The Seventh AACR American Cancer Society Award Lecture on Cancer Epidemiology and Prevention

The Past, Present, and Future of the Prevention of Lung Cancer

Ernst L. Wynder
American Health Foundation, New York, New York 10017

Abstract

The article relates details of the history of research into the causal association of cigarette smoking and lung cancer on the basis of multidisciplinary studies that have explored the epidemiology, biology, chemistry, and biochemistry of tobacco carcinogenesis and research in behavioral sciences and health education that has sought to address one of our nation’s foremost public health problems. Recalling past and present challenges and achievements in all of these areas, the author then outlines his vision for addressing this health problem in the future. This is laid out for various segments of the research community and for society as a whole, i.e., Cancer Centers and hospitals, epidemiologists, laboratory scientists, legislators, educators and behavioral scientists, and the media. It is proposed that for the current policy initiatives in tobacco-related cancer control to succeed, there needs to be a focus on preventing the initiation of tobacco use among children and adolescents. All segments of society can help to achieve this goal. In the nation’s research planning, there needs to be a proper balance between basic and applied research, including research on and application of preventive principles, because cancer need not be an inevitable consequence of aging but is largely preventable.

The Past

History provides a valuable guide to the events of the past and, thus, impacts on the present and on our planning for the future. Succeeding generations can learn from our experience and can thereby avoid actions that were detrimental in our time. History should be reviewed closely, especially by those who produce or disseminate products that may be harmful to the health of people. Also, and even more importantly, those who have the mandate and the authority to protect the health of our people need to heed the lessons of history. This communication highlights one of the more intriguing and as yet unfinished chapters in the history of public health of the twentieth century, which has been the central theme of my career.

As I reflect on my activities in disease prevention, I recognize the contributions of several physicians and scientists who have had a major impact on my endeavors and without whom I might not have succeeded. I was fortunate at the very onset to enter the outstanding Medical School of Washington University in St. Louis. It was there in 1946, during my freshman year, that Dr. Edmund V. Cowdry, Professor of Anatomy, encouraged me to study cancer. In 1948, I introduced me to Dr. Evarts A. Graham, Professor of Surgery, a world-renowned thoracic surgeon, who among many notable achievements had performed the first successful pneumonectomy in 1933 (1). Both Dr. Cowdry and Dr. Graham helped create a highly supportive environment in which I was able to initiate my research activities. This nurturing continued after my residency in internal medicine (1951–1954) at Memorial Hospital and Sloan-Kettering Institute for Cancer Research in New York, when the institute’s president, Dr. C. P. Rhoads, appointed me “Head of Epidemiology” and encouraged me to establish a research program.

In 1951, Dr. John R. Heller, Director of the NCI, introduced me to Jerry Cornfield, who became my mentor in statistics. In 1957, I was joined at the Sloan-Kettering Institute by Dr. Dietrich Hoffmann, a graduate of the Max Plank Institute for Biochemistry in Germany, who has since then made major contributions to our knowledge of tobacco toxicology and environmental carcinogenesis. Later, in the 1970s, I met Dr. Joseph M. Cullen, Associate Director of Cancer Prevention and Control at the NCI, with whom I shared a deep interest in health promotion. Dr. Cullen too has had a major guiding influence on my research in health behavior and on implementation of health behavior changes. I owe much to each of these individuals for their contributions to the development of my career and attainment of research goals. Yet, despite all of the support and encouragement, the progress was not easy, as is to be expected when one deals with particularly challenging issues.

Dr. Cowdry had taught me to “listen to nature” when looking for the cause of disease. To me, this meant examining the circumstances surrounding disease. In the late 1940s, the need for analyzing the relationship of tobacco and lung cancer was “in the air.” Some 35 years had passed since Adler in his monograph on lung cancer had described this as “the rarest of cancers” (2). During the 1930’s and 1940’s, lung cancer was on the rise among men but not among women, suggesting a male gender-connected association (Fig. 1). Lung cancer rates had risen in response to an increase of cigarette smoking, because the habit had become very popular during World War I, and even more so as a result of the development of automated cigarette-making machines. Dr. Fritz Lickint in Germany and Dr. Alton Ochsner in the United States had been among the first to suggest a link of cigarette smoking and lung cancer (3, 4). Also, in 1939, Dr. Hermann Müller in Germany had written a thoughtful epidemiological study of 86 cases and their controls.
In the summer of 1948, prior to my residency, I was studying chemical carcinogens and their effects on mouse skin in the laboratory of Dr. Norton Nelson at New York University. My idea was to compare the responses of three strains of mice to low doses of topically applied benzo(a)pyrene, one of the first known chemical carcinogens isolated from coal tar. I thought that any differences I would observe would be due to genetic factors. However, contemplating what research direction I should follow, I recalled that I had recently participated in an autopsy on a 42-year-old man with a large mass in the lung that was diagnosed as primary lung cancer. Having heard about a possible connection of lung cancer to smoking, I felt compelled to review the chart of this patient, only to find that no history of tobacco use was given. Curious, I contacted the wife of the deceased and learned that he had been a two-pack-a-day cigarette smoker. I wonder what would have happened to my career if this lung cancer patient had been a nonsmoker.

I then proceeded to develop a questionnaire relative to vital data, smoking, and other lifestyle issues. I received permission to interview lung cancer patients and controls without a known tobacco-related disease at Bellevue Hospital (in those days, permission of an Institutional Review Board was not required). Each night I would enter the data I had gathered into flow sheets. At that time, one had to do most entries by hand, and although this was tedious, it gave immediate insight into the data and readily showed trends. After completing my first 20 interviews, a strong link between smoking habits of cases and their lung cancers appeared evident to me. In the winter of 1948, I visited the ACS in New York City, where I was encouraged to submit a grant application together with Dr. Graham. Shortly thereafter, we received our first grant through the good auspices of the Medical Director, Dr. Charles Cameron. Thus, we were able to expand the study of the relationship of environmental factors to lung cancer and my life-long career as a "self-trained" epidemiologist was born. The ACS funding also permitted us to employ a first-rate laboratory worker. She helped us greatly to make our initial contribution to the epidemiology and biology of tobacco-related lung cancer.

Dr. Graham initially doubted that smoking could cause lung cancer. He reasoned that although he had seen many cases of lung cancer, these neoplasms often developed a long time after these patients had quit smoking—and, if tobacco were a cause of lung cancer, he wondered, why didn't we see more bilateral lesions? However, over time, he became more and more convinced of the hypothesis that cigarette smoking was the reason for the many cases of lung cancer we saw, and he became very involved and supportive of this research. He even quit smoking in 1951, but ironically, he died of bilateral lung cancer in 1957. His associate, Dr. Thomas Burford, had tried his best all along to discourage me from undertaking research on smoking as a cause of lung cancer. Dr. Burford argued that he had seen many cases of lung cancer among nonsmokers. Nonetheless, I had Dr. Graham's permission to interview lung cancer patients on his service. In 1949, I presented data on 200 cases of lung cancer and their controls, reporting a high degree of association of cases with cigarette smoking at an ACS meeting in Memphis, TN. My excitement was buoyed by the fact that many distinguished thoracic surgeons, physicians, and scientists were in the audience; yet, to my amazement, no questions were asked so that there was no discussion following my presentation. In striking contrast, a paper on pulmonary adenomatosis in sheep merited half an hour of discussion by the same audience. Needless to say, I was very discouraged.

In May of 1950, our findings were published as a lead article in the Journal of the American Medical Association describing 684 lung cancer cases and their controls and reporting a high association between smoking and lung cancer (Fig. 2; Ref. 6). This association was soon confirmed by a similar large-scale study in the United Kingdom, which was reported by Richard Doll and Austin Bradford Hill in September of 1950 in the British Medical Journal (7). Our paper did not contain any statistical evaluations and yet, I strongly felt that our data looked undeniably and convincingly significant and that they...
were biologically plausible. However, my convictions found no lasting echo in the public health arena, nor within the medical establishment at large, nor in the media.

In 1953, we reported on the production of skin cancer in mice painted with tobacco tar solutions; a similar study on the ears of rabbits followed in 1957 (Refs. 8 and 9; Fig. 3). The tobacco industry claimed that skin epithelium was not lung epithelium and challenged us to induce lung cancer in laboratory animals. We knew that this was hardly possible because laboratory animals are obligatory nose breathers, equipped with intricate defense mechanisms that would capture most of the smoke aerosol particles before these could enter the lung (10). Moreover, unlike humans, laboratory animals do not make an effort to inhale smoke deeply into their lungs; in fact, their breathing becomes rather shallow when they are placed into atmospheres that are contaminated with smoke aerosols. As is so often the case at the crossroads of research decisions, in this situation one needed to know what not to do. Pursuing another aspect of the laboratory evidence, Dietrich Hoffmann established classical proof for the presence in smoke of the chemical carcinogen benzo(a)pyrene by isolating and crystallizing the compound in addition to documenting its spectral characteristics as being identical with those of the authentic reference compound (11). Now, we had epidemiological evidence as well as biological and chemical criteria for the carcinogenicity of tobacco smoke.

In the late 1950s, several prospective studies, notably those by Sir Richard Doll and Sir Austin Bradford Hill on British physicians, by Dr. E. Cuyler Hammond and Dr. Daniel Horn on American Cancer Society volunteers, and by Dr. Harold Dorn on U.S. veterans, confirmed and substantiated the correlation of smoking and lung cancer (12–14). The impact on society’s smoking habits and public health reaction in the United States and in Great Britain was still very limited.

During the 1950s, we also reported on the relationship of tobacco use to other cancers, notably cancer of the mouth, larynx, and esophagus (15–17). Amid all of the sad realities, I remember an incident relating to my work that typically sounds like a clinical anecdote. It seemed amusing then and even now. I had occasion to interview a male patient with a triple primary cancer of the mouth, larynx, and esophagus. In answer to the standard question: “How many drinks of whiskey do you drink per day?”, he replied, “seven.” For some reason, I queried, “Is that all?”; to which he replied, “No, I also drink at night.” This taught me how careful one has to be in phrasing one’s questions.

In 1954, based on Koch’s postulates on causality in the etiology of infectious diseases, I developed criteria for causality in cancer etiology and referred to cigarette smoking for the first time as a “cause” of lung cancer (18). Meanwhile, the impact of smoking on lung cancer rates in men continued to increase, and cigarette smoking became more common among women in our country. Well-recognized statisticians such as Dr. Joseph J. Berkson from the Mayo Clinic and Dr. R. A. Fischer from Cambridge threw doubts on the data presented and were consequently cited by the tobacco interests (19, 20). Fisher had suggested a “constitutional” factor regulated by some gene that both made a person smoke and gave him or her lung cancer at the same time. Although there is some evidence that a specific set of genes may increase one’s susceptibility for lung cancer (21–23), Fisher’s “vision” that the same gene also caused one’s dependence on nicotine is certainly not even believed today. I suggested at that time, that if a person had stopped smoking and his risk of lung cancer had declined, the gene had to have lost its effect as well. Furthermore, we had recently shown that Seventh Day Adventists, whose church teachings prohibited tobacco smoking, had in fact extremely low rates of lung cancer. Did this mean that the gene responsible for cancer susceptibility also prevented one from joining the Seventh Day Adventists’ Church (24)?

In 1961, I was asked to debate Dr. Clarence Cook Little before the Massachusetts Medical Society. Dr. Little had formerly been the Director of the Jackson Memorial Laboratory in Bar Harbor, ME, where I had studied genetics during the summer, after completing my freshman year in medical school. What was unusual about the debate was not that Dr. Little, now the Director of the Tobacco Research Council, attempted to throw doubt on the extensive epidemiological evidence and supportive laboratory studies, but that the New England Journal of Medicine in an editorial entitled “The Great Debate” gave approximately equal weight to both of our presentations, as reflected in the following citations: (a) “. . . 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”; and (b) “. . . each individual must
choose his own course, whether wooing the lady nicotine or
abjuring the filthy weed, while the search for the truth con-
tinues" (25-27). Clearly, the distinguished New England Journal
of Medicine did not endorse smoking as a cause of lung cancer.
Only 1 year later, the Royal College of Physicians in England
labeled cigarette smoke "a cause of lung cancer," and 2 years
thereafter, the U. S. Surgeon General's Report on Smoking and
Health followed suit (28, 29). It is noteworthy that the Amer-
ican report contained a succinct chapter on "criteria of judg-
ment (of causality)". On the basis of these criteria of judgment,
Sir Austin Bradford Hill elegantly detailed his version of such
principles, stating that, along with the other criteria, biological
plausibility has a pivotal role in assigning any causative infer-
ence (30). As an aside, it is of interest to observe that nowadays,
some investigators routinely talk about causation when dealing
with rather small odds ratios, without reflecting on the full
spectrum of the criteria of judgment that should be considered
by all of us before using the term "cause" as a factor. Clearly,
in the relationship between smoking and lung cancer, the cri-
teria have been met for a long time, and yet, even the Surgeon
General's Report of 1964, which received considerable initial
publicity, had a relatively small effect on smoking habits in the
United States.

At the Sloan-Kettering Institute for Cancer Research
where we conducted epidemiological and experimental re-
search primarily with support from the NCI and the American
Cancer Society, there had been a change in the directorate,
following the untimely death of Dr. Rhoads in 1961. The new
Director, Dr. Frank L. Horsfall, an eminent virologist, strongly
believed that the evidence on smoking as a cause of lung cancer
was far from being established. This prompted me to first begin
dreaming of, and then actively planning, the creation of an
institute that would not only focus on the issue of smoking and
health, but, in a broader sense, on cancer prevention and con-
trol. By the end of 1969, I was able to formally establish the
AHF. Let me add that, especially during the past two decades,
I have sustained a highly productive association with the Mem-
orial Sloan-Kettering Cancer Center, where we are involved
in several joint investigations. My plans for the AHF would not
have been realized without the devotion to preventive principles
and the generous support of William Levitt, Eleanor Naylor
Dana, and the Charles Dana Foundation, and David Mahoney,
to all of whom I am forever grateful.

It was fortunate that the AHF was in place 2 years before
the passage of the National Cancer Act, and that our efforts
were very much encouraged by the successive NCI Directors,
Dr. Carl Baker, and Dr. Frank J. Rauscher. Today, the AHF is
an NCI-designated Cancer Center with a staff of 180, engaged
in interdisciplinary research linking epidemiology, laboratory
studies, health behavior, and health education. As such we are
committed to research on the etiology, prevention, and control
of human cancer. From the very onset, it seemed evident that
research activities dealing with tobacco and tobacco smoke, as
well as nutritional carcinogenesis, would function optimally if
undertaken by an interdisciplinary research unit. Fig. 4 outlines
the constituency of such a unit; its advantage is that each of the
main components, epidemiology, laboratory studies, and health
promotion, together with their individual subspecialties, opera-
tes synergistically, thus providing a truly comprehensive an-
alytical approach to research challenges and pointing to solu-
tions toward cancer control (31). Cancer, as a disease that is
caused and also prevented by an array of multiple factors, will
be most constructively addressed through the establishment of
such integrated research units.

Clearly, when one deals with cancer risk that is attributed
to a personal habit such as tobacco use, cancer prevention will
face many obstacles. These come in the form of self-denial of
individuals and an illusory sense of immortality harbored by so
many of us (32), complemented by the medical profession's
primary interest in curing disease, and conflicting with the
enormous financial influence that tobacco interests have on the
national and state governments and also on the media. Among
the media, the Reader's Digest deserves commendation in that
early on they refused to accept tobacco advertisements and
engaged in educating the public about the health hazards of
smoking (33). Although one can understand the hesitancy of

\begin{figure}[h!]
\centering
\includegraphics[width=\textwidth]{tumor_induction.png}
\caption{Tumor induction by type of lesion in CAF\textsubscript{1} mice. Based upon data from Wynder \textit{et al.} (8).}
\end{figure}
those involved with the tobacco industry because of economic concerns. I have never understood the relative apathy with which the health professions and the health establishments have met the issue of smoking and disease. As physicians, we are, of course, primarily trained to diagnose and treat ongoing disease, and indeed, healing people appears to be most gratifying and rewarding. But, the fact remains that we should also have been in the forefront of educating the public and seeking legislative support at both the state and federal level. If this had been actively pursued, we would have reduced tobacco use by both adults and youths far more significantly than we have done during the past half-century. Many productive lives could have been prolonged, and the ever-escalating health care costs could have been held down. Here, we have come to witness once again what so many prominent scientists throughout history have expressed, i.e., that the discovery of an idea is often easier than its application. When the application of preventive principles affects "commercial intercourse," as John Snow so aptly stated during the last century, "it certainly meets many obstacles." (34).

In the 1960s, the ongoing investigations in epidemiology and in experimental tobacco carcinogenesis and the knowledge of a dose-response effect in the relationship of smoking and disease led to the question whether modifications in the make-up and composition of cigarettes would lead to selective reduction of harmful agents in the smoke and thus offer those who were unable to give up the habit an alternative that carried a lower risk. Thus, Dietrich Hoffmann and I undertook a review of the organoleptic properties of tobacco, manufacturing technology of cigarettes, chemical analytical issues, and the biology of tobacco and tobacco smoke carcinogenesis, which was published in 1967 (35). Although the concept of diminished exposure and reduced risk appeared logical, we had yet to learn that the complexity of tobacco smoke as a matrix with multiple biological activities, and above all, pharmacological activity, would get in the way of a successful approach. Cigarettes with lower smoke yields did become a reality and would determine a change, yet bring no solution to the tobacco and disease dilemma.

During the 1970s and 1980s, research scientists continued epidemiological studies primarily to determine whether smoking low-yield cigarettes carried a different risk for lung cancer than smoking cigarettes with higher yields of tar and nicotine. In fact, during these years, a number of cohort and case control studies have reported a 20–50% reduction in lung cancer risk for long-term smokers of filter cigarettes (36–41). From the perspective of the 1990s, we now fail to understand why that reduction in lung cancer incidence occurred and then vanished in the ensuing years, as I will discuss later.

Dr. Dietrich Hoffmann and his associate, Dr. Stephen Hecht, have over many years conducted research that was focused on identifying various toxins and carcinogens in tobacco and tobacco smoke and elucidating their mode of action with a view toward modulating them (42–44). Their work has added considerable knowledge to our understanding of structure/activity relationships in chemical carcinogenesis, metabolic activation and/or detoxification, and interaction of carcinogen metabolites with cellular macromolecules. The discovery of tobacco-specific N-nitrosamines as a new class of chemical carcinogens (including the major organ-specific carcinogens N-nitrosornicotine and NNK) has also led to widely used model assays in laboratory animals that allow the determination of the potential and efficacy of chemopreventive agents (43, 44).

Yet, cancer control through chemoprevention requires tedious laboratory studies and lengthy clinical trials. These efforts need to be paralleled by health promotion and health education activities. Our Know Your Body program, which focuses on comprehensive, school-based health education, is one such targeted effort. We were able to demonstrate that such a program can impact the onset of smoking among youths, provided that the program began early, was intense, and of high quality (45, 46). In a Know Your Body study with Dr. Heather Walter in the late 1980s, we have shown that over a 5-year period, the onset of smoking could be significantly delayed in both boys and girls, provided that the program was initiated by age 9 or 10 and the anti-smoking messages were strongly delivered and were a component of an overall comprehensive school health education activity (Ref. 47; Fig. 5). Absence of smoking was verified by determining cotinine, a major metabolite of nicotine, in the saliva. Through these interventions, we became particularly interested in the preteen age group as a focal point of health education efforts.

Politically, progress against tobacco use was made in that Congress passed the Federal Cigarette Labeling and Advertising Act in 1965, requiring warning labels on cigarette packages (Public Law 88-91). Still, labels on United States cigarette packs are relatively unobtrusive by comparison to those on

---

**Fig. 4.** Tobacco-related prevention research and application at Cancer Centers and community-related activities.
tobacco products in other countries. The implementation of the Tobacco Control legislation has contributed much to reducing cigarette use among current smokers. Later, in the mid-1980s, doubling of the federal excise tax on tobacco contributed at least temporarily to a decline in per capita cigarette consumption. During this time, although fewer men smoked, cigarette use among women continued to increase (48–50).

The Present

Today, cigarette consumption in the United States is significantly declining, especially among men. As our data show, this decline is highly prevalent among the more educated segments of our population and particularly so among those in the health professions (49–50, Fig. 6). Regrettably, we are observing that lung cancer is becoming a disease of the less educated (51). It is most disheartening that among young people, cigarette consumption in recent years has increased alarmingly, as the latest survey by the Center for Disease Control is revealing (52). Here too, the less educated smoke more. Among school drop-outs, smoking rates are as high as 42% (53). An exception to the increased cigarette smoking rates in youths had been seen for a while among African-American youngsters (54), but, according to the latest Centers for Disease Control survey, it is apparently now eroding (49, 52).

Over the past few decades, we have very much advanced our knowledge about tobacco toxicology and tobacco carcinogenesis and about epidemiological and health promotion methodology in this area. Tobacco, because of its interrelationship with other lifestyle variables, has provided us with the knowledge that many exogenous and endogenous factors interact. Studies with tobacco and tobacco smoke, a leading exogenous factor for cancer, have been highly informative about the action and interaction of tumor initiators, tumor promoters, cocarcinogens, and their interaction with specific cellular components (summarized in Refs. 43 and 44). Because tobacco usage is widely spread throughout many societal strata and many nations, we have gained new insight into human risk-taking behavior, which has helped us develop new initiatives in health promotion. Researchers in tobacco-related sciences, therefore, can have a very far-reaching impact on cancer etiology and prevention.

As we are investigating the value of chemoprevention, the prospective study by Dr. Larry Clark’s group suggests 50% reduction of lung cancer among men who have received daily supplements of 200 μg of selenium for 8 years (55). Laboratory assays with major tobacco carcinogens in well-defined animal models have confirmed the crucial role of dietary supplements in altering the course of carcinogenesis. A major research goal in our laboratories is the development of new, highly efficacious organoselenium compounds that inhibit carcinogenesis but have lower toxicity than the historical selenium compounds, such as sodium selenite and selenomethionine. The results of a series of experiments conducted by Dr. Karam El-Bayoumy’s group in our institute clearly show that the organoselenium compound 1,4-phenylene-bis(methylene)selenocyanate significantly reduces the multiplicity of NNK-induced lung tumors in A/J mice when given during the initiation phase and even when given after initiation (56). It has also been demonstrated that 1,4-phenylene-bis(methylene)selenocyanate is an effective inhibitor of lung tumors induced by a mixture of two key carcinogens in tobacco smoke, i.e., benzo(a)pyrene and the tobacco-specific nitrosamine NNK.4

We are planning to combine chemical chemoprevention with a low-fat diet to determine whether these two variables act synergistically in the inhibition of lung tumor development, as has already been shown by Dr. Bandaru Reddy in a colon cancer model (57). We have stressed for some time that nutritional factors play a vital role in carcinogenesis, including tobacco carcinogenesis (44). Such factors include total caloric intake as well as the intake of specific fatty acids, and of certain micronutrients, especially those with antioxidant effects. Nutrition will not only affect the initiation of many cancers but also play a role in the modulation of cancer promotion and progression. In fact, in experimental tobacco carcinogenesis, Hoffmann et al. (58) have shown that a high dosage of corn oil can accelerate development of NNK-induced pulmonary tumors in rats. Therefore, nutrition-related cancer research demands far greater attention by the cancer research community.

Although studies in the 1970s had shown a decline in lung cancer rates for long-term filter cigarette smokers compared with smokers of nonfilter cigarettes (36–41), in epidemiology, we no longer see significant differences in lung cancer risk among smokers of low-yield cigarettes (<1.2 mg of nicotine yield in the smoke) in comparison to the risk of smokers of high-yield cigarettes (>1.2 mg of nicotine in the smoke) that were available in the 1970s (59–61). Until the mid-1970s, the best-selling filter cigarettes yielded 1.3–1.7 mg of nicotine in the smoke when smoked according to machine-smoking standard conditions for smoke analysis (62, 63). Then nicotine yields began to decline to an average of 0.9 mg/cigarette. Recent research has ascertained that it is nicotine that governs the intensity with which a smoker draws puffs and inhales the smoke (64, 65). Consequently, smokers of cigarettes with low smoke yields of nicotine draw puffs in a manner that exposes them to proportionally larger amounts of the toxins, carcinogens, cocarcinogens, and promoters in smoke than one would expect on the basis of analytical data that are established with fixed machine smoking parameters. They are also known to inhale the smoke more deeply into the lung (66).

We are now observing a significant rise in the incidence of AdC so that the ratio of AdC to SCC of the lung is changing in both men and women, but particularly in men (Refs. 44 and 59–61; Fig. 7). In our 1950 study, the AdC:SCC ratio in the lung in men was 0.059:1 (6). Today, this ratio is 1.43:1; obviously a significant finding that demands explanation. This change is likely due to changes in cigarette composition, which

---

4 AHF, unpublished data.
These findings in the Mediterranean region of Europe must be related to more intense puff drawing and larger puff volumes drawn by the smokers of contemporary low-yield cigarettes that is governed by the smokers’ addiction to a certain level of nicotine. This manner of smoking permits the smoke carcinogens to enter the deeper portions of the lung that are less resistant to their insult than the major bronchi with their protective layer of ciliated columnar epithelium (44, 59-61). In our case control studies, Steven Stellman et al. (60) have shown that smoking filter-tipped cigarettes seems to have some positive impact on reducing the incidence rates of SCC but no impact on the development of AdC of the lung. Epithelial cells are first affected by cilia-toxic smoke constituents and undergo transformation to metaplasia and then neoplasia (59). In both men and women, but particularly in women, AdC has always been relatively more common than SCC and particularly small cell cancer of the lung in nonsmokers than in smokers (59-61). We have therefore reasoned that with AdC of the lung, there has to be an additional risk factor in women that is probably endogenous and likely hormonal in nature (44, 61).

Examining current rates of lung cancer among different population groups, an exercise that has always been of interest to us, crystallizes four epidemiological leads that we are pursuing:

(a) African-American males have a higher rate of lung cancer than white males, although the former smoke fewer cigarettes (66, 67). We suggest that this may relate to some genetic differences and/or a high intake of dietary fats among African-Americans (68). A role of certain fatty acids in tobacco carcinogenesis, and for that matter, in chemical carcinogenesis in general, is also indicated by the observation of accelerated pancreatic tumor development in rats given tobacco-specific nitrosamine NNK (58). The role of dietary fats is also evident in humans, for example in Greece, Spain, and southern Italy, where in spite of a very high tobacco consumption among males, the lung cancer rates in these populations are markedly lower than those in northern Europe or in the United States. (69) These findings in the Mediterranean region of Europe must be seen in light of the high intake of olive oil, and concurrently, the high intake of fresh fruits and vegetables in these areas. Studies in our laboratory have demonstrated that oleic acid, which is a major fatty acid component of olive oil, and omega-3 fatty acids, found in fish, have quite a different impact on biochemical parameters relating to tumorigenesis than omega-6 fatty acids stemming from animal fats (70).

(b) Cigarette-smoking women appear to have a higher risk of lung cancer than male smokers, given similar amounts of tar exposure as shown by Dr. Edith Zang and confirmed by Dr. Harvey Risch (61, 71). We speculate that the difference may be due to an effect of estrogens (61). It is perhaps not coincidental that, just like premenopausal breast cancer in women, AdC of the lung in women is more common in those with lower body weight after the data have been adjusted for cigarette smoking (72).

(c) Japanese men, although smoking significantly more cigarettes than American men for several decades, have a lower risk of lung cancer (73). Factors that may singly or collectively be responsible for this include that Japanese males begin to smoke later, and they leave a longer unsmoked cigarette butt. During the past two decades, up to 75% of the cigarettes sold in Japan have charcoal filter tips; in the United States, charcoal filter cigarettes make up only 1% of total cigarette sales. Charcoal filter tips reduce the levels of several volatile and cilia-toxic agents in the smoke (35). Japanese cigarettes have a lower smoke yield of carcinogens like NNK, and the traditional Japanese diet is low in fat and includes protective fish oils. These factors are currently being studied in a collaborative effort with colleagues in Nagoya.

(d) It is of special interest that small cell lung cancers are twice as common in men in the United States than in Japanese men. The basis for this finding needs to be explored.3 In this Figure 6. Change in current smoking rate by education level and sex, 1969–1996.
regard, we need to consider that the tar and nicotine yields published by the Federal Trade Commission for contemporary cigarettes are based on standardized machine-smoking methods and are obtained by taking one 35-ml puff of 2-s duration once per minute (63). However, Dr. Mirjana Djordjevic and Dr. Dietrich Hoffmann have found that smokers of today's low-yield cigarettes take on average two puffs of 48-ml volume each, twice a minute, so that total tar and nicotine intake from such products is quite similar to what it was years ago when both tar and nicotine levels in the smoke were considerably higher (64, 65, 74). In respect to the importance of depth of inhalation, we know that primary cigar smokers generally do not inhale the smoke deeply because of its alkaline character and they have a significantly lower rate of lung cancer compared with cigarette smokers (75, 76). As was already mentioned, the increased rate of AdC among cigarette smokers in recent years could in part be due to an increase in carcinogenic nitrosamines in the low-yield cigarette but may also be attributed to deeper smoke inhalation (44, 59–61). The phenomenon of different smoke inhalation patterns may well explain why the decline in the rate of lung cancer among men in the United States has not been as pronounced as had been expected on the basis of the large number of men who have given up smoking. When these data were presented in a workshop arranged by the ACS and AHF in 1997, we could find but few investigators with expertise and interest in the subject, which clearly had broad academic and public health implication (77).

Importantly, the findings from the American Cancer Society's CPS-1 and CPS-2 studies, reported by Dr. Michael Thun and Dr. C. W. Heath, show that both smokers and nonsmokers in the 1980s had a lower risk of heart attack than those in the 1960s (Refs. 78 and 79; Fig. 8). This reduction in coronary deaths can be due to several factors: the lower intake of saturated fats; the increased use of unsaturated fats; better treatment of hypertension as well as heart attacks themselves; and the fact that the number of coronary bypasses and angioplasties have significantly increased over recent years. Whether the cigarettes with lower smoke yields of nicotine played some independent role here remains to be determined. On the other hand, the risk for lung cancer increased in the 1980s for smokers, whereas it remained stable among nonsmokers (Ref. 80; Fig. 8). This appears to suggest that environmental factors may have become more prevalent.

We also need to consider a major difference between effects of smoking cessation on coronary artery disease versus those on lung cancer. Although there is a reduction in risk of coronary artery disease within the first year, lung cancer risk may even increase in the first 4 years before it finally slowly declines, though never reaching the low level of risk seen in never-smokers (49, 81). On the basis of our assessment of the current state of lung cancer and smoking in the United States, we need to ask what to do next. After all, (a) lung cancer continues to remain the leading cause of death in both men and women; (b) for the adult population at large, we have reached a level of approximately 25–27% smokers, and it appears that these individuals are largely nicotine-dependent and therefore have great difficulty to quit smoking; and (c) so many young people take up cigarette smoking today, and in recent years, we have made virtually no progress in dissuading tobacco use (53, 54). We also need to be concerned that many countries, and especially developing nations, face as yet escalating tobacco-related cancer morbidity and mortality.

Fig. 7. Relative increase of AdC over SCC by sex, 1950–1998.

The Future
What then, should be our approach to future research and interventions? I would like to summarize my suggestions as a "take home" message for those involved in and concerned with tobacco-health issues.

Cancer Centers and Hospitals
Interdisciplinary tobacco research units could certainly have greater impact on all aspects of tobacco-related cancers in a more efficient and coherent manner than investigators working independently. Such units combine expertise in epidemiology,
Tobacco use, established as one of the main causes of cancer, will lead to more successful intervention methods in the future. Modern technology has given us ever-increasing opportunity to identify genes and mechanisms underlying tumor promotion by omega-6 fatty acids and tumor inhibition by omega-3 fatty acids (70).

On the molecular level, more studies need to detail the interaction of tobacco carcinogens with various genes. Genetic susceptibility to tobacco carcinogens obviously varies for different smokers, and this research offers both academic challenges and opportunities for prevention. Modern technology has given us ever-increasing opportunity to identify genes and gene products that define individuals or populations with an increased susceptibility toward developing lung cancer or nicotine addiction (21–23). How to use such knowledge in finding a specific treatment modality toward diminishing cancer risk in such cases is a primary challenge for the future.

For the Legislators
We need to help design and support appropriate legislative efforts toward reducing tobacco-related morbidity and mortality. Legislation on the local and national levels over the past two or three decades has perhaps contributed more to smoking cessation among adults than any specific educational effort, in part, because it increasingly made smoking a socially undesirable habit. Although this message has been heard and needed, particularly among the more educated segment of our population, the resurgence of cigar smoking in these social strata of

For Epidemiologists
The chronology of cancer rates in the United States shows the rarity of lung cancer, yet the high frequency of stomach cancer in the 1930s and how dramatically these rates have changed since then. The unplanned triumph of the decline of stomach cancer teaches us that most cancers are not the inevitable consequence of aging (82). The continuing high mortality of lung cancer in both men and women (Fig. 8) and the high prevalence of smoking among our young people clearly represent challenges we will need to address with increasing resolve. What we will accomplish in respect to the prevention of smoking will have the most notable effect on all tobacco-related cancers. Examining the changing histopathology of lung cancer deserves our particular scrutiny. Small cell lung cancer, for example, almost never occurs in nonsmokers, and the increasing prevalence of AdCs, which arise largely in the peripheral portion of the lung, may make chest X-rays as a screening technique more effective than they are with neoplasms in the upper part of the lung. This too needs to be explored. Future research should also focus on the possible benefit of high intake of fruits and vegetables and specifically of certain antioxidants; also, we need to investigate epidemiologically what risks may be associated with the consumption of various different fatty acids. As epidemiologists, we should be mindful of Dr. Cowdry’s message that states “listen to nature.” We need to be aware that in tobacco carcinogenesis we deal with metabolic overload, just as in the case of alcohol abuse and cirrhosis of the liver, and excessive estrogen production and breast cancer; nature has not equipped us with defenses that can handle such metabolic overload.

Beyond following the current epidemiological leads that provide clues about the metabolic and molecular mechanisms and beyond studying such covariables as specific fatty acids and estrogens, we need foremost to focus on the prevention of onset and on the cessation of smoking. Ideally, epidemiological investigations of ongoing patterns of smoking and other tobacco use will lead to more successful intervention methods in the future. Epidemiology and marker techniques can also play a key role in identifying persons who may be at elevated risk for tobacco-related cancer due to genetic predisposition.

For the Laboratory Scientists
Tobacco use, established as one of the main causes of cancer deaths in humans, continues to challenge laboratory scientists in respect to elucidating the nature of established human carcinogens, their metabolic pathways leading to activation and/or detoxification, and their interaction with each other and with cellular macromolecules. These processes also serve to measure the success or failure of natural or synthetic chemopreventive agents, distinct nutritional regimens, and other interventions. There is ample opportunity for research on macro- and micronutrients that might be protective, especially antioxidants. Another area of research needs is the investigation of endogenous factors that modulate tobacco carcinogenesis, such as estrogens. Because estrogen status is strongly linked to intake of certain fatty acids, we need to further elucidate the phenomena and mechanisms underlying tumor promotion by omega-6 fatty acids and tumor inhibition by omega-3 fatty acids (70).

For the Legislators
We need to help design and support appropriate legislative efforts toward reducing tobacco-related morbidity and mortality. Legislation on the local and national levels over the past two or three decades has perhaps contributed more to smoking cessation among adults than any specific educational effort, in part, because it increasingly made smoking a socially undesirable habit. Although this message has been heard and needed, particularly among the more educated segment of our population, the resurgence of cigar smoking in these social strata of
society (76) indicates the need for further educational and legislative effort toward countering this trend. In line with the McCain bill (S-1415) that is about to be introduced, the ACS focuses on increasing excise tax and bringing tobacco under regulatory control of the Food and Drug Administration, primarily to ensure bringing down smoking rates among children. This involves, of course, active participation by all of us.

Relative to the Food and Drug Administration’s role in controlling the composition of cigarettes, we urge that the agency, together with various institutes at the NIH and private research centers, become involved in biochemical, biological, and epidemiological monitoring of the relative toxicity and carcinogenicity of the smoke of all commercial cigarettes. Specifically, it needs to be ascertained that levels of tobacco smoke carcinogens and/or toxic agents are not increasing when cigarettes are being reformulated or modified in any way. Obviously, there is no “safe” cigarette, but as the ACS also emphasized, at the very least, we must make certain that cigarettes do not become even more hazardous. Without oversight, it is quite possible that some cigarettes may prove to be more carcinogenic and toxic than others because of their makeup and/or because of the manner in which their smoke is inhaled. Such monitoring needs to be demanded by our public health authorities.

Special attention should be given to the tar and nicotine ratio in the smoke, which governs the depth of smoke inhalation. Cigarette filters might yet be improved to remove specific toxic components, particularly those occurring in the volatile fraction of the smoke. Although the low-yield filter-tipped cigarettes have clearly been of no benefit in reducing the overall toxicity of the smoke, which governs the depth of smoke inhalation, they appear to have diminished the risk for cancer of the oral cavity, largely because they prevent direct contact of oral surfaces with tobacco juices. Also, smoke particles from low-yield cigarettes tend to be inhaled more deeply into the lung rather than being deposited in the upper airways so that the larynx, for example, is less affected.

For Educators and Behavioral Scientists

In 1994, an estimated 48 million adults (25 million men and 22.7 million women) were current smokers in our nation (83). Of course, there are even more millions of adult and teenage smokers worldwide, thus, it is imperative that we address smoking cessation. We have as yet much to learn about better ways of helping heavily addicted smokers to quit (84). The NCI has recommended a five-step program of intervention for all smokers that encourages these tobacco users to ask for help and compels health professionals to advise, assist, and arrange for smoking cessation (85).

Of far-ranging importance are our efforts to curtail the adoption of smoking and other tobacco habits among our young people. This will not happen by what we say but by what we do. Whatever funds come from tobacco settlements, as well as from existing NIH and Centers for Disease Control budgets, monies must be set aside to deal with the prevention of onset of tobacco habits among our youths. The onset of smoking relates to three major influences: parents, schools, and media, who need to act in unison to have an optimal impact on dissuading smoking among children and teens. Although we still need to learn more about the factors that make some children more prone to take up smoking than others, parents need to know that their own smoking contributes toward their children’s decision to take up the cigarette habit. Schools need to realize that health education, like any other education, flourishes when given at the right dose, intensity, and duration. For this reason, we urge that health education should begin at least in kindergarten and ideally in pre-school activities. Our Know Your Body program is one model of such targeted education with age-appropriate instruction and activities from kindergarten through all of the grades (45–47). The program needs to be comprehensive in that all risk factors are known to constellate; thus, if we affect smoking, we also affect drug abuse and teenage pregnancy; by improving self-esteem through health knowledge and health consciousness, we help our children’s emotional well-being, and we may well prevent violence. Ideally, a motivated health education specialist is put in place as a coordinator in each teaching environment. Such health education personnel should be trained with the support of the United States Department of Education.

School health education efforts should be evaluated each year through an appropriate health survey and testing for health knowledge. The school health movement should be, not just that it raises the children’s self-esteem and their expectation for a productive future. Offering afternoon activities, perhaps with input from parents and community groups, will enable children to interrelate with adults, participate in extracurricular activities such as music, arts, chess-playing, and health- and fitness-related subjects (Fig. 9).

It will be a fundamental challenge to our society; yet, we must work toward universal school education with a strong element of health education, beginning at the age of 3 or 4 and continuing through all 12 grades. Such stimulating environment will help students involve themselves more deeply in learning and should lead them to become more productive members of society. Like language, behaviors may well be genetically “imprinted” early in life and, as certain portions of the brain are particularly sensitive to language, so are others to behavioral messages via synapses that are especially susceptible to be stimulated in the first few years of life. Health behaviorists should pursue studying this matter both in the laboratory and in the practical setting of life itself. Implementing such programs need to be a mandate for all members of society, not just those concerned with the prevention of tobacco-related illness.

The current status surrounding the “tobacco legislation” requires resolution by the executive and legislative branches of our government in collaboration with the public health community and with the tobacco interests. It is opportune for those of us in public health to strive for reduction of tobacco use among our population and especially among our youths. Appropriate legislation can go far to address this matter; however, with the ongoing debate, we sense that the politics and the economics of the issue may lead to a pragmatic solution that will please none of the participants.

Clearly, the need to reduce smoking among our young people is a most definitive one, and it appears to have the consensus of all parties at this time. I suggest that although the finishing touches are being placed on legislative efforts with regard to the level of excise tax, the Food and Drug Administration authority over tobacco as a nicotine delivery system, and the overall cost of “the settlement”—which may yet require many months and will probably be delayed along the way because of constitutional and other issues that may be raised—we may well set aside a “starter fund.” This should be applied toward congressional launching of a behavioral intervention involving parents, schools, and the media to socially immunize children against tobacco use. If successful, such a program would actually concomitantly reduce other risk-taking by children and could therefore be joined by groups that are concerned with specific behaviors that put children at risk for...
disease and disability. The vision for such a program is outlined in Fig. 9.

Once finalized, the proposed legislation in the 105th Congress (introduced by Senator McCain as S-1415 and probably as yet being shaped by many amendments) will obviously have some impact. This needs the full support of the public health community to establish behavioral strategies that reach into every home, every school, and every sector of the media (85).

One needs to attract the best behavioral scientists to lead in the effort to make parents responsible for their children’s health habits by leading example, to encourage the teaching of good health habits schools beginning at the kindergarten level under the leadership of trained health educators. The media could lend much support by broadcasting health-promoting children’s programs or at least thoughtful public service announcements and especially televising programs that have a positive influence on the health attitudes and health behavior of children. The best time for this is of course during the prime viewing time on Saturday mornings.

We call for a “Manhattan Project” effort directed toward optimizing the health behavior of our children, and we encourage Congress and the legislators in each state to pay as much attention to this issue than they currently apply toward building better highways. It is imperative that we receive matching funds from the tobacco industry toward a future in which youths are free of tobacco use as well as of other health risk behaviors.

Fig. 9. Comprehensive, community-supporting school health education model, as proposed by the AHF.

Cancer risk factors addressed

Tobacco
Alcohol
Nutrition
Sunlight
Sexual hygiene

Fig. 9. Comprehensive, community-supporting school health education model, as proposed by the AHF.

For the Media
The media can and have played an enormous role in shaping public opinion and social acceptance of life-style habits. Early in the history of lung cancer and tobacco use, most of the members of all media were less than active in conveying proper health messages to the smoking public. Undoubtedly, this was related to their direct and indirect commercial ties to the tobacco interests. In recent years, of course, the media have taken on a more active role, although still not as proactive a stance as would appear warranted on the basis of available evidence. We are suggesting, particularly to leaders of the television industry, to take a meaningful and proactive role in the education of our very young about the ill effects of tobacco and tobacco use. It seems reasonable to suggest the implementation of a more expansive youth health education program that could be successfully integrated with prime television viewing time, such as the Saturday morning children’s cartoon shows. Federal Trade Commission regulations now mandate that the television industry provides prescribed hours of educational programming for the young members of our society. The AHF has created a cartoon pediatrician, Dr. AAAH, the “Healthy People Doctor.” We envision a set of “Health Minutes” featuring Dr. AAAH, who, in an entertaining and educational manner, encourages 3- to 8-year-olds to learn about a variety of good and healthy behaviors and also unhealthy behaviors, including that of tobacco use. Dr. AAAH signs off with the reminder to “remember that nobody takes better care of you than you,” encouraging the children to take charge of their very own health behavior. Those who have followed the beneficial impact of Sesame Street in educating children early and of Barney in espousing friendship and loving care will appreciate the impact that a cartoon or character can have on the thought and learning processes and subsequent behavior of young children. There is a pressing need for an antidote to Joe Camel; in a recent study in children, ~30% of 3-year-olds and 91.3% of 6-year-olds were able to match Joe Camel with a picture of a cigarette (86).

I believe that all of us, including the tobacco industry, can agree that we need to prevent the onset of smoking among our young. We also know that most risk-taking behavior and health habits in children are correlated, so that a multifactorial approach toward enhancing the health habits and health knowledge of very young children will be a very cost-effective endeavor. We therefore call upon the leaders in the advertising and television industry to work with us specifically on the development of Dr. AAAH and his “Health Minute.” Subsequently, we envision a more expansive youth health education program that should be aired when most young children see television on Saturday morning. We hope to demonstrate that a concept like this can enhance the present and future health of our children and provide a benefit to all members of our society.
Table 1  Comparison of the date of discovery of a measure to prevent a disease with the date of identification of its true causative or preventive agent

<table>
<thead>
<tr>
<th>Disease</th>
<th>Preventive measure</th>
<th>Causative or preventive agent*</th>
<th>Year of discovery</th>
<th>Discover of agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scurvy</td>
<td>J. Lind</td>
<td>(Ascorbic acid)</td>
<td>1928</td>
<td>A. Szent-Gyorgi</td>
</tr>
<tr>
<td>Scrotal cancer</td>
<td>P. Post</td>
<td>Benzo[a]pyrene</td>
<td>1933</td>
<td>J. W. Cook et al.</td>
</tr>
<tr>
<td>Smallpox</td>
<td>E. Jenner</td>
<td>Orthopoxivirus</td>
<td>1958</td>
<td>F. Fenner</td>
</tr>
<tr>
<td>Puerperal fever</td>
<td>I. Semmelweis</td>
<td>Streptococcus</td>
<td>1879</td>
<td>L. Pasteur</td>
</tr>
<tr>
<td>Chorea</td>
<td>J. Snow</td>
<td>Vibrio cholerae</td>
<td>1893</td>
<td>R. Koch</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>W. Reed et al.</td>
<td>Flavivirus</td>
<td>1928</td>
<td>A. Stokes et al.</td>
</tr>
</tbody>
</table>

* Preventive agents are listed in parentheses.

### Epilogue

So many in cancer research, including colleagues at AHF, are engaged in molecular and genetic research with the hope that such efforts will lead to basic knowledge about the etiology and ultimately to the successful prevention and therapy of cancer. These endeavors are important. Let us also accept a lesson from history and acknowledge that disease can be prevented without knowing the precise mechanism of pathogenesis (87). This is presented by some illustrious examples (Table 1). Lung cancer fits into this category in that its prevention can be addressed by various means before we comprehend all of the molecular and genetic nuances of tobacco carcinogenesis. In our research planning, we need to strike the proper balance between basic and applied research, or what Stokes recently referred to as basic and use-oriented basic research (88). Cancer is not an inevitable consequence of life and aging. Cancers, particularly those induced by tobacco and tobacco smoke, to a large extent can be prevented in the absence of a full comprehension of details of their pathogenesis.

All of us in cancer research, and in scientific research in general, need to be grateful to the American people and their representatives in government for having so generously supported our work. A special commendation needs to go to President Clinton for being the first president to take on the tobacco challenge personally. In terms of legislation, the momentum has been created for a comprehensive, sustained strategy that, if appropriately seized by the Congress and the White House, can considerably reduce tobacco smoking among the American people and especially among our young people. If this initiative is to truly benefit the health of the nation, this cannot be “politics as usual.” At this point in time, it appears that all involved parties are insisting that only their view must prevail. Perfection seems to get in the way of progress. There does seem to be a consensus that the focus ought to be on the prevention of initiation of tobacco use by young people. If rhetoric is accompanied by action, we have the tools at hand to assist in creating a generation of future nonsmokers.

As a final thought, I reflect on what Dr. Graham told me when he saw the final draft of our 1950 manuscript (6). He said “you are going to have many difficulties. The smokers will not like your message. The tobacco interests will be vigorously opposed. The media and the government will be loathe to support these findings. But,” he added, “you have one factor in your favor.” Expectantly, I got off my chair to hear what would follow. “What you have going for you,” he exclaimed, “is that you are right.” In my 1961 paper in the New England Journal of Medicine, the debate with Dr. Little, I wrote: “there are fields of human endeavor in which facts can be suppressed and at times submerged forever. Not so, however, in science. Here, facts may be destructively criticized and misrepresented, but if indeed they are facts, they will eventually be accepted, as the history of scientific progress testifies. It is this aspect of science that has always appealed to me as one of its greatest assets” (25). More than three decades later, this view has been supported in that there are, at long last, once again strong indications that the scientific truth will prevail.

### Acknowledgments

Current studies in tobacco carcinogenesis and in epidemiology and health promotion are supported through Cancer Center Grant CA 176123, Grant CA 70972 “Tobacco Carcinogenesis and Chemoprevention,” and Grant CA-68384 “Interdisciplinary Studies in Cancer Epidemiology” from the NCI.

I extend my thanks for contributions to the research on tobacco-related studies by many American colleagues and by collaborators from many nations, and I gratefully acknowledge 40 years of close collaboration and friendship with Dietrich and Ilse Hoffmann, first at the Sloan Kettering Institute for Cancer Research, and since 1969 at the AHF.

### References


