indicated. Table XIII shows deaths principally associated with smoking through confounding with other aetiological agents; it is possible also that there is a small proportion of childhood cancers due to mutations in paternal sperm.[99]

Beneficial Effects

Finally, there are eight or nine diseases that may be alleviated or prevented by tobacco smoke (Table XIV). Most are uncommon or seldom fatal, and their

TABLE X Cancer Sites and Type Caused Partly by Smoking

Lip	Pharynx*	Liver
Nose	Oesophagus*	Kidney pelvis
Lung*	Stomach	Kidney body
Larynx*	Pancreas	Bladder
Mouth*		
	Myeloid leukaemia	

*Risk increased five or more times.

TABLE XI Vascular and Respiratory Diseases Caused Partly by Smoking

Pulmonary heart disease*	Subarachnoid haemorrhage
Ischaemic heart disease	Cerebral thrombosis
Myocardial degeneration	Cerebral haemorrhage
Hypertension (fatal)	Chronic obstructive lung disease*
Arteriosclerosis	Pneumonia
Aortic aneurysm*	Asthma
Peripheral vascular disease*	Pulmonary tuberculosis
Buerger's disease*	

*Risk increased five or more times.

TABLE XII Other Conditions Caused Partly by Smoking

Gastric ulcer	Reduced growth of fetus
Duodenal ulcer	Periodontitis
Crohn's disease	Tobacco amblyopia*
Osteoporosis	Age-related macular degeneration
Reduced fecundity	Cataract

*Risk increased five or more times.

TABLE XIII Causes of Death Associated with Smoking That may be Largely or Wholly Due to Confounding Factors

Cancer of cervix uteri
Cancer of large bowel
Cirrhosis of liver
Suicide
Poisoning

TABLE XIV Diseases Inversely Associated with Smoking

Parkinson's disease	Fibroids
Ulcerative colitis	Nausea and vomiting of pregnancy
Aphthous ulcers	Pre-eclampsia
Allergic alveolitis	Alzheimer's disease (possibly)
Cancer of body of uterus	

combined impact on mortality as a result of smoking is less than 1% of that of the conditions caused by smoking. Whether Alzheimer's disease in fact is related inversely to smoking is uncertain. It has appeared to be so in case-control studies, but not in several cohort studies,[100] and the inverse relationship may be an artifact due to the study of prevalent cases rather than incident cases.

TOTAL EFFECT ON RISK OF DEATH

In sum, the total effect of cigarette smoking appears to double the risk of death in both sexes, the relative effect being greatest in middle age, when the mortality in continuing cigarette smokers is about treble that in lifelong nonsmokers. In the Figure, this is shown for American men in the American Cancer Society's cohort followed from 1984 to 1988.[101]

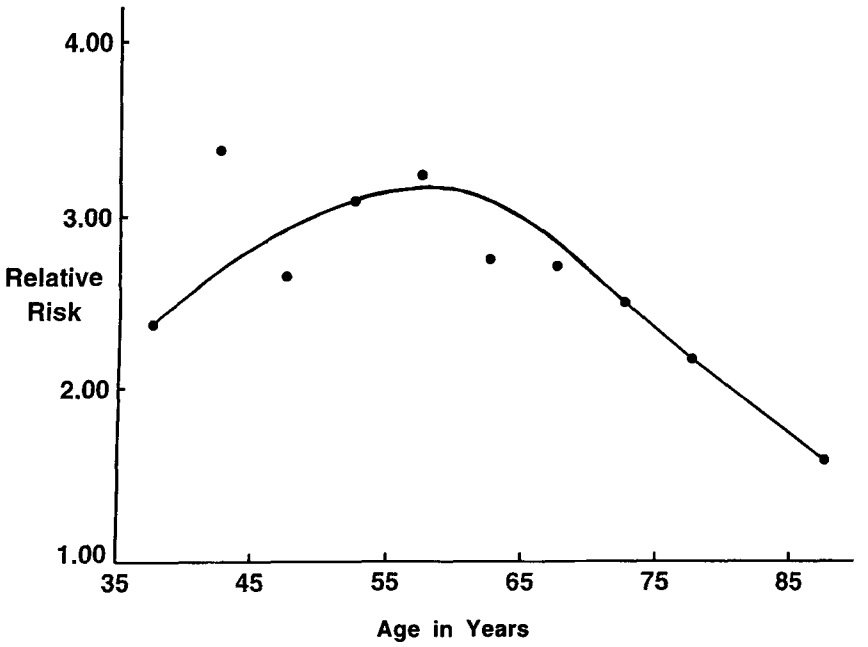

FIGURE Ratio of mortality rates in regular cigarette smokers and life-long non-smokers by age: men in American Cancer Society's second cancer prevention study[101] in years 3 to 6 inclusive, 1984–88.

Some 6% of the excess mortality in men is due to diseases that are listed in Table XIII as caused by factors with which smoking is confounded, and this might be thought to reduce the risk that the avoidance of smoking could avoid. In fact, it does not, for confounding can operate in both directions, and confounding with the consumption of alcohol reduces the effect of smoking because alcohol reduces the risk of vascular disease, which in developed countries is the principal cause of death. This more than compensates for the attribution to smoking of the excess mortality from other causes with which smoking is associated through confounding (such as cirrhosis of the liver and accidents), and the estimate that prolonged cigarette smoking causes the risk of death to be doubled is likely to be too small rather than too large. On the assumption that it doubles the risk, it will cause one regular cigarette smoker in four to die under 70 years of age because of his smoking habit, losing on average 20 years of life, and one in four to die later, losing on average 8 years of life.

CONCLUSION

In retrospect, it may be surprising that resistance to the idea that smoking causes so much disease was initially so strong. Three factors, at least, contributed to it. One was the ubiquity of the habit, which was as entrenched among male doctors and scientists as among other men and had dulled the sense that tobacco might be a major threat to health. Another was the novelty of the epidemiological techniques, which had not been applied previously to any important extent in the study of noninfectious disease. The findings were undervalued consequently as a source of scientific evidence. A third was the primacy given to Koch's postulates for determining causation. The evidence that lung cancer occurred in nonsmokers was taken consequently to show that smoking could not be *the* cause, and the possibility that it might be *a* cause was doubted inappropriately. The manner in which lung cancer was linked to smoking, however, was not unique. All the other major diseases related to smoking were found to be so by epidemiological enquiry, and laboratory evidence of physiological effects that provided plausible mechanisms by which smoking might cause them was obtained only later; in some instances, this evidence is still awaited.

All the diseases related to smoking that cause large numbers of deaths should have been discovered by now, but further effects like age-related macular degeneration, which was linked firmly to smoking only 3 years ago,[102–104] may well be revealed by cohort studies that are able to link morbidity data with people's personal characteristics through personal identity numbers.

With so much evidence of the harmful effects of tobacco, it might be thought

that governments would have reacted quickly and energetically to discourage its use, and even more so when it was appreciated that the tobacco smoke released to the general environment had harmful effects, albeit relatively small, on nonsmokers who inhaled it involuntarily.[105] This, however, did not happen. Reaction was slow and limited, and the tobacco industry has continued its efforts to expand the use of its products throughout the world. In consequence, there has been a resurgence of antitobacco movements dedicated to reducing the prevalence of smoking; these movements have now spread equally widely. The history of this resurgence and the gradual recognition by governments of their responsibility for the control of tobacco in the interests of public health is, however, an aspect of the medical history of tobacco that I must leave to another occasion.

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