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## REVIEWS AND COMMENTARY

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### Tobacco as a Cause of Lung Cancer: Some Reflections

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Around 50 years have now passed since the odyssey of the effort to link cigarette smoking to cancer began. Today, the causative association of cigarette smoking and lung cancer is well established. In many developed countries, we are beginning to see the first results of cancer control efforts, while lung cancer death rates in third world nations have as yet to experience the full impact of the tobacco-related cancer epidemic. Thus, much more effort will be needed to curb tobacco use and to apply other measures of health promotion.

Few people know how difficult it was in those early years to attract attention to the vital scientific and public health issues in regard to the relation between smoking and lung cancer. In retrospect, the initial apathy of health professionals and their reasons for neither accepting nor promoting the evidence relating lung cancer to smoking some five decades ago make for an astounding lesson of public health history. This communication will not deal with the outright resistance and active counter-propaganda of the tobacco interests, the basis of which would seem to be self-evident and which has been recently well reviewed by Richard Kluger in his book, *Ashes to Ashes* (1). Nor will it be concerned with the role of the press, radio, and television, groups that obviously can be influenced by various commercial interests related to tobacco. I will also not dwell on the fact that scientists who

received support from tobacco interests were muted. Yet, I would like to describe the attitudes and actions encountered within the health professions, and among their recognized leaders, in response to our early findings. Public health policy that is based on legislative measures depends on the vocal involvement of the medical and scientific leadership. As long as these voices were silent, there existed only uncertain and divided action, and no significant public health policy against smoking could be effectively implemented.

Why then were the leaders of the health authorities and of the medical professions so late in reaching a decisive conclusion and recommending public health action regarding the impact of smoking on cancer when the conclusion was so clear to those who had done the initial research? Was it the lack of appreciation of epidemiologic evidence and of laboratory science, or doubt about the production of cancer in laboratory animals with tobacco tar, or was it the persuasive power of a personal habit that so many of them "enjoyed"? Even more bothersome, could it have been the strong concern over such an important economic and political power as the tobacco industry? Likely, it was a combination of all of these factors.

Although the magnitude of the tobacco and health issue appears to be rather unique, this communication will provide a brief personal account that may serve to stimulate and encourage young investigators who may face similar opposition to new data, particularly if new discoveries have industrial implications. Perhaps we confront here a defect of human nature; few of us will "fight"—even in the case of powerful evidence—if the economic and political opposition is strong. My history begins in 1947.

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Abbreviations: ACS, American Cancer Society; *JAMA*, *Journal of the American Medical Association*.

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## THE LATE 1940s

To set the time frame, I am indebted to Sir Richard Doll (personal communication, January 13, 1997) for pointing out that the 1947 edition of Osler's *Principles and Practice of Medicine*, edited by H. A. Christian and J. G. Gray, included only five lines on tobacco-related amblyopia, and that the text made reference to tobacco merely as a contributing factor to Buerger's disease, and as an aggravating but not causative factor in the etiology of peptic ulcer. Thus, generally, the medical profession in those days did not seriously think about smoking as a potential cause of major diseases.

As a freshman year medical student at Washington University, St. Louis, Missouri, I became involved in the studies on experimental skin carcinogenesis in the laboratory of Dr. Edward Cowdry. During the summer, I took a course in cancer genetics taught by Dr. Clarence C. Little in Bar Harbor, Maine. Early on, therefore, I was exposed to cancer research. It was during the summer of 1948, while working in the laboratory of Dr. Norton Nelson at New York University, that it occurred to me to undertake a lung cancer study with patients at Bellevue Hospital in New York City. I was not then familiar with the publications of Dr. Franz Hermann Mueller (2) and Drs. Alton Ochsner, Michael E. DeBakey, and J. Leonard Dixon (3), nor with textbooks on lung cancer diagnosis such as that by Dr. Eli H. Rubin (4), all of which implicated tobacco use as having a role in lung cancer. I had not heard about the science of epidemiology and certainly had never been exposed to the term "case-control studies." I had recently participated in an autopsy of a 42-year-old male patient whose pre-death diagnosis had been uncertain; the post-mortem diagnosis was lung cancer. No history was given in the medical write-up, but I learned from the patient's widow that he had been a 2-pack-a-day cigarette smoker. Thus, impressed by this "mini"-course in epidemiology, I began my study at Bellevue Hospital by devising an interview form and selecting lung cancer patients with confirmed histologic diagnosis as well as controls whose disease was considered to be unrelated to smoking. After examining the first 20 cases, it was clear that the association between cigarette smoking and lung cancer was strong.

On my return to St. Louis in September 1948, my mentor, Dr. Cowdry, arranged an introduction to Dr. Evarts A. Graham, Chairman of the Department of Surgery at Washington University School of Medicine. I requested permission to continue my interviews during my junior year on his service. Dr. Graham was not convinced of the need for such a study. He suggested that if smoking were a cause of lung cancer, it

would occur more often bilaterally, and that he had seen many cases of lung cancer in patients who had quit smoking long before the cancer was diagnosed. He referred me to Dr. Thomas Burford, his senior associate, for further advice. While he smoked, Dr. Burford told me I was wasting my time, because he was certain that smoking was not a cause of lung cancer. To his credit, Dr. Graham, who was a cigarette smoker until 1951, nevertheless permitted me to interview lung cancer patients on his service. The point here is that two distinguished thoracic surgeons were not convinced of my concept or even of the initial results from my first case-control study. During the winter holiday vacation, I visited the American Cancer Society (ACS) in New York City and introduced myself to its medical director, Dr. Charles Cameron, who at that time was also a smoker. His opening statement, even before I had a chance to present my request for support from the ACS, was: "On smoking and lung cancer, my mind is closed." After he saw my preliminary data, he suggested that I return to St. Louis, and together with Dr. Graham request funding from the ACS. Fortunately, this funding came through. These early experiences as a medical student were disconcerting in that even though I was permitted to continue the work, doubt as to its significance was expressed by leaders in medicine. It was particularly difficult for me to understand that the "biologic plausibility" of the data, which was so obvious to me, could not be similarly appreciated by senior members of the medical profession.

During the rest of my junior year, particularly during the summer recess, I crossed the country with an appropriate introduction from Dr. Graham to enable me to interview lung cancer patients from New York to California. While in Los Angeles, I met an established epidemiologist who was to become my lifelong friend—Dr. Lester Breslow, Dean of the School of Public Health at the University of California at Los Angeles. Dr. Breslow sent one of his assistants to accompany me while interviewing patients. The assistant reported back to Dr. Breslow that my interviewing style was such that it was not surprising that I was getting positive results. This created doubt in Dr. Breslow's mind, and he began to repeat our study, only to find similar results (5). Dr. Breslow also seemed initially skeptical about the biologic plausibility of our findings. By February 1949, together with Adele Croninger, we had interviewed some 200 cases and 500 controls. Because we were funded by the ACS, I was invited to Memphis, Tennessee, to attend the 1949 Annual Meeting of the ACS, the subject of which was to be lung cancer. There were no formal speakers but only selected topics, including tobacco. I

introduced myself to Dr. Walter Heston, the Chairman, and I asked him to call on me when the tobacco subject came up. Many scientists with familiar names were in the audience, including Drs. Michael E. DeBakey, Alton Ochsner, Thomas Watson, Evarts A. Graham, and E. Cuyler Hammond. I presented my data which demonstrated a high association between smoking and lung cancer. When Dr. Heston asked for comments on my presentation, not a single statement was made, nor was any question posed. The meeting then went on to the next subject, which was pulmonary adenomatosis in sheep; this topic was vigorously discussed for 30 minutes. During the subsequent coffee break, a physician from Glasgow, Scotland, put his hand on my shoulder and said, "If you had reported on betel nut chewing in India, everyone would have been interested." I was disappointed that I had received no reaction from some of the key lung cancer surgeons and cancer researchers in our country—a disturbing event for me as a medical student. I wondered what closed the eyes of so many scientists to the evidence.

However, my presentation did receive the attention of William L. Laurence, an experienced science writer for the *New York Times*. In an article published on February 27, 1949 (6), Laurence mentioned interviewing Dr. Graham. He then wrote that "no conclusions can be drawn from these studies that cigarette smoking, no matter how heavy, will itself cause cancer of the lung, no matter over how long a period, since 50 per cent of the control patients smoked the same amount over the same period without developing lung cancer." Laurence also stated that Dr. Graham and other researchers stressed that "Cancer of the lung, like all other forms of cancer, . . . springs from a number of causes, most of them at present unknown." Clearly, in February 1949, Dr. Evarts A. Graham did not consider causality. However, his view would change as we completed our study.

## THE 1950s

Early in 1950, Dr. Graham and I submitted our paper on 684 proven cases of lung cancer and their relation to cigarette smoking to the *Journal of the American Medical Association (JAMA)* (7). This paper concluded that "excessive and prolonged use of tobacco, especially cigarets [sic], seems to be an important factor in the induction of bronchiogenic carcinoma" (7, p. 336). Obviously, even we were hesitant to use the word "cause" at that time. The late Dr. Morton Levin, who at this time had also submitted a paper on the same subject to *JAMA*, told the story that the editors were not going to publish his paper, but when our manuscript with a larger sample of cases

appeared, the editors thought that both papers deserved to be published (8). No doubt, having Dr. Evarts A. Graham's distinguished name on the paper was of considerable help; still, the editors of *JAMA* were initially not convinced that data on smoking and lung cancer deserved publication. Nonetheless, our paper appeared as a lead article and received some, albeit not very broad, national attention. However, it appeared to make no lasting impact, even though the importance of our observation was underscored by a similar large case-control study among patients in large hospitals in London which was published in the *British Medical Journal* in September of the same year by Sir Richard Doll and Sir Austin Bradford Hill (9). They concluded that "there is a significant and clear relationship between carcinoma of the lung and smoking" (9, p. 746), and "that cigarette smoking is more closely related to carcinoma of the lung than pipe smoking" (9, p. 747).

If well-established scientists such as Dr. Lester Breslow had some concern as to the reliability of the retrospective studies regarding possible interviewee and selection bias, such doubt must initially also have affected others. It is of historic interest to recall the reaction of Dr. E. Cuyler Hammond, the chief ACS statistician, when he reviewed our data in spring 1950. He could not believe the strength of the correlation between smoking and lung cancer, and assumed that a statistical error had been committed, or that the interviewing had been done in a biased or erroneous manner. Later on, Dr. Hammond, in collaboration with Dr. Daniel Horn, made outstanding contributions to the elucidation of this relation through his large-scale statistical examinations of smoking and death rates and causes (10, 11).

At the time of our early investigations, it troubled me that some colleagues not connected with the tobacco interests failed to acknowledge that our data were consistent with biologic plausibility, and that the data were in line with the observation that the burning of any organic matter creates carcinogens. The cancer-causing potential of burned organic matter has surely been known ever since Sir Percivall Pott's classical observation on scrotal cancer in chimney sweeps in 1775 (12). Other biologically plausible factors were that inhalation irritates the bronchi leading to a cough reflex; that much of the inhaled smoke is retained in the lungs; and that the increase in the rate of lung cancer correlates well with increasing cigarette use (dose response), especially among men who, at that time, smoked significantly more than women. I have always felt that biologic plausibility added a significant dimension to the criteria for causality of the association of smoking and cancer, i.e., its consis-

tency, its strength, its specificity, its temporal relation, and its coherence. These criteria were later well described by the Advisory Committee to the Surgeon General of the US Public Health Service in 1964 (13) and were elegantly expanded by Hill in 1965 (14). When I first used the term "cause" in respect to smoking and lung cancer in 1954, I did so on the basis of epidemiologic variables and evidence for biologic plausibility (15). That it took 4 years for me to use the word "cause" rather than merely the term "association" reflects my own initial difficulty of implying "causation" in spite of the strong evidence in its favor.

In 1953, when Adele Croninger, Evarts A. Graham, and I published the novel results on skin cancer induction by tobacco tar in mice, this research again received some attention, but nothing commensurate with our own perception of the importance of our work (16). Even production of skin cancer in rabbit ears with metastasis to the lymph system, which we induced with cigarette tar, led to no decisive public health action (17). Some critics held that the epithelium of the skin was not fully representative of the epithelium of the lung, and that to establish a causal relation to lung cancer, inhalation studies should be done with animals. Although some investigators undertook such assays, they had to recognize that laboratory animals are obligatory nose breathers and that smoke inhalation as practiced by humans cannot be replicated in a laboratory setting (see review in reference 18). During the 1950s, we reported that smoking was also a significant factor in the etiology of cancer of the mouth, larynx, and esophagus, all areas that came in contact with tobacco (19–21). We observed that among populations such as the Seventh-day Adventists, who did not smoke, tobacco-related cancers were quite rare (22, 23). In 1959 and 1960, my colleague Dr. Dietrich Hoffmann isolated the carcinogen benzo(a)pyrene and other polynuclear aromatic hydrocarbons from tobacco tar, thereby providing further evidence toward the plausibility of cancer induction by tobacco smoke (24, 25). In the mid- to late 1950s, important prospective studies were published by Doll and Hill on physicians in England (26), by Hammond and Horn on ACS volunteers (25), and by Harold Dorn on US veterans (27, 28, cf. also reference 29). Those data fully corroborated the results from the retrospective studies. By that time, the requisite epidemiologic evidence was certainly well established.

In *Ashes to Ashes*, Kluger (1) presents in considerable detail the manner in which tobacco interests during the 1950s influenced the medical and scientific professions. That the industry could attract individuals with an apparently impeccable scientific background such as Drs. Clarence C. Little, Albert Tannenbaum,

and Walter Gardner to chair the Tobacco Research Council, and that they, in turn, appointed other recognized scientists and health professionals to this Council, suggests that as yet some scientists with established credentials could not be won to the concept that the case for smoking as a cause of lung cancer had been made. Renowned statisticians such as Dr. J. Berkson of the Mayo Clinic (30) and Dr. R. A. Fisher of Cambridge University (31–33; cf. also references 34 and 35) presented their doubts based on what are now known to be unacceptable ideas. This added fuel to the notion that full proof for the causal link of cigarette smoking to lung cancer had not been agreed upon. As could be expected, against this background of apparent diversity of opinion, the health professions were not actively involved in the anti-tobacco education, nor in the anti-tobacco movement. Thus, the public at large remained to be convinced. It is noteworthy that Dr. LeRoy Burney, the Surgeon General of the US Public Health Service, having made a first statement on the likely causality of excessive smoking and lung cancer in 1957 (36), in 1959 published a paper in *JAMA* (37) in which he noted that

the Public Health Service believes that the weight of the evidence at present implicates smoking as the principal etiologic factor in the increased incidence of lung cancer and that cigarette smoking particularly is associated with an increased chance of developing lung cancer. (37, pp. 1835–6).

At the time, this statement received little attention from the media, and the US Public Health Service did not give forceful emphasis to the severity of the cancer risk from cigarette smoking until the early 1960s when Surgeon General Dr. Luther Terry called for a reevaluation of Burney's statement in *JAMA* (37)—as stated in the foreword of the 1964 Surgeon General's Report on Smoking and Health (13)—and for the formation of the Advisory Committee that generated the now famous 1964 Report. We can well understand why, in view of the climate of the late 1950s, the public at large and most physicians were still on the sidelines with regard to the smoking and lung cancer issue. In 1959, a number of us got together—Jerome Cornfield, William Haenszel, E. Cuyler Hammond, Abraham Lilienfeld, Michael Shimkin, and I—and we responded to every critical point that had been suggested as casting doubt on the causal effect of smoking on lung cancer. In a paper published in the *Journal of the National Cancer Institute* (38), we concluded that absolutely no doubt existed about the nature of the relation, that all criticisms could be answered, and that cigarette smoking was, in fact, a cause of lung cancer.

## THE 1960s

In the summer of 1961, in a debate published in *The New England Journal of Medicine*, Dr. Clarence C. Little, the Head of the Tobacco Research Council in Boston, and I discussed the lung cancer/smoking issue (39, 40). Accompanying the published debate was an editorial entitled "The Great Debate" (41). This editorial stated:

both authors are dedicated, sincere proponents of their points of view, each upholding what he believes as to the truth, and nothing but the truth, each ready to admit that the whole truth has not yet been revealed to aspiring man.

Clearly, this was not a strong endorsement for the contention that smoking is a cause of lung cancer. The editorial concluded:

each individual must choose his own course, whether wooing the lady nicotine or abjuring the filthy weed, while the search for the truth continues.

The search for the truth, I thought, had long been completed. Apparently, *The New England Journal of Medicine* in June 1961 thought otherwise. Accordingly, it quoted Mark Twain's satirical remark about statistics and lies, "it is generally believed that statistics in the hands of a master can be made to prove almost everything." Our first paper in 1950 (7) actually had not included a single statistical analysis, in part because at that time Washington University did not have a Department of Statistics, and in part because I always believed that "if something looks so clearly significant, it is significant." This is particularly true if the magnitude of the association and the biologic plausibility are both strong.

After our debate, Dr. Little informed me that I was about to get a new director at the Sloan-Kettering Institute of the Memorial Sloan-Kettering Cancer Center, an individual whom he thought was terrific. When I first met Dr. Frank Horsfall a few months later at a cocktail party, he had a drink in one hand and a cigarette in the other, and he told me that he did not believe in my work relative to smoking and lung cancer. In 1962, Dr. Horsfall informed me that 1) my conclusion of a causal relation of smoking with lung cancer was irresponsible, and 2) that all future publications from our group would have to be cleared through his office. He stated that he hated censorship in science; yet, I had left him no choice. When I discussed the matter with some of the senior department heads and advisors at Sloan-Kettering Memorial, the only individual to come to my aid was the venerable and honorable Dr. Peyton Rous, distinguished scientist at Rockefeller University. As a member of the Board of Trustees of Memorial Sloan-Kettering, Dr.

Rous immediately called Dr. Horsfall advising him that he would take the matter of censorship to the Board. Thus, the censorship mandate was rescinded. Clearly, the lines had been drawn, and for each of the subsequent years the budget of the Section of Epidemiology and its associated biologic and bioanalytical laboratories was reduced, so that by 1969 I became firm in my resolve that our future lay elsewhere, and that it was best to take charge of it. Thus, the idea for an independent multidisciplinary chronic disease prevention center was born.

This led to the founding of the American Health Foundation, which turned out to be a better career path for me and my associates in preventive medicine. Let me hasten to emphasize that the episode I described relates to a single individual; it reflects in no way on Memorial Sloan-Kettering Cancer Center, an institution with which I have had a close scientific and personal relationship ever since.

While the case for tobacco use as a cause of certain cancers had gained strength in the 1950s, and was scientifically settled by the end of that decade, it still took medical authorities considerable time to issue reports that had a major impact on the public. The report of the Royal College of Physicians in the United Kingdom (42) preceded the report by the Advisory Committee to Surgeon General of the US Public Health Service (13) by two years. Both reports clearly stated that smoking had been found to be a cause of certain types of cancer, including cancer of the lung. As expected, these publications received much media attention and, for the first time, there was some reduction in cigarette sales (43).

## REFLECTIONS

In reflecting on the health professionals' initial apathy toward the smoking and health issue, it is clear that most physicians consider themselves foremost to be healers of disease. They do not regard themselves as political activists and few of them are experts in behavioral medicine. Surely, the tobacco interests played their own card by influencing the opinions of many. In the early days, the media were reluctant to act against their very best advertisers. The lobbying of the tobacco interests in the United States Congress and the concerns of national and state governments about tobacco taxes kept legislation at bay until the 1980s and early 1990s, when political activists began to coalesce. The legal profession saw an economic opportunity, and political leaders finally had the courage to address the issue, because they recognized a weakened foe.

Perhaps part of the problem early on was that the medical profession as well as science writers have had

generally a critical view of epidemiology. This was borne out in a recent editorial in *The New York Times* (44) on the death of Dr. Oscar Auerbach, a pathologist whose studies on lung cancer greatly exonerated the causal evidence. The editorial stated that "the initial evidence came from the reputedly 'soft' science of epidemiology" and concluded that ". . . such population studies are subject to the criticism that statistical correlation does not prove causality." These remarks reflect the critique of tobacco interests as well as that of Berkson (30) and of Fisher (31–33) in the 1950s. The editorial ignores the reality that properly executed epidemiology that is based on internal and external consistencies, on appropriate strength of association, consistency with time trends, and supported by a sound biologic rationale, *can* in effect establish causation.

Independent of the views just expressed, I recently communicated with Sir Richard Doll, whose initial work in the 1950s made such important contributions to our understanding of the causation of lung cancer. In my letter to him (personal communication, January 8, 1997), I asked Sir Richard to express his views as to why the health professions were relatively unresponsive of this work in the 1950s. In his reply (personal communication, January 13, 1997), he stated:

I think the skeptical reaction of the medical and cancer research scientists was partly because they smoked themselves and partly because they were unaccustomed to the interpretation of epidemiologic data and tended to judge causality by Koch's postulates. Advisors to the government were pathologically scared of causing cancer phobia by undertaking any publicity about cancer, even to the extent of opposing education about the need for early diagnosis. Within government there was anxiety about the effects of reduced sales on tax income and there was certainly a desire to work with the industry rather than against it.

In a subsequent letter to me (personal communication, April 30, 1997), Sir Richard added that in Britain the Medical Research Council had, in his opinion, dealt with the smoking and health issue quite forcefully when it emphasized in 1957 that smoking was responsible for the increase in lung cancer mortality (45). When Doll and Hill (46) published their second paper about their prospective study in 1957, the great majority of British physicians had certainly accepted the opinion of the Medical Research Council. Even though a consensus had developed among scientists and members of the medical community, there was, however, still no great impact on the media and on government in Britain until the 1962 Report of the Royal College of Physicians (42). From the public health point of view, the lesson to be learned is that consensus of opinion among experts is not sufficient to

create action unless such consensus is translated into preventive or control measures, and this requires the experts, government, and the media and educators to act in concert. Scientists and physicians cannot be content with discoveries until their beneficial or protective outcome for the population has been fully realized. This means that the members of the scientific and medical community must become more proactive in public health matters.

None of the foregoing should be construed by the tobacco industry as a defense or as an excuse for not being forthcoming in response to the knowledge and data developed in the 1950s. The evidence that smoking was the major cause of major types of cancer in both men and women, and that it adversely influenced an array of diseases, including myocardial infarction and emphysema, was known during the 1950s, when most of the evidence on cancer accumulated, was established, and confirmed. If the health professions with the support of government forces had taken on this issue forcefully when the first indicting reports were published, the decline in cigarette smoking that we have now finally observed among men in most industrialized countries would have occurred much earlier; the incidence of many of the tobacco-related diseases from which our society suffers today would surely have been reduced. Clearly, the public depends on the knowledge, attitudes, and guidance in health behavior presented to them by the health professionals, either directly, or through the media. It is true that as a whole the health professions in the 1950s did not serve the public well in regard to the hazards of cigarette smoking. The major decline of cigarette smoking we see today may not be so much a result of knowledge that the public holds, but a consequence of social pressure finally being brought to bear by health professionals and by the media to make cigarette smoking an unacceptable habit, at least among certain groups within society.

## EPILOGUE

What are we to learn from this brief reflection on the past relative to the early days of the lung cancer and cigarette smoking issue? In all of us there exists a certain wish bias. For industrialists, and for scientists associated with industry, there is a wish bias related in part to the demands by corporate lawyers; it will always be their wish, if not a sheer necessity, to avoid admitting that their company's products are hazardous. It was the wish bias of the smokers in the 1950s, some 50–60 percent of the male population (47), including many physicians, to conceal the fact that their "enjoyable" cigarette habit may, in fact, be damaging to their health. It is also part of human nature

that few of us want to become actively involved in a controversy, particularly if the opponent is strong. Thus, as we reflect on the 1950s, it is understandable that those who struggled to demonstrate through science that smoking caused human cancer often felt alone. I suppose this is a lesson for many of our young scientists who establish strong evidence of risk but who fight in an unpopular cause or against an influential foe. However, what has always attracted me to science is that when the evidence is strong, it will, in due time, be accepted because scientific truth in the long run always triumphs! Importantly, in public health issues that affect millions of people, scientists have a moral obligation to be involved proactively.

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