The Health Consequences of Smoking

THE CHANGING CIGARETTE

a report of the Surgeon General

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Office on Smoking and Health

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THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

The Honorable Thomas P. O'Neill, Jr.
Speaker of the House of Representatives
Washington, D. C. 20515

Dear Mr. Speaker:

I hereby submit to you the Health Consequences of Smoking-The Changing Cigarette. This report is in response to two Congressional requirements. The Public Health Cigarette Smoking Act of 1969 calls upon this Department to issue annual reports on the health consequences of smoking and to submit legislative recommendations. Section 403 of the Health Services and Centers Amendments of 1978 asks for a "study or studies of (1) the relative health risks associated with smoking cigarettes of varying levels of tar, nicotine, and carbon monoxide; and (2) the health risks associated with smoking cigarettes containing any substances commonly added to commercially manufactured cigarettes."

In preparing this report, the scientists and scientific agencies of this Department have reviewed all current scientific evidence and have concluded that the search for less hazardous cigarettes has not yielded a product which can be considered "safe." The person who changes to a cigarette with lower measured yields may reduce certain hazards of smoking, but the benefits will be small compared to the benefits of quitting entirely.

The most important conclusion of this report is that government and the private community alike must intensify their efforts to remind the public of the hazards of smoking and to assist those who do smoke to quit. We must step up our programs to persuade young people not to take up the habit in the first place.

This report also notes that we must continue to monitor the changing cigarette to insure that when new cigarette products appear they do not bring with them new hazards to health. Throughout this report the need to know about substances added to cigarettes is stated repeatedly. At present, there is no mechanism by which government or the scientific community can require disclosure of these additives, which must obviously be a first step in assessing their health effects. This needs to be corrected by voluntary action or, if necessary, by legislation.

On a number of occasions previous Secretaries of this Department have called for new and stronger health warnings, the establishment of maximum levels of "tar" and nicotine and the disclosure of more information about cigarette products. This 1981 report establishes the need to move forward on these recommendations. In particular, I believe the manufacturers should list yields of "tar", nicotine and other hazardous components on their packages and in their advertising with appropriate explanatory information on the health significance of these measurements. This would be a minimum first step in giving cigarette consumers full and adequate information about the products they are buying.

Sincerely yours,

Patricia Roberts Harris

Enclosure

PREFACE

This is the fourteenth report on the health consequences of smoking which the Public Health Service has issued since 1964 and the third to be issued during my term as Surgeon General. By Congressional directive it considers the relative health effects of cigarettes with varying levels of "tar" and nicotine and the relative health effects of cigarette additives.

At the present time, a third of all smokers, some 18 million persons, are smoking cigarettes with measured yields of less than 15 mg "tar," and this number is increasing by approximately 5 percent per year. Most of these persons have changed to lower yield cigarettes in the expectation that this will somehow reduce the hazards of their smoking. It is in the interest of these persons, and in the public interest, to know to what extent these expectations are justified.

In 1966, the Public Health Service held that "The preponderance of scientific evidence strongly suggests that the lower the tar and nicotine content of cigarette smoke, the less harmful would be the effect."

In 1979, the Public Health Service confirmed this statement, citing new evidence, but was more cautious. "In presenting information to the public," I wrote in the Preface to the 1979 Report, "three caveats are in order: consumers should be advised to consider not only levels of tar and nicotine but also (when the evidence becomes available) levels of other tobacco smoke constituents, including carbon monoxide. They should be warned that, in shifting to a less hazardous cigarette, they may in fact increase their hazard if they begin smoking more cigarettes or inhaling more deeply. And, most of all, they should be cautioned that even the lowest yield of cigarettes presents health hazards very much higher than would be encountered if they smoked no cigarettes at all, and that the single most effective way to reduce the hazards associated with smoking is to quit."

In this 1981 Report, the Public Health Service has reviewed the question again and in far greater depth than before. Overall, our judgment is unchanged from that of 1966 and 1979: smokers who are unwilling or as yet unable to quit are well advised to switch to cigarettes yielding less "tar" and nicotine, provided they do not increase their smoking or change their smoking in other ways. But our

new review raises new questions and suggests an even more cautious approach to the issue.

Here are the basic findings of this Report:

1. There is no safe cigarette and no safe level of consumption.
2. Smoking cigarettes with lower yields of "tar" and nicotine reduces the risk of lung cancer and, to some extent, improves the smoker's chance for longer life, provided there is no compensatory increase in the amount smoked. However, the benefits are minimal in comparison with giving up cigarettes entirely. The single most effective way to reduce hazards of smoking continues to be that of quitting entirely.
3. It is not clear what reductions in risk may occur in the case of diseases other than lung cancer. The evidence in the case of cardiovascular disease is too limited to warrant a conclusion, nor is there enough information on which to base a judgment in the case of chronic obstructive lung disease. In the case of smoking's effects on the fetus and newborn, there is no evidence that changing to a lower "tar" and nicotine cigarette has any effect at all on reducing risk.
4. Carbon monoxide has been impugned as a harmful constituent of cigarette smoke. There is no evidence available, however, that permits a determination of changes in the risk of diseases due to variations in carbon monoxide levels.
5. Smokers may increase the number of cigarettes they smoke and inhale more deeply when they switch to lower yield cigarettes. Compensatory behavior may negate any advantage of the lower yield product or even increase the health risk.
6. The "tar" and nicotine yields obtained by present testing methods do not correspond to the dosages that the individual smokers receive: in some cases they may seriously underestimate these dosages.
7. A final question is unresolved, whether the new cigarettes being produced today introduce new risks through their design, filtering mechanisms, tobacco ingredients, or additives. The chief concern is additives. The Public Health Service has been unable to assess the relative risks of cigarette additives because information was not available from manufacturers as to what these additives are.

In evaluating the public health significance of the finding of reduced risk of lung cancer, it is important to recognize that the largest component of excess mortality caused by smoking is cardiovascular disease deaths. There is not sufficient evidence to conclude that use of lower "tar" and nicotine cigarettes causes any reduction in this burden. The same is true of the other major diseases caused by cigarette smoking, most notably chronic obstructive lung disease and adverse effects on pregnancy.

These findings raise important questions of public policy. Some appear to be easily resolved. It should be possible to work out procedures so that cigarette manufacturers can disclose the additives they use while still protecting their legitimate interest in trade secrets; an effort to accomplish this is now underway. It should also be possible to develop better methodologies to measure smoke constituents, although no machine will ever be able to duplicate human smoking behavior exactly. And longitudinal surveys are now being carried on in an effort to monitor smoking behavior, and to help answer some of the behavioral questions raised in this Report.

Other questions pose greater difficulty. A common thread running through the sections of the Report is that too much reliance in the past has been placed on the nonselective measure of "tar" as a measure of risk to the neglect of other constituents and approaches to risk assessment. Additional epidemiologic and bioassay work is required, as is a better definition of the fundamental mechanisms of smoking-related disease. Further study is necessary to examine the addictive nature of smoking and its impact on initiation, maintenance, and cessation, especially in light of the recent statement of the National Drug Abuse Advisory Council that cigarette smoking is addictive. These questions cannot be answered quickly or without expenditure of scientific resources.

The questions raised by this Report suggest action in both the public and private sector.

In the research community, a research plan is needed to enable us to monitor the changing cigarette and to answer the many research questions put forth in this Report, with special emphasis on the issues of initiation and cessation. New measures and markers of relative toxicity are needed to supplement "tar" and nicotine. As stated, a voluntary disclosure and testing program needs to be developed with cigarette manufacturers to assess the relative health risks of cigarette additives and to protect against new hazards.

In the regulatory area, this Report suggests the need to increase the public's access to information about the product it buys. Advertisements and packages alike should display yield figures more prominently, including measures of carbon monoxide and possibly other hazardous ingredients. Marketing terms such as "low-low" and "ultra-low" need to be standardized.

In the area of public information and education, much more needs to be done both by the Government and by private health and educational agencies. The overriding objective must be to persuade young people not to take up smoking and to encourage present smokers to quit. Smokers of the lower yield cigarettes should be warned not to begin smoking more cigarettes or inhaling more deeply. Pregnant women should be cautioned that lower yield cigarettes are not an alternative to quitting.

Since 1964, when the first Public Health Service Report was issued, smoking has declined in the United States from 40.3 percent of the population to 32.5 percent. Per capita consumption of cigarettes is now at the lowest level since 1957. There is less smoking by boys than in many years, and smoking by girls has declined from the higher levels of the mid-1970s. This is a tribute to the educational efforts of our teachers, of our health professionals, and of our educational and health agencies. There is every reason to hope and believe these trends will continue.

Yet 54 million Americans continue to smoke, unwilling or unable to quit. This population is at extra risk of lung cancer, heart disease, chronic lung disease, and other diseases; it is a population with a life expectancy months and years less than the population of nonsmokers. The evidence presented in this Report shows that there is no "safe" cigarette available to these smokers, but that some cigarettes may be less hazardous than others, reducing the risks of smoking in a limited and selective fashion.

Julius B. Richmond, M.D.
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January 12, 1981

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Introduction

Great changes have taken place in the cigarette product in recent decades. In 1954, the average "tar" yield of the sales-weighted average cigarette was 37 mg and average nicotine yield was 2 mg. In 1980, the comparable figures are expected to be less than 14 mg of "tar" and less than 1 mg of nicotine. No cigarette marketed in the United States in 1979 yielded more than 30 mg of "tar."[1]

Smokers have turned to these new products because of health concerns. In the 1950s, cigarette manufacturers introduced cigarette filters as "health protection" and advertised them widely. The 1964 Report of the Surgeon General's Advisory Committee on Smoking and Health did not discuss cigarette smoke filtration, but in 1966 the Public Health Service reviewed the issue of smoke constituents. That report stated, "The preponderance of scientific evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the less harmful would be the effect." Thereafter, Government and tobacco industry scientists conducted studies of cigarette engineering and tobacco cultivation that could lead to lower "tar" and nicotine yields. Later, when new products appeared, cigarette manufacturers aggressively promoted them through advertising.

The request by Congress for an assessment of the "relative health risks associated with smoking cigarettes of varying levels of 'tar,' nicotine, and carbon monoxide," and "the health risks associated with smoking cigarettes containing any substances commonly added to commercially manufactured cigarettes" has come at an appropriate time. In the 2 years since Congress called for the present study, manufacturers have marketed cigarettes that yield as little as 0.01 mg of "tar" when measured by present Federal Trade Commission technology.

The technology of producing lower "tar" cigarettes has progressed well beyond a simple reduction in the amount of tobacco in the cigarette or the removal of a portion of the "tar" by filtration. Present technology has achieved "tar" reduction by alterations in plant genetics, changes in the cultivation and processing of the tobacco leaf, and changes in cigarette paper and filtration of the cigarette.

The methods used in testing cigarettes by machine may not correspond to the way persons actually smoke. There is evidence to suggest that the cigarette yields measured by machine are very different from the yields that the consumer actually obtains by smoking the cigarette, due in part to the difference in patterns of smoking between testing machines and individual smokers. Therefore, "tar" measurements of current cigarettes may not reflect the same

[1] "Tar" is the term given to the particulate matter of cigarette smoke that is retained by a Cambridge filter pad after extraction of nicotine and water. In this Report, the term "tar" is placed in quotation marks to emphasize that "tar" is not a single constituent but consists of many different chemical constituents and classes of constituents.

estimate of risk provided by the "tar" measurement of cigarettes manufactured at the time of the 1966 Public Health Service Review.

Another closely related concern about lower "tar" and nicotine cigarettes is the use of flavorings and other chemical additives. In order to enhance consumer acceptability, flavoring substances are added to cigarettes; it may be that the lower the "tar" yield, the more flavoring additives are used. It is impossible to make an assessment of the risks of these additives, as cigarette manufacturers are not required to reveal what additives they use. No agency of the Federal Government currently exercises oversight or regulatory authority in the manufacture of cigarette products. Further, no agency is empowered to require public or confidential disclosure of the additives actually in use by the cigarette manufacturers.

At the same time that changes have occurred in the cigarette, marked changes have occurred in the smoking patterns of the U.S. population that may have substantially altered the risk of smoking lower "tar" cigarettes. Over recent years, smokers have been taking up regular smoking at younger ages, and the number of women who smoke currently far exceeds the number from several decades previously. The multiplicative risks of smoking and oral contraceptive use is an example of how changes in the population of smokers can make both quantitative and qualitative changes in the nature of the risk. The proportion of the population that smokes has declined, but the average number of cigarettes smoked by each smoker appears to have increased over several decades. Changes have occurred in the environment, dietary habits, and behavioral patterns of the population, which may alter the interaction between cigarette smoking and other risk factors for disease. Thus, we have a continually changing population of smokers who smoke a continually changing cigarette in a continually changing manner.

Dose-Response Relationship

A clear dose-response relationship has been established between cigarette smoking and a number of disease states; this constitutes a major part of the evidence suggesting that lower "tar" cigarettes may be less hazardous. It is important to understand this dose-response relationship and the limits of the data.

The major prospective studies on smoking and disease show that the risk of coronary heart disease and lung cancer increases in a roughly linear manner with increasing numbers of cigarettes smoked per day. There is also a marked increase in the risk of death from chronic lung disease with the number of cigarettes smoked per day, but problems in classification of this disease make it unclear whether the relationship is linear. There is no clear evidence of a threshold effect in any of these studies. The relationship between number of cigarettes and disease is strengthened by showing that the risk increases with longer duration

of the smoking habit and with younger age at initiation of regular smoking. Risk is thus closely related to smoke dose as measured by number of cigarettes consumed. The relationship may result from the effect either of repetitive doses or of cumulative smoke dosage. The effect on risk of the time interval between cigarettes has not been thoroughly examined, but there is evidence to suggest that risk is related to the total dose of smoke delivered to the smoker, regardless of the time pattern of exposure. Overall, disease risk clearly increases with increasing depth of cigarette smoke inhalation. Pipe and cigar smokers who do not inhale have a lower risk of tobacco-related diseases. Thus, it is logical to hypothesize that a reduction in the actual dose of cigarette smoke to the smoker would be accompanied by a reduction in the risk of developing heart and lung disease.

"Tar" is a major portion of the total particulate matter of cigarette smoke. To the extent that the machine measurements of "tar" yield of cigarettes reflect the actual smoke exposure resulting from use of that cigarette, a lower "tar" cigarette should be less hazardous. In order for the measured "tar" yield of a cigarette to reflect smoke exposure, a number of conditions would have to be met.

First, changing the "tar" yield should not change the pattern, or style, of cigarette use. If the smoker compensates for reduced yield by increasing the number of cigarettes, the depth of inhalation, or the volume or frequency of puffs, a reduction in "tar" might not result in a reduced smoke exposure. The possible increase in the average number of cigarettes smoked by each smoker and the possibility that the depth of inhalation and puff volume may also have increased as the average "tar" yield of the cigarette has declined raise a real concern that the shift to the use of lower "tar" cigarettes may not have resulted in a proportionate drop in smoker exposure.

A second assumption in equating lower "tar" yield per cigarette with lower smoke exposure, and therefore lower risks of disease, is that the reduction in "tar" is accompanied by a similar reduction in all of the constituents of smoke, or at least all of those constituents related to disease. As long as the lowering of the "tar" yield was largely secondary to a reduced amount of tobacco in the cigarette or a filtration of the smoke, a reduced "tar" yield could be assumed to represent a lower smoke exposure. Prior to 1971, the reduction in "tar" yield was very similar to the reduction in weight of tobacco per cigarette (see Figure 8, Section 8), but since that time the reduction in "tar" has been proportionately somewhat greater than the reduction in weight of tobacco per cigarette, and this difference appears to have increased since 1975. As discussed in this Report, the recent reductions in "tar" yield have been accomplished by altering tobacco growth and processing and by changes in cigarette manufacture. These changes may have produced a "tar" with a different composition from that of

old higher "tar" cigarettes, and may have changed the concentrations of some of the constituents contained in the gas phase of the smoke.

An additional concern is that the production of cigarettes with lower "tar" and nicotine yields may involve the increasing use of additives for tobacco processing or flavoring. Some additives available for use are either known or suspect carcinogens or give rise to carcinogenic substances when burned. The use of these additives may negate beneficial effects of the reduction of "tar" yield, or might pose increased or new and different disease risks. Therefore, the "tar" yield of cigarettes currently being manufactured probably cannot be used as a precise measure of current smoke exposure risk, nor be compared quantitatively with the smoke exposure risk of the older higher "tar" cigarettes. The major prospective studies that provide the data for our assessment of smoking-related health risks examined persons who smoked these older, higher "tar" cigarettes.

A third assumption in equating "tar" yield with smoke exposure is that the "tar" yield of a machine-smoked cigarette be equal to or at least proportional to the yield of the same cigarette when it is consumed by the smoker. Later sections of this Report clearly establish that the "tar" yield of the current cigarette may vary markedly with style of smoking, with much higher yields being produced by higher puff volumes or occlusion of the perforations in the cigarette wrapper. Thus, the manufacturing changes that have resulted in low "tar" yield measurements may not have resulted in a comparable reduction in the exposure of the individual cigarette smoker.

Relative Risks of Lower "Tar" Cigarettes for Specific Diseases

Having examined the nature of the dose-response relationship and some of the limitations of using "tar" measurements as the measure of dosage, we can now examine the evidence available that assesses the relative risk of lower "tar" cigarettes for specific disease processes. An understanding that the different health consequences of smoking may be caused by different smoke constituents is pivotal to these assessments of relative risk. Our understanding of the specific etiologic mechanisms by which cigarette smoke constituents cause different diseases remains incomplete at this time.

The individual sections of this Report review in detail evidence on the relative health hazards of lower "tar" and nicotine cigarettes. Assessment of the relative risk of these cigarettes requires the integration of this information; final assessment of the overall relative health hazard of these cigarettes has not been reached. The major issue is the potential and actual health impact of the introduction of these cigarettes into the marketplace. Assessment of this requires understanding of the changes that have taken place in the cigarette product, the effects of those changes on smoking initiation, cessation, and patterns of cigarette use, and the probable health effects of the net

change in cigarette smoke dose. It also requires an understanding of the changes in risk that occur secondary to switching to lower "tar" cigarettes distinct from the risks of lifelong use of these products.

Lung cancer is the disease process in which the relative risk of lower "tar" and nicotine cigarettes has been most clearly evaluated. Approximately 85 percent of the incidence of lung cancer can be directly attributed to cigarette smoking; there are relatively few problems with changing criteria for classification of cause of death, and there is a clear, linear dose-response relationship. Moreover, the "tar" portion of the smoke probably contains most of the carcinogenic activity of the whole smoke. If the reduction in machine-measured "tar" yield is accompanied by an actual reduction in smoker exposure dose, then there should be a relatively proportionate reduction in lung cancer risk.

Lower "tar" cigarettes are associated with a reduction in the risk of developing lung cancer, although the proportionate reduction in risk is substantially less than that of "tar" yield.

A smaller percent reduction in lung cancer risk versus that of measured cigarette "tar" yield could result from several factors, including compensation (such as an increased depth of inhalation or a greater number of cigarettes smoked per day), or from a lack of comparable reductions in other carcinogens.

For several reasons, it is difficult to extrapolate these risk reduction data to the current very low "tar" cigarettes. Because the lower "tar" yield of the cigarettes evaluated in the published studies probably was accomplished predominantly by reducing the weight of tobacco in the cigarette and by removing "tar" through filtration, use of these cigarettes might reasonably be expected to result in a lower smoke exposure if compensation did not occur. It is not clear, however, that the alterations in the techniques of tobacco processing and cigarette manufacture that have produced the very low machine-measured "tar" yields can be expected to result in similar reductions in actual smoker exposure to toxic smoke constituents. In addition, the potential carcinogenic effect of the substances added to these cigarettes has not been evaluated. The demonstrated reduction in mouse skin tumorigenicity of "tar" has not, however, been accompanied by a reduction in the incidence of or mortality rates due to lung cancer among humans.

Cigarette smoking is an independent risk factor for coronary heart disease, one that interacts synergistically with other risk factors such as hypertension and hypercholesterolemia. The effect of cigarette smoking in coronary heart disease risk is clearly dose related, and cessation of smoking reduces the risk. Estimation of the impact of varying cigarettes on coronary heart disease risk is difficult, because the exact etiologic agent(s) have not been identified. A number of agents have been suggested to be active in the development of coronary heart disease, including nicotine and carbon monoxide. Any change in risk that might occur because of switching to lower "tar"

and nicotine cigarettes might be expected to become evident more rapidly for coronary heart disease risk than for cancer risk, due to the acute effects of cigarette smoke in causing adverse coronary heart disease events such as sudden death.

As in the case of cancer, the expectation that a risk reduction for coronary heart disease would accompany the use of lower "tar" and nicotine cigarettes is based on the premise that the use of lower "tar" cigarettes results in a reduction of exposure to the responsible smoke constituents. This assumption is reasonable if nicotine is a major etiologic agent, because there is a close relationship between the "tar" and nicotine yields for individual cigarettes. That is, among the cigarettes currently available in the United States, a lower "tar" cigarette is also a lower nicotine cigarette.

The variations of the other constituents in the particulate phase of the smoke in relation to "tar" yield is largely unknown, especially in those cigarettes specially formulated to produce very low machine measurements of "tar" yields.

Carbon monoxide is one gas in cigarette smoke that may be closely associated with coronary heart disease risk, perhaps through interference with myocardial oxygenation, enhancement of platelet adhesiveness, or promotion of atherosclerosis. The relationship between carbon monoxide yield and "tar" yield, however, has not been as thoroughly examined as that between "tar" and nicotine. The factors that influence the carbon monoxide yield are closely related to the manufacturing process (e.g., porosity of the paper, filter ventilation, etc.), and therefore may vary somewhat independently of "tar" yield. In addition, the absorption of carbon monoxide is more dependent on depth of inhalation than is the absorption of nicotine and, if the use of lower "tar" products results in a compensatory increase in depth of inhalation, smoker exposure to carbon monoxide may remain unchanged or actually increase. The reality of this concern is borne out by those studies that show no lowering of carboxyhemoglobin levels in smokers who switch to lower "tar" cigarettes. If carbon monoxide is an active etiologic agent for cigarette-related coronary heart disease, and if significant compensatory changes in the style of smoking occur with use of lower "tar" cigarettes, then the risk of coronary heart disease with lower "tar" cigarettes may be similar to, or possibly greater than, the risk of smoking higher "tar" cigarettes.

Some other agents in the gas phase of cigarette smoke have also been suggested as possible contributors to the development of coronary heart disease. Little is known about the relationship between the yield of the gas phase of the smoke and the "tar" yield. The change in formulation that allows the reduction in "tar" yield of the new lower "tar" cigarettes has not been examined for its effect on the yield of individual gas phase constituents. The potential for creating new substances and for increasing the yields of existing gas phase

constituents by changes in formulation cannot be assessed from existing data, but may well impact on the risk of coronary heart disease produced by smoking lower "tar" cigarettes.

It is not surprising that the studies looking at the relative risk of lower "tar" cigarettes reviewed in the cardiovascular section have not produced a clear estimate of relative risk, given the difficulty in relating a difference in "tar" yield to a difference in coronary heart disease risk and the existence of gaps in our understanding of the etiologic agents in smoke that cause coronary heart disease. Thus, the impact of a reduction in the "tar" yield of cigarettes on the coronary heart disease risk produced by smoking cannot be estimated at this time.

Approximately 70 percent of chronic obstructive lung disease deaths are attributable to cigarette smoking. The number of deaths attributed to chronic obstructive lung disease is much smaller than the number of lung cancer deaths. This fact, and the relatively long interval of time between the onset of symptomatic chronic airflow limitation and death from respiratory failure, reduce the usefulness of mortality data from chronic lung disease in assessing the relative risks of lower "tar" cigarettes. Therefore, attention has focused on the level of symptoms and measured reductions in air flow for evaluating relative risk of chronic obstructive lung disease.

As reviewed in the section on chronic obstructive lung disease, there are three major aspects of cigarette-induced lung injury: chronic mucous hypersecretion, airway inflammation and narrowing, and alveolar septal destruction. The causal agents for each type of lung injury may be different, and therefore each type may be affected quite differently by a reduction in the "tar" yield of the cigarette.

The mucous hypersecretion and cough are a response of the lung to the chronic irritant effects of cigarette smoke. To the extent that a reduction in "tar" yield reflects a reduction in smoke exposure, smoking lower "tar" cigarettes should result in reduced cough and sputum production. In the studies that have looked at this question, the expected decrease in cough and sputum production has indeed accompanied the use of lower "tar" cigarettes.

Airflow limitation is not produced by mucous hypersecretion *per se* but rather by airway narrowing and loss of parenchymal lung units. The same studies that showed a reduction in symptoms with the use of lower "tar" cigarettes failed to show a similarly reduced effect on air flow limitation. This finding may indicate that tests of air flow limitation are not sufficiently sensitive to measure the differences in extent of disease. It could also result from a failure to produce lower exposure to the causative agent(s) with the use of lower "tar" cigarettes, either due to a lack of reduction in concentration of the agent(s) or to compensatory changes in smoking behavior.

The loss of parenchymal lung units that is the hallmark of emphysema is extremely difficult to measure during life, but there has been substantial progress toward an understanding of how this disease is produced by cigarette smoking. This work is reviewed in detail in the section on chronic obstructive lung disease; it is suggested that alveolar walls are destroyed by excess proteolytic activity. Cigarette smoke may promote this excess activity through a combination of an increased cellular release of proteolytic enzymes and the oxidative inactivation of the inhibitor of these proteolytic enzymes. Since the airways filter out most of the particulate matter in the smoke, it is felt that the gas phase may be the component of smoke responsible for the changes in enzymatic activity. The gas phase contains a number of agents capable of oxidative inhibition of the enzyme inhibitor alpha$_1$-antitrypsin. Therefore, the risk of developing emphysema may not be related to the "tar" yield of the cigarette smoked. Even if the reduction in "tar" yield results in a reduction in smoker exposure to "tar," a pattern of compensation that produces a deeper inhalation may deliver a greater dose of the gas phase of that smoke to the alveoli where it produces a pathologic effect. In addition, the techniques used in formulation of the newer very low "tar" cigarettes may result in an increase in the concentrations of etiologic agents in the smoke. Therefore, the relative risk for lower "tar" cigarette usage in the development of chronic obstructive lung disease is highly problematical. The lower "tar" and nicotine cigarettes may well produce less of the symptomatic component of this disease, but even if they do result in a reduction of total smoke exposure, the pattern of that smoke exposure may negate any reduction in risk.

The relative risks for both the mother and the fetus of smoking lower "tar" and nicotine cigarettes during pregnancy are of great concern, both because of the numbers of young women who smoke and because of younger women's more frequent use of lower "tar" cigarettes. The increased use of cigarettes with lower "tar" yields has not been investigated for its effect on changes in risk of adverse effects of smoking on pregnancy. Accordingly, no reduction in risk relative to higher "tar" and nicotine cigarettes has been demonstrated.

Of particular concern is the potential teratogenic effect of additives and their combustion products. Thus, it is not possible to assume that switching to a lower "tar" cigarette would have an effect in reducing risk during or after pregnancy. It is clear that the only recommendation that can be made to reduce risk in the smoking mother is for her to quit smoking.

The ultimate assessment of risk is, of course, overall mortality. One study examined the effect of smoking lower "tar" and nicotine cigarettes on overall mortality. Persons smoking cigarettes with lower "tar" and nicotine yield exhibited a decline in mortality rate from any cause of approximately 15 percent in comparison with that of smokers

of higher "tar" cigarettes. Direct extrapolation of these overall mortality results to current smoking exposure is not possible. The lowest "tar" categories in that study included cigarettes that would be considered higher "tar" products today; the mechanisms by which subsequent reductions have been achieved may differ from earlier techniques. There was no evidence available on the duration of use of lower "tar" products in this population.

Methodologies for Assessing Relative Risk

The task of monitoring the relative risks of lower "tar" cigarettes is complex, but it is not impossible. Four approaches can be used: constituent toxicology, bioassay systems, observational epidemiology, and the study of fundamental mechanisms of disease production. Each approach makes a unique contribution to our understanding of relative risk. Each approach also has significant limitations to its contribution to a complete assessment of risk. It is necessary to combine the information gathered by each of these methods in order to understand the risk. The final assessment of relative risk requires data from each of these four methodologies. To the extent that information from any one area is lacking, the estimation of relative risk is incomplete.

The first approach is that of constituent toxicology. A tremendous amount of time and effort has been spent to characterize cigarette smoke and to identify disease-producing smoke constituents. Several thousand individual constituents have been identified. Much has been learned about the effects of cigarette reformulation on the pyrolytic process. Studies have led to a better understanding of human absorption of these substances and how this is influenced by differing patterns of puffing and inhalation. The identification of carcinogens, oxidants, and ciliatoxic compounds represents an important advance in understanding the risks of cigarette smoking. The fundamental strength of this approach is that it might ultimately allow risk to be measured by examining the chemical composition of the smoke and its absorption. Thus, assessment of risk might be made prior to allowing human exposure to the smoke. It could lead to the selective removal of toxic substances from smoke.

The major limitation of this approach is the sheer magnitude of the task. It would be necessary to identify each of the several thousand substances, the site and amount of absorption with different patterns of smoking, and the toxicity for each organ system. It would also be necessary to address the more complicated question of the potential interactions between smoke constituents, environmental and occupational exposures, and other exposures, such as medications. The monumental nature of this task does not mean that constituent toxicology is unable to contribute to our assessment of relative risk. It simply means that it alone cannot solve the problem. The choice of what substances to measure in order to assess risk must be guided by

an understanding of the basic mechanisms of disease production and must be correlated with changes in disease occurrence in human populations. In this way the search can be, and is being, focused on those areas and substances that may provide the best measure of risk.

A second method of assessing risk is through the use of bioassay systems. The term "bioassay" is used broadly to include animal models as well as cellular or organ responses. This approach can also rapidly provide information on risk without human exposure and has the additional advantage that whole smoke or major fractions of smoke can be tested rather than individual constituents. The limitation of this method is that the estimate of risk is only as good as the bioassay system. Unless the system truly approximates the disease process of concern, changes in that system may not reflect risk of disease. A number of bioassay systems exist for the study of cigarette risk. Unfortunately, none of them can be said to exactly duplicate human disease. At the present time, estimates derived from these systems cannot stand alone, but must be interpreted in the light of information derived from other methods.

The ultimate "bioassay" is, of course, human exposure. The occurrence of disease in human populations would provide the most accurate estimate of the relative risk of lower "tar" cigarette smoking. An important drawback to this approach is that it permits the development of that disease in the population prior to measuring risk and taking appropriate public health action. An additional limitation of the observational epidemiology is that the risk being measured is caused by a product and a pattern of use that occurred in the past. Because of the long time lag between regular exposure to smoke and the development of most cigarette-related diseases, and the time lag between development of disease and diagnosis of that disease, the relative risk determined by observational epidemiologic methods may lag many years behind the current risk. It may take 20 to 30 years before smoking-related disease is observed. With a rapidly changing cigarette product, it is necessary to estimate the risks of current exposures rather than those of past exposures. This assessment is complicated by the difficulty of defining and measuring any differences in individual smoker exposure resulting from changes or individual variations in styles of smoking. Nonetheless, despite these difficulties, the epidemiologic method remains the major tool in assessing the relative health risks of differing cigarettes.

Some of the limitations of the observational epidemiologic method can be overcome by incorporating information from the other approaches to risk assessment. Information on the toxicology of cigarette smoke might allow epidemiologists to sharpen their measurement of actual smoker dosage, and might identify earlier tests of toxicity than the traditional end points of disease occurrence or death. Information on the basic mechanisms of disease production could improve the

estimation of relative risk by directed measurement of the basic pathophysiologic processes or their biochemical or metabolic sequelae. An excellent example of this kind of potential interaction is the testing of populations of smokers for the byproducts of elastin degradation suggested in the section on chronic obstructive lung disease.

The fourth method of assessing relative risk is the definition of the fundamental mechanisms of disease production. An obvious attraction of this approach is its potential to provide information that would permit the prevention or cure of the disease process.

The difficulty with this method of risk assessment is our limited understanding of these fundamental mechanisms. It is important to incorporate what understanding we do have into the risk assessment produced by other methods, and equally important to incorporate information from other methods into the search for disease mechanisms. As an example, it would be fruitless to examine the effect of a given substance on the cell function in alveoli if it has been learned from absorption studies that the substance is absorbed in the upper airway and never reaches the alveoli.

Once the mechanism of disease is understood, however, an estimate of relative risk might be made, not only by measuring the dose of etiologic agents in smoke, but also those determinants of the disease process pre-existing in a given individual.

Conclusion

In summary, the final estimation of the relative risk of smoking lower "tar" and nicotine cigarettes must be based on a synthesis of the information derived from several methodologies. Despite the lack of comprehensive and conclusive evidence currently available, the Public Health Service policy on lower "tar" and nicotine cigarettes must remain unchanged. The health risks of cigarette smoking can only be eliminated by quitting. For those who continue to smoke, some risk reduction may result from a switch to lower "tar" and nicotine cigarettes, provided that no compensatory changes in style of smoking occur.

This Report of the relative risks of lower yields of "tar," nicotine, and carbon monoxide has defined the following more clearly: the conclusions warranted by present evidence; the difficulties and importance of defining and monitoring changes in cigarette yields and actual smoker exposure; and the major questions remaining unanswered, which constitute the major areas for future research efforts.

Summaries of the available data on the relative risks of cigarette-related diseases among smokers of differing cigarettes follow. They are grouped by topic.

Following these summaries are the research recommendations from the Working Meeting, "Research Needs on Low-Yield Cigarettes."

These recommendations are combined, reflecting the common underlying concerns among disciplines.

Summaries

Pharmacology and Toxicology

1. Several thousand constituents have been identified in tobacco and tobacco smoke. Of these, nicotine appears to be the most important acute-acting pharmacologic agent. Nicotine's physiologic effects include increased heart rate and blood pressure. Nicotine also can permit the formation of tobacco-specific nitrosamines, which are potent carcinogens, and nicotine itself may be a significant cocarcinogen. The carcinogenic potency of cigarette smoke condensates appears to depend on the nicotine content of the "tar." This relationship may be due in part to the conversion of nicotine to tobacco-specific nitrosamines or to the coexistence of nicotine and some other unidentified carcinogen. Whether the carcinogenic effects of nicotine as determined in animal studies are directly applicable to humans is not known at present.
2. In an important study to predict the carcinogenic activity of cigarette smoke condensate, the amount of available nicotine delivered to the mice was found to be a factor in every term but one of the predictive model.
3. Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are two prominent classes of tumor initiators found in the smoke condensates of commercial cigarettes. Of the polycyclic aromatic hydrocarbons formed during combustion, benzo[a]pyrene (BaP) may be the most important and has been studied the most extensively. A correlation has been found between benzo[a]pyrene levels and the carcinogenic activity of smoke condensates from several types of cigarettes, but other studies have failed to show that carcinogenic potential is significantly dependent on benzo[a]pyrene content. However, the interaction of BaP with nicotine does appear important in carcinogenesis.
4. The tobacco-specific nitrosamines (TSNA) are formed during curing and fermentation of tobacco leaves and combustion of cigarettes. TSNAs induce cancer in the lungs and trachea of hamsters and may be of particular importance in the induction of human laryngeal cancer. They may be active as contact carcinogens, or their metabolism at distant sites may produce carcinogens that are then transported to a target site.
5. It is not known whether the unidentified mutagens in cigarette smoke are an important cause of lung cancer in humans, but

added exposure to any tumor initiators probably carries an increased risk of cancer.

6. Cigarette smoke contains oxidants that have been shown to reduce the activity of alpha$_1$-antitrypsin in animals and man. This inhibitory function is distinct from the effect whole smoke has on increasing levels of elastolytic enzymes released by neutrophils and macrophages.
7. The great variety of tobacco types makes it possible to manipulate the plant genetically to change the content of the constituents of the leaf. The chemical content of the leaf is also affected by agricultural practices and curing methods. The nicotine content of tobacco, for example, is related to the amount of nitrate fertilizer used in cultivation. Modification of tobacco as reconstituted sheet incorporates substantial amounts of tobacco stems that contain less nicotine than the leaf. The physical nature of reconstituted sheets can be controlled to change their burning characteristics and smoke composition.
8. Vapor-phase constituents of cigarette smoke inhibit ciliary motility and mucous flow in experimental animals.
9. Cigarette smokers metabolize several compounds more rapidly than do nonsmokers. This effect is believed to be caused by the induction of microsomal oxidases, which include aryl hydrocarbon hydroxylase (AHH). Induction of AHH activity appears to be caused by systemic exposure to the smoke compounds themselves or to the metabolites of those compounds. The AHH system may be involved in the metabolic formation of ultimate carcinogens from procarcinogen precursors.
10. In recent years, a number of flavoring additives or cellulose-based tobacco substitutes may have been included in manufactured cigarettes. The nature and amounts of such additives as actually used are not known, nor is it known what influence these additives may have on the chemical composition or subsequent biological activity of cigarette smoke.
11. Cigarette design has a major effect on smoke composition. The filter is the design characteristic that has the most impact on "tar" yield; it can also selectively remove nitrosamines and semivolatile phenols from smoke. The porosity of cigarette paper and the presence of holes in the mouthpiece influence smoke composition because ventilation reduces the quantity of "tar" and dilutes the gas phase of smoke.
12. Because of the complexity of cigarette smoke, the total impact of any cigarette modification on smoke composition will probably never be fully known.
13. Many laboratory studies of the effects of smoke constituents have been carried out using smoking machines that control puff volume, frequency and duration, butt length, and other factors

according to standardized parameters. However, the most widely used parameters were established in 1967, and the type of cigarettes generally smoked today are substantially different with respect to length, paper porosity, "tar" and nicotine content, and concentration of gas phase constituents. Evaluation of the toxicological and pharmacological properties of smoke from new types of cigarettes requires detailed knowledge of the manner in which those cigarettes are smoked, as well as of how smoking patterns affect smoke composition.

Cancer

1. Today's filter-tipped, lower "tar" and nicotine cigarettes produce lower rates of lung cancer than do their higher "tar" and nicotine predecessors. Nonetheless, smokers of lower "tar" and nicotine cigarettes have much higher lung cancer incidence and mortality than do nonsmokers.
2. Smokers of lower "tar" and nicotine cigarettes may tend to smoke larger numbers of cigarettes, to inhale more deeply, to have relatively higher amounts of carboxyhemoglobin than predicted from machine measurements of carbon monoxide yield, and to have higher than predicted carbon monoxide in exhaled air.
3. In attempting to develop a "less hazardous" cigarette, singular emphasis has been placed on reducing the "tar" yield of cigarette smoke because of the early demonstration of a causal relationship between "tar" and lung cancer. Comparable data on changes in yield of constituents in the gas phase of smoke are not publicly available.
4. The occurrence of laryngeal cancer has been reported to be reduced among smokers who use filtered cigarettes, compared with those who use nonfiltered cigarettes.
5. There is no epidemiologic evidence to prove or to disprove a decreased occurrence of cancers of other sites in humans who smoke lower "tar" and nicotine cigarettes.
6. In evaluating the effect of smoking lower "tar" and nicotine cigarettes on histologic changes in the bronchial epithelium, it was determined in one autopsy study that male smokers who died between 1970 and 1977 had fewer histological changes than those smokers who died between 1950 and 1955.
7. Even among those who do not develop cancer, histologic changes in the tracheobronchial tree are more advanced at autopsy in smokers of cigarettes with higher "tar" and nicotine than among smokers of cigarettes with lower yields.
8. The "tar" content of smoke condensate of today's cigarettes is less tumorigenic to mouse skin than that of cigarettes of 30 years ago. Levels of the known carcinogen benzo[a]pyrene are lower in

the smoke of today's cigarettes than in that of cigarettes of 30 years ago. Flavor additives used in lower "tar" and nicotine cigarettes produce traces of mutagenic compounds.

9. Although studies point to polycyclic aromatic hydrocarbons in the "tar" of inhaled cigarette smoke as potential carcinogens for humans, additional work is needed to determine whether nicotine plays a major role as a carcinogen. Definition of the role of nicotine in carcinogenesis is necessary prior to advocacy of cigarettes yielding less "tar" but more nicotine.
10. Animal studies have shown that a significant reduction of "tar" and a selective reduction of tumor initiators and cocarcinogens can markedly reduce the tumorigenic potency of cigarette smoke.

Cardiovascular Diseases

1. Epidemiological studies show that the incidence of coronary heart disease (CHD) increases as the daily number of cigarettes smoked increases and that the incidence of CHD decreases among those who quit smoking. These dose-related effects suggest that lower "tar" and nicotine cigarettes might be associated with lower risks of CHD. However, the overall changes in the composition of cigarettes that have occurred during the last 10 to 15 years have not produced a clearly demonstrated effect on cardiovascular disease, and some studies suggest that a decreased risk of CHD may not have occurred.
2. Of the several thousand substances found in cigarette smoke, only a few have been implicated in cardiovascular risk. A number of substances have not yet been adequately assessed. Further, the changes in smoke constituents that have resulted from changes in the cigarette product have not been documented.
3. Linking cigarette smoke yields to cardiovascular disease is complicated by the evidence that smokers of lower "tar" and nicotine cigarettes may smoke more "intensively," although they may not smoke a substantially greater number of cigarettes daily than do smokers of higher "tar" and nicotine cigarettes. The net result could be to decrease the actual intake of "tar," nicotine, and carbon monoxide less than that expected on the basis of machine measurements.
4. Nicotine stimulates the sympathetic nervous system, producing a rise in catecholamines that in turn increases heart rate, elevates systolic blood pressure, constricts cutaneous blood vessels, and increases levels of free fatty acids. The nicotine-stimulated release of catecholamines has been suggested as the cause of increased platelet stickiness and aggregation, pointing to a potential role in coronary disease. There is some evidence that these physiological effects may be dose related and somewhat diminished with lower nicotine varieties of cigarettes.

5. Carbon monoxide has a negative inotropic effect on the myocardium of patients with angina pectoris. When combined with hemoglobin in the form of carboxyhemoglobin, carbon monoxide may increase the permeability of the blood vessel walls to lipids, thereby promoting atherosclerosis.
6. Cigarettes with unperforated filters yield lower "tar" and nicotine levels than unfiltered cigarettes, but they yield more carbon monoxide than do unfiltered cigarettes at the same "tar" yield. Carbon monoxide yields are lower in cigarettes with perforated filters, but as the composition of cigarettes has changed, carbon monoxide yields have decreased much less in proportion to the decrease in "tar" and nicotine yields.
7. In studies of patients with angina pectoris, increased carboxyhemoglobin levels significantly shorten exercise time until the onset of angina pectoris.
8. Myocardial ultrastructural changes have been found in rabbits exposed to carbon monoxide.
9. Most cardiovascular studies have focused on nicotine and carbon monoxide rather than on "tar," which has not been shown to have a major acute role in cardiovascular disease. Even less is known about other constituents of cigarette smoke.
10. Not all cigarettes that produce a lower yield of one substance necessarily provide a lower yield of other substances.
11. Evidence on the association between CHD and filter cigarettes is somewhat conflicting. One major study showed a reduction of 10 to 20 percent in coronary deaths among persons smoking lower "tar" and nicotine cigarettes as compared with those who smoked higher yield cigarettes, but other surveys have shown a slightly increased risk of coronary mortality in people who smoked filter cigarettes relative to those who smoked nonfiltered cigarettes. Recent unpublished data from the Framingham Study do not show a lower CHD risk among smokers of filter cigarettes.

Chronic Obstructive Lung Disease

1. The relationship between cigarette smoking and chronic obstructive lung disease (COLD) is well documented. The constituents of cigarette smoke that are responsible are currently not known. Whether a difference in risk of COLD has occurred with lower "tar" and nicotine cigarettes as compared with higher "tar" and nicotine cigarettes is currently unknown.
2. Cigarette smoking is associated with the release by alveolar macrophages of an increased amount of the elastolytic enzymes, which degrade alveolar tissue, and with reduced activity of $alpha_1$-antitrypsin, the primary elastase inhibitor. This mechanism has not yet been directly related to the development of human emphysema. To date there are no published studies that

compare the effects of higher versus lower "tar" and nicotine cigarettes on elastolytic enzymes and inhibitor activity.

3. Cigarette smoke also contains relatively high levels of oxides of nitrogen. The nitrogen oxides produce lung damage in animals that is similar to that induced in humans by cigarette smoke. The oxides of nitrogen may be responsible for the early lesions of human emphysema.
4. An individual's smoking pattern is one of the most important determinants of the relative concentration of smoke constituents that reach the lungs and of the subsequent response of the airways to smoke inhalation. Holding smoke in the mouth before inhaling it into the lungs produces less response of the airways than direct inhalation, which causes spirometric changes indicative of bronchoconstriction. This effect is independent of the "tar" content of the cigarette.
5. Pulmonary mucous hypersecretion and symptoms of cough and phlegm appear to be affected by the "tar" content of cigarette smoke. The development of airway obstruction is closely related to the number of cigarettes smoked. Smokers of lower "tar" and nicotine cigarettes who compensate by smoking more or inhaling more deeply might thereby increase their risk of developing obstructive airway disease.
6. Population studies that have examined the rate of decline of lung function in relation to the number of cigarettes smoked have shown variable results, and most of the available data do not relate lung function to cigarette yield. Overall, the mean difference between the rate of decline of FEV_1 in asymptomatic smokers and nonsmokers is very small, but there is a subgroup of the smoking population that shows more rapid decline and is apparently more likely to develop significant pulmonary disease.

Pregnancy and Infant Health

1. Cigarette smoking during pregnancy has been shown to have adverse effects on the mother, the fetus, the placenta, the newborn infant, and the child in later years. There is no evidence available that lower "tar" and nicotine cigarettes decrease or increase these health risks, relative to those posed by higher "tar" and nicotine cigarettes.
2. Problems that have been linked to smoking during pregnancy include placenta previa, abruptio placentae, vaginal bleeding, and reduced average birthweight of newborn infants.
3. Smoking by pregnant women increases the risk of spontaneous abortion, premature delivery, fetal death, and perinatal death. Parental smoking is associated with the sudden infant death syndrome.

4. The fetuses of smoking mothers have higher blood carboxyhemoglobin levels and lower fetal arterial oxygen levels than do the mothers.
5. Children of smoking mothers appear to show a greater susceptibility to some adverse health effects, such as bronchitis, pneumonia, and respiratory disease, during early childhood. Slight differences in physical growth and other forms of behavioral and intellectual development may be found in children as old as 11 years of age.
6. Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke produce deleterious effects, the specific etiologic agents and their mechanisms of action for adverse effects on pregnancy are not clearly determined. Thus, the relative importance of "tar" and nicotine, or carbon monoxide and other constituents of tobacco smoke in the etiology of adverse gestational and fetal events is not known.

Behavioral Aspects

1. Nicotine appears to be the primary pharmacological reinforcer in tobacco, but other pharmacological and psychosocial factors may also contribute a reinforcing effect.
2. It appears that some smokers make compensatory adjustments in their smoking behavior with cigarettes of different yields that might increase the amounts of harmful substances entering the body. The frequency and amount of spontaneous compensatory changes in smoking style with different cigarettes require further investigation.
3. Additional information is needed on the role of lower "tar" and nicotine cigarettes in the initiation, maintenance, and cessation of smoking.
4. Rigorous comparative behavioral studies involving animals are needed to provide comprehensive, experimentally valid results on behavioral aspects of smoking.
5. Laboratory techniques developed for study of opioids and alcohol should be adapted for studies of tolerance and dependence on nicotine.
6. Improved laboratory facilities are necessary for more tightly controlled behavioral research. A particular need exists for clinically acceptable cigarettes with standardized ingredients.
7. Smoking-machine measurements that more closely simulate the practices of human smokers must be developed.

Lower "Tar" and Nicotine Cigarettes: Product Choice and Use

1. Public awareness of the dangers of smoking has steadily increased since 1965. In 1978, more than 90 percent of all Americans believed cigarette smoking to be hazardous to health.

2. Cigarette product choice has shifted dramatically since the 1950s. In 1979, 91.7 percent of U.S. smokers used filter-tipped cigarettes, compared with 1.4 percent in the early 1950s.
3. Lower "tar" cigarettes conventionally have been defined as yielding 15 mg of "tar" or less per cigarette. The proportion of all cigarettes consumed in the United States that are lower "tar" has increased from 3.6 percent in 1970 to almost 50 percent in 1979. In 1979, 58.5 percent of all cigarette brands marketed in the United States yielded 15 or fewer mg of "tar."
4. Since 1968, the "tar" content of the "average cigarette" in the United States has declined by 32.2 percent, and nicotine content has fallen by 25.6 percent. These declines may be partially accounted for by lower tobacco weight per cigarette—down 23.8 percent from 1968 to 1978—and by the greater length of the filter and overwrap of the average cigarette, which could result in a declining number of machine puffs per cigarette.
5. The prevalence of smoking in the U.S. adult and adolescent populations has continued to decline. In 1979, 32.5 percent of the adult population smoked cigarettes (36.1 percent of men and 29.4 percent of women). However, evidence suggests that the average daily number of cigarettes consumed by those adults who continue to smoke has increased over several decades. The availability and use of lower "tar" cigarettes have increased over recent years.
6. In 1979, 33.3 percent of adult regular smokers used cigarettes yielding 15 mg "tar" or less. Studies show that women smokers are more likely to use lower yield cigarettes than men are, and white smokers use lower yield cigarettes in greater proportions than do blacks. Smokers of higher income and education also select lower yield cigarettes in a higher percent of cases.
7. A large national survey found that smokers in older aged cohorts choose both the lowest and highest yield cigarettes in higher proportions than do younger cohorts.
8. Although black smokers choose cigarettes of higher "tar" and nicotine in greater proportions than do whites, the lower daily number of cigarettes smoked by blacks suggests that their average daily intake of "tar" and nicotine may be lower than that of white smokers.
9. In 1979, 33.5 percent of adolescent smokers (age 12 to 18) used lower "tar" cigarettes, compared with 6.7 percent in 1974. Boys and girls smoke cigarettes of about the same level of "tar" content.
10. Adult smokers started smoking regularly at the average age of 18 years. One survey showed that the higher the "tar" level of the cigarette currently smoked, the younger the reported age of beginning smoking.

11. Evidence from a large national survey does not support a correlation between a greater mean number of cigarettes smoked per day by users of lower "tar" and nicotine cigarettes than by higher "tar" users.
12. In a national survey, smokers of lower "tar" and nicotine cigarettes more frequently reported having attempted to quit at least once, and among these smokers, a higher proportion report having attempted unsuccessfully to quit multiple times. The applicability of these data to defining the role of "tar" or nicotine yields of cigarettes in quitting behavior is not clear in the absence of more detailed longitudinal data.
13. Although a greater proportion of unsuccessful quitters reported smoking the lowest "tar" and nicotine products than did recent successful quitters in one large survey, interpretation of these data is made difficult by the noncomparability of brand reported (i.e., unsuccessful quitters reported the brand smoked after an attempt, successful quitters reported the brand smoked prior to the attempt).
14. In a large national survey, the mean duration of the latest unsuccessful attempt to quit shows no clear relationship to "tar" or nicotine yields.

Research Recommendations From the Working Meeting "Research Needs on Low-Yield Cigarettes"

The following list is an overview of research recommendations submitted as a result of the working group reports from the June 1980 conference "Working Meeting: Research Needs on Low-Yield Cigarettes." No attempt has been made to place them in order of priority.

- It must be determined whether lower "tar" and nicotine cigarettes change smoking behavior. For instance, compensatory adjustment, such as deeper, longer, and more frequent puffs, may turn a nominally lower yield cigarette into a higher yield cigarette. Studies are needed to determine whether adjustments made by smokers of lower "tar" and nicotine cigarettes may inadvertently increase their exposure to "tar" and carbon monoxide beyond that expected from a less intensively smoked higher yield cigarette.
- Because of changes in cigarette composition, further retrospective and prospective epidemiologic studies are needed to assess the health effects of these changes. A primary need is to establish whether there are measurable differences in morbidity between smokers of higher "tar" and nicotine cigarettes and smokers of lower "tar" and nicotine cigarettes. Efforts should include ongoing long-term studies that are adaptable to such epidemiologic inquiry.

- The increased use of nonhuman primate models might permit comparison of the effects of lower "tar" and nicotine cigarettes with those of higher "tar" and nicotine cigarettes under controlled conditions.
- More indepth studies on the mechanisms of cardiovascular and pulmonary disease are needed to assess new brands of lower "tar" and nicotine cigarettes. With improved noninvasive techniques, scientists will be better able to determine how a particular cigarette affects cardiac function and other physiological activities. Genetic markers should be explored as a possible method of identifying high-risk groups who are more likely to develop tobacco-related diseases if they smoke.
- Additional emphasis should be given to both human and animal research models for the developmental mechanism of chronic obstructive pulmonary disease and its possible alteration by lower "tar" and nicotine cigarettes. The elastase-inhibitor imbalance hypothesis of emphysema pathogenesis needs confirmation for human disease. Recently developed tests that measure lung elastin degradation products in plasma and urine need rapid clinical evaluation.
- Emphasis should be placed on studies that determine the character and magnitude of the health hazards that lower "tar" and nicotine cigarettes pose for pregnant women and their offspring. Specifically, the smoking habits of pregnant women should be analyzed in prospective epidemiologic studies to determine the effect of varying cigarettes on the course and outcome of pregnancy. Careful laboratory measurements of various physical capacities and functions of newborn infants and pregnant women should be performed in case-control and prospective studies to determine the influence of smoking on pregnancy outcome. Clinical and experimental studies using animals should be conducted to evaluate the effect of individual constituents of cigarette smoke on tissues and physical responses. Direct intervention strategies should be aimed at pregnant adolescents who smoke.
- Another research need is routine, frequent surveillance of current and future lower "tar" and nicotine cigarettes for specific chemical constituents and biological activity. In addition to "tar," nicotine, and carbon monoxide yield, new types of cigarettes should be monitored regularly for delivery of other potentially harmful constituents, such as benzo[a]pyrene, phenols, catechols, nitrosamines, nitrogen oxides, volatile aldehydes, and radionuclides. More frequently updated ratings of "tar," nicotine, and carbon monoxide content would permit more accurate studies on the potential impact of cigarette components on health.

- More data are also needed on cigarette flavor additives and their combustion products. Flavoring agents and additives should be studied by cigarette companies for carcinogenicity and toxicity before their commercial use is permitted, and the results of such studies should be made available.
- Research should be done on the distribution, partitioning, and penetration of lower "tar" and nicotine cigarette smoke in the lung, with consideration of potential changes in smoking patterns by those who smoke lower "tar" and nicotine cigarettes. Cigarette smoking-machines currently in use and the techniques by which animals inhale cigarette smoke in research models may not be representative of the human situation because human smokers are able to take larger, more frequent, and higher velocity puffs. To conduct meaningful assays of cigarette yields and the biological activity of cigarette smoke, it must be determined how smokers actually smoke various types of commercial cigarettes. When this information is available, it will be possible to design smoking-machines that yield more accurate estimates of human risk.
- Controlled studies are needed to determine the role of nicotine as a primary reinforcer in cigarette smoking and to determine whether there are other chemicals in addition to nicotine that may contribute to or reinforce the smoking habit. By analyzing the mechanisms whereby nicotine reinforces smoking behavior, it may be possible to design more efficacious methods of smoking cessation.
- Research should be conducted to define what effects modifications of the physical and chemical properties of leaf tobaccos have on the pharmacology of cigarette smoke. Since tobacco culturing and curing practices are continually changing, it is important to determine whether such changes as the use of new pesticides also alter the composition and biological activity of cigarette smoke.
- Standardized experimental cigarettes have frequently proved unpalatable and unacceptable for behavioral research. Prototype cigarettes should be especially designed to deliver a wide range of constituent concentrations, particularly those that approximate commercial cigarettes. This would allow researchers to predict the behavior of smokers of new types of cigarettes more accurately.

Section 2. PHARMACOLOGY AND TOXICOLOGY

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Introduction

Tobacco and tobacco smoke are very complex mixtures. In 1968, Stedman (*155*) reported that they contained more than 1,200 clearly identified substances in addition to a number of polymer classes, such as pigments, resins, and proteins, that were not resolved into specific compounds. Since that time, many additional compounds have been isolated; at least a thousand additional constituents were found in tobacco and tobacco smoke in the following 10 years (*67*). Cigarette smoke components arise through distillation of volatile and semivolatile materials from the leaf and from the pyrolytic decomposition of leaf constituents. In addition, nonvolatile components of tobacco leaf can be transferred to the smoke without degradation. Thus, the components of smoke are very diverse. Many suspected or proved toxic agents have been identified in the gas phase (Table 1) or in the particulate matter (Table 2) of smoke (*190*). It is not surprising that chronic exposure to such a complex mixture will lead to a variety of pharmacologic and toxicologic responses.

TABLE 1.—Major toxic agents in the gas phase of cigarette smoke (unaged)*

Agent	Biologic activity[a]	Concentration/cigarette	
		Range reported	U.S. cigarettes[b]
Dimethylnitrosamine	C	1–200 ng	13 ng
Ethylmethylnitrosamine	C	0.1–10 ng	1.8 ng
Diethylnitrosamine	C	0–10 ng	1.5 ng
Nitrosopyrrolidine	C	2–42 ng	11 ng
Other nitrosamines (4 compounds)	C	0–20 ng	?
Hydrazine	C	24–43 ng	32 ng
Vinyl chloride	C	1–16 ng	12 ng
Urethane	TI	10–35 ng	30 ng
Formaldehyde	CT, CoC	20–90 μg	30 μg
Hydrogen cyanide	CT, T	30–200 μg	110 μg
Acrolein	CT	25–140 μg	70 μg
Acetaldehyde	CT	18–1,400 μg	800 μg
Nitrogen oxides (NO_x)[c]	T	10–600 μg	350 μg
Ammonia	T ?[d]	10–150 μg	60 μg
Pyridine	T ?[d]	9–93 μg	10 μg
Carbon monoxide	T	2–20 mg	17 mg

*Cigarettes may also contain such carcinogens as arsine, nickel carbonyl, and possibly volatile chlorinated olefins and nitro-olefins.

[a] C denotes carcinogen; TI, tumor initiator; CoC, cocarcinogen; CT, cilia toxic agent; and T, toxic agent.

[b] 85 mm cigarettes without filter tips bought on the open market 1973–1976.

[c] NO_x >95% NO; rest NO_2.

[d] Not toxic in smoke of blended U.S. cigarettes because pH <6.5, and therefore ammonia and pyridines are present only in protonated form.

SOURCE: Wynder and Hoffmann (*190*).

TABLE 2.—Major toxic agents in the particulate matter of cigarette smoke (unaged)*

Agent	Biologic activity[a]	Concentration/cigarette	
		Range reported	US cigarettes[b]
Benzo[a]pyrene	TI	8–50 ng	20 ng
5-Methylchrysene	TI	0.5–2 ng	0.6 ng
Benzo[j]fluoranthene	TI	5–40 ng	10 ng
Benz[a]anthracene	TI	5–80 ng	40 ng
Other polynuclear aromatic hydrocarbons (>20 compounds)	TI	?	?
Dibenz[a,j]acridine	TI	3–10 ng	8 ng
Dibenz[a,h]acridine	TI	?	?
Dibenzo[c,g]carbazole	TI	0.7 ng	0.7 ng
Pyrene	CoC	50–200 ng	150 ng
Fluoranthene	CoC	50–250 ng	170 ng
Benzo[g,h,i]perylene	CoC	10–60 ng	30 ng
Other polynuclear aromatic hydrocarbons (>10 compounds)	CoC	?	?
Naphthalenes	CoC	1–10 μg	6 μg
1-Methylindoles	CoC	0.3–0.9 μg	0.8 μg
9-Methylcarbazoles	CoC	0.005–0.2 μg	0.1 μg
Other neutral compounds	CoC	?	?
Catechol	CoC	40–460 μg	270 μg
3- & 4-Methylcatechols	CoC	30–40 μg	32 μg
Other catechols (>4 compounds)	CoC	?	?
Unknown phenols and acids	CoC	?	?
N'-Nitrosonornicotine	C	100–250 ng	250 ng
Other nonvolatile nitrosamines	C	?	?
β-Naphthylamine	BC	0–25 ng	20 ng
Other aromatic amines	BC	?	?
Unknown nitro compounds	BC	?	?
Polonium-210	C	0.03–1.3 pCi	?
Nickel compounds	C	10–600 ng	?
Cadmium compounds	C	9–70 ng	?
Arsenic	C	1–25 μg	?
Nicotine	T	0.1–2.0 mg	1.5 mg
Minor tobacco alkaloids	T	0.01–0.2 mg	0.1 mg
Phenol	CT	10–200 μg	85 μg
Cresols (3 compounds)	CT	10–150 μg	70 μg

* Incomplete list.

[a] C denotes carcinogen; BC, bladder carcinogen; TI, tumor initiator; CoC, cocarcinogen; CT, cilia toxic agent; and T, toxic agent.

[b] 85 mm cigarettes without filter tips bought on the open market 1973-1976.

SOURCE: Wynder and Hoffmann (*190*).

Experimental Systems for Assay of Relative Risks of Cigarette Smoking

Lung Cancer

Animal Models

The mouse skin carcinogenesis assay is thus far the most fruitful method of evaluating smoke condensates from different types of cigarettes for carcinogenic potency for the human lung (*46, 51, 89, 106*).

This model for the development of cancer dates back to 1915 (*191*). A large body of laboratory experience has provided consistent evidence for the quantitative validity of this relationship. Procedures providing good dose-response relationships are in use in many laboratories. Assays can be standardized to give relatively consistent results within a laboratory, and probably among laboratories (*62, 63, 64, 65*).

The assay depends on a number of similarities between the laboratory model and human experience. The epithelium of both the skin and lung is directly exposed to the presumptive carcinogenic agent—in this case, cigarette smoke or cigarette smoke condensate. Rabbit and mouse skin develop tumors after exposure to coal tar, a known occupational carcinogen. Mouse skin assays have predicted occupational induction of human lung cancer by bis-chloromethyl ether (*148, 177*).

It is conceivable that the mouse skin carcinogenesis assay may give a misleading measure of the relative risk of various types of cigarettes. Skin is covered with a lipid film, and the pilo-sebaceous apparatus is particularly suited for penetration of lipid materials into the skin. In contrast, the airway surface is covered by an aqueous film and might be less readily penetrated by fat-soluble materials. There is no evidence, however, that such a difference is important. Indeed, the response of mouse skin to different types of experimental cigarettes is roughly parallel to the response of hamster larynx to the same materials (*49, 50, 189*).

The hamster larynx has been used for comparative studies of different types of cigarettes (*17, 50, 52*). Invasive carcinomas of the larynx were induced in 37 percent of inbred hamsters exposed to cigarette smoke for 59 to 80 weeks. Both the cancer incidence and the incidence of other epithelial changes were dose related. Exposure of rats and mice to cigarette smoke for up to 2½ years resulted in a small incidence of respiratory tract tumors, primarily pulmonary adenomas (*44, 68, 72*). Cigarette smoke produced changes in cultured human gastric epithelial cells suggestive of malignancy (*158*).

Lung Carcinogens in Cigarette Smoke

Experience in man and with the mouse skin system indicates that two or more distinct classes of carcinogenic stimuli lead to the occurrence of tumors (*16, 26, 48*). Tumor initiators appear to alter the genetic constitution of the cell; tumor promoters accelerate and enhance the neoplastic expression of previously initiated cells. Both may play a role in the induction of tumors. Other types of cocarcinogens may also play a role in the induction of mouse skin tumors by cigarette smoke condensate (*16, 74, 89, 176*). If similar mechanisms act in man, it may not be possible to differentiate between a human carcinogen in the conventional sense and a cocarcinogen or tumor

promoter acting on a diverse population already exposed to low levels of a variety of tumor initiators.

Two prominent classes of tumor initiators are found in smoke condensates of commercial cigarettes—polycyclic aromatic hydrocarbons (PAH) and tobacco-specific nitrosamines (TSNA). Other carcinogens or tumor initiators are present in cigarette smoke as well; however, they appear to be less significant because they either are less potent or are present at lower concentrations than are PAH or TSNA.

Polycyclic Aromatic Hydrocarbons

A large variety of PAH molecules are formed by the pyrolytic process during combustion of the cigarette (*87, 105*). Of the PAHs, benzo[a]pyrene (BaP) is the most prominent and has been studied most intensively. Chemical assays for BaP in smoke condensates are well established, and it has been suggested that such assays can serve as indicators of production of all of the PAHs. This appears to be generally true. Among smoke condensates from 98 experimental cigarettes, the correlation coefficient between BaP and benz[a]anthracene content was 0.78 (*15*). Although highly significant, the value is sufficiently low to indicate that real differences do exist in the ratios of these cyclic molecules in the various cigarette smokes. Nevertheless, BaP appears to be the most important single member of this class of compounds, taking into consideration both its concentration and its relative carcinogenic potency.

The contribution of BaP or PAH in general to mouse skin carcinogenesis by cigarette smoke condensate cannot be fully measured at this time. Wynder and Hoffmann (*188*) found a correlation between BaP levels and carcinogenic activity of smoke condensates from several types of cigarettes. A much larger series of experimental cigarettes was studied in the smoking and health program of the National Cancer Institute. No significant dependence of carcinogenic potency on BaP content was observed (*62, 63, 64, 65*). The relationship between chemical composition of the experimental smoke condensates and the biological activity of this series was examined extensively by Bayne (*15*). He employed the linear terms, squared terms, and all interaction terms between any 2 of 10 independent variables. Starting with a 66-term regression equation, he searched for simpler prediction models that would provide useful estimates of carcinogenic activity. The simplest model (Table 3) that retained good predictability contained nine terms. The interaction of BaP with the nicotine term was one that appeared important.

BaP and other tumor initiators are particularly important because humans are already exposed to a number of initiators in the environment. The effect of initiators is cumulative and irreversible. Hence, any additional exposure to initiators such as the PAH might be expected to increase tumor incidence in smokers.

TABLE 3.—Coefficients and standard deviations of coefficients for Prediction Model 10

Terms[a]	Coefficients	Standard deviation of coefficients
1 Intercept	2.637	0.292
2 C	-3.793 E-2	0.274 E-2
3 C^2	4.688 E-4	0.408 E-4
4 pH	-4.434 E-1	0.980 E-1
5 VWA	1.242 E-1	0.555 E-1
6 N x N	2.450 E-5	0.588 E-5
7 pH x pH	3.663 E-2	0.875 E-2
8 N x pH	-7.078 E-4	1.664 E-4
9 N x BAP	-1.770 E-3	0.377 E-3

[a]C = Concentration (mg/day); VWA = very weak acids (mg/g); N = nicotine (mg/g); and BAP = benso[a]pyrene (μg/g).
SOURCE: Bayne (*15*).

Tobacco-Specific N-Nitrosamines

During tobacco curing, fermentation, and burning, nornicotine gives rise to N′-nitrosonornicotine (NNN), nicotine to NNN and to 4-(N-methyl-N-nitrosamino)-1-(3-pyridil)-1-butanone (NNK), and anatabine to N′-nitrosoanatabine (NAT). NNN is a moderately active carcinogen, inducing tumors in the respiratory tract of mice, rats, and hamsters. NNK is a strong carcinogen, inducing lung carcinoma in each of the three animal species (*75, 84, 86*). The concentration of these carcinogens in cigarette smoke is very high in comparison with usual environmental exposures, being 1 to 85 ppm in tobacco and 1 to 9 μg in the smoke of a cigarette (*57*). These tobacco-specific N-nitrosamines may play a role in the development of several types of human cancer. NNN is metabolically activated by human liver microsomes (*76*) and, together with NNK and NAT, may be formed *in vivo* from the tobacco alkaloids.

Other Mutagenic or Co-mutagenic Agents

It is generally believed that tumor initiators are mutagens that can be detected by one or more short-term biological assays (*2, 103*). A number of fractions of cigarette smoke condensate are positive in the Ames assay system (*93, 101*). The agents responsible for this activity have not been fully identified, but probably include products of protein pyrolysis (*119*). Ames test activity, however, does not predict the activity of fractions in the mouse skin carcinogenesis assay. Fractions of smoke condensate that show activity as complete carcinogens (*89*) or in a promotion assay that would detect skin carcinogens as well as tumor promoters (*24*) are not correspondingly active in the Ames system (Table 4). It cannot be determined whether the unidentified mutagens in cigarette smoke are an important cause of lung cancer in

TABLE 4.—Comparison of mutagenic and tumor-promoting activity of fractions of cigarette smoke condensate

Sample	Mutagenic activity— as a percentage of whole condensate (Kier et al. (*101*))	Promoting activity*— tumor yield as a percentage of that seen with whole condensate (Bock et al. (*24*))
Whole condensate	100	100
Reconstituted	89	115
Bases before, insoluble	21	4
Bases after, insoluble	26	11
Bases, ether soluble	11	4
Bases, water soluble	1	2
Weak acids, insoluble	30	3
Weak acids, ether soluble	5	80
Strong acids, insoluble	2	1
Strong acids, ether soluble	<1	3
Strong acids, water soluble	<2	3
Neutrals, 80% methanol soluble	2	7
Neutrals, cyclohexane soluble	≤1	13
Neutrals, nitromethane soluble	2	28

*From tests of fractions, equivalent to 30% condensate.

humans; however, added exposure to any tumor initiators probably carries an incremental risk of cancer.

Weak Acids

Cigarette smoke contains weak organic acids that exhibit tumor-promoting or cocarcinogenic activity (*24, 74, 176*). The concentration of very weak acids in cigarette smoke condensates was one of the terms predictive of the skin carcinogenic activity of smoke condensates (Table 3). Of the weak acids, catechol appears to be the most important on the basis of concentration and activity (*74, 176*).

It is probable that the weakly acidic constituents of smoke act as tumor promoters or cocarcinogens rather than as tumor initiators. This is true for phenols and for catechol (*27, 176*). There is no reason to believe that tumor promoters or other types of cocarcinogens exhibit either a cumulative or an irreversible effect. Indeed, for tumor promotion in mouse skin by croton oil, clear thresholds for frequency of application and for the amount of promoter in each applied dose are apparent (*26*). If this is also true for man, the risk of very small doses of weak acids might be negligible. Phenol (*126, 188*), but not catechol (*29*), can be selectively removed by filters. The extent to which the cocarcinogenic weak acids are reduced by selective filtration cannot be determined at this time.

Nicotine

Nicotine exhibits neither complete carcinogenic activity nor tumor-promoting activity. The nicotine content of cigarette smoke condensate did not affect its carcinogenic activity when suspended in beeswax-tricaprylin pellets implanted in rat lungs (*43*); however, in mouse skin bioassays, this alkaloid is an important cocarcinogen (*20*). Not only is nicotine active in models with other compounds such as BaP and 12-O-tetradecanoylphorbol-13-acetate (TPA), but also the measured carcinogenic potency of cigarette smoke condensates appears to depend on the nicotine content of the "tar." Of all of the individual compounds of smoke condensates assayed in the smoking and health program of the National Cancer Institute, nicotine was most closely related to carcinogenic activity (*62, 63, 64, 65*). In the simplest predictive model developed by Bayne, every term but one involved nicotine concentration, pH, or the concentration of crude condensate (Table 3). The availability of nicotine to the tissues depends on the pH and concentration of condensate. Hence, available nicotine was a factor of all but one term of the prediction model.

Nicotine may also play a role in the development of oral cancer in tobacco chewers. Aqueous extracts or unburned tobacco exhibit tumor-promoting activity when tested on mouse skin. This activity depends on the presence of nicotine acting together with a fraction having a molecular weight greater than 13,000 daltons (*21*). In addition, nicotine gives rise to carcinogenic N-nitrosamines during tobacco chewing (*84*).

Data of Morosco and Goeringer (*122*) suggest that nicotine reduced serum $alpha_1$-antitrypsin activity and elevated pancreatic elastase levels in dogs exposed to cigarette smoke. These workers believe that interference with the protease–protease inhibitor balance may be a factor in carcinogenesis (*123*).

It must be pointed out that the relationship between carcinogenic activity of smoke condensates and their nicotine contents may be caused in part by the conversion of nicotine to tobacco-specific nitrosamines or to the co-occurrence of nicotine and some other unidentified carcinogen. For example, the nicotine level of tobacco is dependent on the amount of nitrate fertilizer used in tobacco culture (*166*). High levels of tobacco-specific nitrosamines were found in the unburned tobaccos usually raised with high levels of nitrogen fertilizer (*77*). The level of volatile nitrosamines in cigarette smoke also depends on nitrate fertilizer (*170*). One may postulate that the nicotine level of cigarette smoke condensates is an indicator of such nitrogenous carcinogens that were not measured directly. At present, however, there is no direct evidence that this is the case. In any event, the carcinogenic activity of mixtures of pure BaP and TPA are enhanced by the concomitant application of nicotine under conditions such that nitrosamine formation would not be expected (*20*).

Whether the cocarcinogenic effects of nicotine are important for man is a matter of speculation. Tumor-promoting activity of croton oil exhibits a threshold both for frequency of application and for the quantity of agent present with any given treatment (*26*). The animal studies in which nicotine acts as a cocarcinogen employ nearly lethal levels of nicotine administered once or twice a day. In contrast, smokers are exposed to a large number of low doses of nicotine daily. If a threshold amount of nicotine per dose is required for cocarcinogenic activity, human smokers may not be affected in a manner similar to that of the mouse skin system.

Polonium 210

There have been repeated suggestions that ^{210}Po might contribute to the carcinogenic activity of cigarette smoke in man (*137*). Polonium levels in tobacco result primarily from the use of phosphate fertilizers that are contaminated with radium decay products, particularly ^{210}Pb, a precursor of ^{210}Po (*162, 168*). Very little ^{210}Po is found in tobacco leaf, but some is transferred to the smoke. Yields of 10 to 15 fCi of alpha emitters were recently reported for experimental cigarettes and 490 fCi/gm for commercial cigarette smoke condensate (*36*). Most of the radioactivity was due to insoluble forms of ^{210}Po. Cancer may arise from a single affected cell. It has been suggested that small amounts of insoluble ^{210}Po concentrated in small areas might deliver an effective carcinogenic dose to a target cell (*112*). Harley et al. (*71*), however, found very few "hot spots" in the lungs of deceased smokers. Based on human experience with radon daughters, they assumed a lifetime risk of lung cancer of 1×10^{-2} for a dose of one rad/year. At most, the radioactivity they detected was estimated to explain only 10 percent of the lung cancers suffered by cigarette smokers. They consider polonium 210 a questionable risk factor in human carcinogenesis.

Polonium 210 contamination of tobacco can be effectively reduced by selection of plant types and sources of phosphate fertilizer, and by removal using chelating agents (*71, 171*).

Volatile N-Nitrosamines

Tobacco smoke contains a number of secondary and tertiary amines. These amines, together with nitrogen oxides, may give rise to the *in vivo* formation of nitrosamines. Although the formation of most nitrosamines is favored at low pH (*110*), a small amount of volatile nitrosamines is found in cigarette smoke and may be formed in the lungs under normal conditions (*30, 84, 170*). The volatile N-nitrosamines are organ-specific carcinogens, which in mice give rise to tumors of the liver and kidney. At present, there is no reason to assume that volatile nitrosamines cause lung cancer in smokers. Nevertheless, it is prudent to limit the presence of any carcinogen in cigarette smoke.

Volatile nitrosamines in smoke can be reduced by selective filtration and by limiting the nitrate content of tobaccos (*30, 121*).

Bladder Cancer

The induction of bladder cancer in animals has been studied intensively over the past several decades. The bladder appears to be a particularly sensitive target for agents that are metabolized in the liver and excreted in the urine. Among the compounds known to produce bladder cancer in both man and animals is β-naphthylamine. The presence of β-naphthylamine in cigarette smoke has been demonstrated (*85*), along with other carcinogenic aromatic amines (*129*). The yield was so low, however, that they did not believe these agents contributed significantly to the risk of bladder cancer in smokers.

The urine of 10 smokers and 21 nonsmokers was examined by Yamasaki and Ames (*192*) for mutagens or for substances that were converted to mutagens by rat liver microsomes. Increased levels of mutagens were found in the urine of seven smokers, but in none of the nonsmokers. If promutagens in urine are responsible for the bladder cancers occurring in cigarette smokers, it is possible that certain individuals are particularly sensitive to bladder carcinogenesis by cigarette smoke. If true, this sensitivity may be exploited for disease prevention. Large quantities of mutagen-containing urine can be collected from sensitive individuals. Isolation and identification of the promutagens might permit removal of the precursors from cigarette smoke.

Laryngeal Cancer

Hamsters develop laryngeal cancer after long-term inhalation of diluted cigarette smoke (*17, 50, 52*). The effect is dose related and has been used to compare different cigarettes. Tobacco-specific nitrosamines induce cancer in the trachea and lungs of hamsters and may be of particular importance in the induction of human cancer of the larynx (*84*). Other carcinogens and cocarcinogens of cigarette smoke that are active in the mouse skin bioassay system may also contribute to induction of laryngeal cancer. Both organ systems involve epithelial tissue directly exposed to the carcinogenic mixture.

Other Cancers

Cigarette smoking is also associated with cancer of the kidney, pancreas, oral cavity, and esophagus (*173*). No animal model of these cancers has been developed to the point where it could be used for quantitative comparisons of different types of cigarettes. Oral cavity and esophageal tumors may be induced by direct exposure to smoke carcinogens. NNN, when given in the drinking water of rats, induces cancer of the esophagus (*84*). This finding suggests that tobacco-

specific nitrosamines may be active as "contact" carcinogens. Alternatively, the carcinogens might be produced through metabolism at distant sites, such as the liver, and then transported to the target site, where they can be further activated. Pancreatic cancer was induced in hamsters with diisopropylnitrosamine (*134*). This observation suggests the possibility of a similar action of smoke nitrosamines. Any carcinogen in cigarette smoke might contribute to induction of cancer distant from the exposure site. To this extent, elimination of the carcinogens causing lung cancer or bladder cancer would reduce the induction of cancer in other organs as well.

Alcohol usage and cigarette smoking show synergistic effects in the induction of cancer in the upper digestive tract (*113, 172*). The effect of alcohol in this circumstance may result from the induction of microsomal enzymes, which are believed to metabolize carcinogens to their active forms (*113*).

Early End Points Suggestive of Carcinogenic Potential

It is generally considered that the induction of cancer requires a specific genotoxic event that may be preceded or followed by ill-defined and less specific epigenetic changes that enhance the manifestation of the genetic event (*182*). In the two-stage carcinogenesis system of mouse skin, the first step—initiation—appears to be genotoxic, and the second step—promotion—appears to be epigenetic. Several other forms of cocarcinogenesis have been described (*16*). Tobacco smoke owes its carcinogenic activity to several carcinogens and cocarcinogens (*24, 87, 176, 188*).

Agents capable of producing genetic change can often be detected by mutagenesis assay systems (*2*). Most carcinogens are mutagens. Conversely, agents capable of inducing mutations are suspect as possible carcinogens. Cigarette smoke condensates and some of their fractions are mutagenic in the Ames salmonella assay systems (*93, 119*). These fractions are clearly of interest because they possess the capability of inducing genetic changes that might lead to tumor formation. Mutagenesis assays may provide a basis for the quantitative comparisons of new cigarettes when the relative importance of the genetic and epigenetic factors in smoke-induced cancer is understood. The Ames test gives poor results for fractions of smoke condensate that appear to be most active in systems designed to detect tumor-promoting activity (Table 4). Furthermore, mutagenesis assays of a series of experimental cigarettes have not provided consistent results (*167*). The complexity of carcinogenesis by tobacco smoke condensates renders mutagenesis assays of uncertain value for quantitative comparisons of relative carcinogenicity.

Several *in vitro* systems measure the transformation of normal cells into malignant cells after exposure to carcinogens. These systems are sensitive to both genetic and epigenetic processes (*90, 186*). Such assays

may prove to be useful short-term indicators of the relative potency of different types of cigarette smoke. The toxicity of most experimental smoke condensates may interfere with the conduct of such studies, however. Experimental cigarettes that yield smoke condensates with a wide range of carcinogenic activity are now available. It should be possible to determine the usefulness of *in vitro* systems with this material. For organ-specific carcinogens, the DNA repair test is a good predictor of relative carcinogenic activity (*186*).

Most chemicals that are carcinogenic to mouse skin selectively destroy the sebaceous glands of the treated skin (*23*). The sebaceous gland suppression assay is a good predictor of the activity of experimental smoke condensates as carcinogens in mouse skin (*22*).

Chronic Obstructive Lung Disease

No animal models for chronic obstructive lung disease are available to measure the potency of smoke from various types of cigarettes. Long-term inhalation studies with hamsters, dogs, and primates have not given rise to disease states comparable to emphysema observed in humans (*17, 50, 52, 114*). In two experiments, Sprague-Dawley and CD rats exposed to cigarette smoke for 6 to 26 months developed emphysematous changes (*104, 124*). Similar results were not reported in other long-term studies with rats (*44, 68*).

A number of pulmonary function tests have been evaluated as measures of early lung disease in man (*31, 61, 73, 100, 135, 154*). Thus far, similar tests have not proved useful as animal assays. They might, however, be useful in comparing the effects of different types of cigarettes on human smokers. Exposure of CD rats to whole tobacco smoke for 6 months led to a loss of lung parenchymal tissue distal to the terminal airways (*124*). This was indicated by a 21 percent decrease in parenchymal tissue and 12 percent decrease in alveolar surface area.

Recent evidence suggests that emphysema results from a shift in the balance of elastase production and elastase inhibition in the lung (*97*). A few individuals with genetically determined very low levels of $alpha_1$-antitrypsin, an elastase inhibitor, are particularly prone to develop the disease (*53*). When purified elastase is instilled into the lungs of dogs, emphysematous changes appear in as little as 90 minutes (*96, 98*).

Cigarette smoke can act on this system in two ways. *In vitro* tests with cigarette smoke condensate show that this material suppressed the antiprotease activity of human serum, pulmonary lavage fluid, and purified human $alpha_1$-antitrypsin (*94*). The suppression of protease inhibitors by cigarette smoke is blocked by the presence of phenolic antioxidants, suggesting that oxidants or free radicals of the smoke were responsible for the effect (*107*). In one study, the serum levels of $alpha_1$-antitrypsin in smokers were higher than in nonsmokers (*76*). Another study found, however, that immediately after smoking, serum

alpha$_1$-antitrypsin *activity* was reduced in smokers (*95*). Likewise, the activity of alpha$_1$-antitrypsin in lung lavage fluid from Sprague-Dawley rats was reduced by 30 to 40 percent after 3 to 6 puffs of cigarette smoke. Similar reductions were observed in lavage fluid from the lower respiratory tract of asymptomatic smokers (*58*). Even greater differences were seen between smokers and nonsmokers with idiopathic pulmonary fibrosis. Cigarette smoke also stimulates the release of elastase from macrophages *in vitro* and *in vivo* and from polymorphonuclear leukocytes *in vitro* (*19, 143, 185*). Thus, smoke may increase the elaboration of elastase in the lung and at the same time suppress its inactivation. The techniques used in these studies could be applied to smoke from various types of cigarettes; they might then serve as short-term end points to evaluate relative cigarette risk.

Dogs exposed to cigarette smoke through tracheostomies for 600 days had significantly higher levels of pancreatic elastase than sham-smoked controls (*122*). The greatest effects were seen in animals exposed to higher nicotine cigarettes, although the blood carboxyhemoglobin levels were the same for both higher and lower nicotine smokers (Figure 1). The lower nicotine cigarettes in this study were produced by removal of the alkaloid by a commercial process (*65*). It cannot be stated with confidence that other constituents were not removed as well.

Sudden Death Due to Cardiovascular Disease

Animal Models

No animal model permitting the quantitative comparison of death rates due to cardiovascular disease induced by different types of cigarettes is presently available. Long-term inhalation studies using smoke-exposed rats, hamsters, dogs, and primates have been conducted (*17, 44, 50, 52, 68, 104, 114*). None has provided an end point comparable to sudden death observed in human smokers. There are, however, several avenues of investigation whose intermediate experimental observations might indicate a mechanism for mortality caused by cardiovascular effects. Much attention has been given to changes induced by nicotine-induced catecholamine release (*138, 156, 160*). Methods to follow these effects in animals are well established. Other short-term end points being studied include lipoprotein levels (*79*), alteration of arterial morphology (*9, 10, 32, 111*), and changes in arachidonic acid metabolism (*12, 82*). These procedures might be adapted for estimation of the relative potency of various types of cigarettes, but there is no direct evidence that any of these changes are either necessary or sufficient indicators of the risk of sudden death due to heart disease.

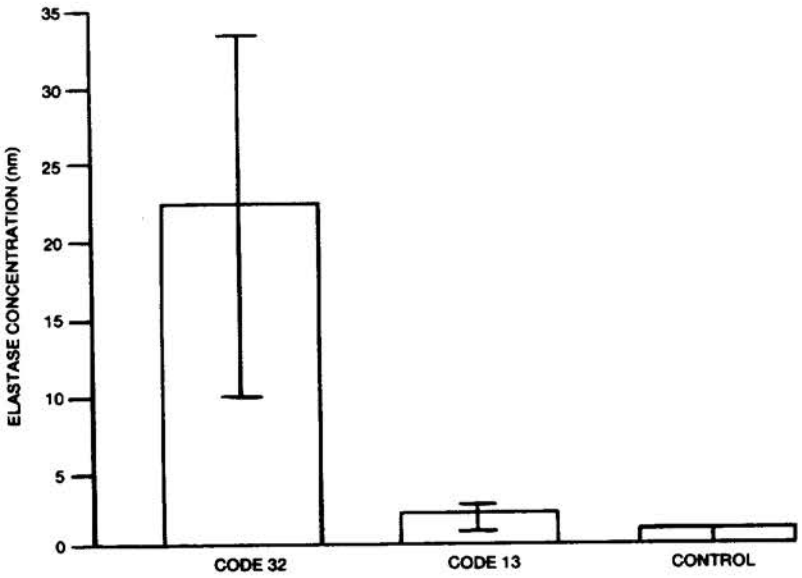

FIGURE 1.—Effect of cigarette smoke differing in selected chemical components on pancreatic elastase levels in beagle dogs after a 600-day exposure protocol of 12 cigarettes per day, 7 days per week. Bars indicate mean ±SD. Animals exposed to code 32 (high-nicotine) and code 13 (low-nicotine) cigarettes differed significantly ($p<0.05$) in pancreatic elastase levels from corresponding sham-exposed controls. Significant differences were also observed ($p<0.05$) between code 32 and code 13 cigarette smokers (Student t-test).

SOURCE: Morosco and Goeringer (*122*).

Nicotine

It has long been known that nicotine elevates blood pressure and heart rate and may increase the onset of angina pectoris attacks. These effects were summarized in the 1976 report, *The Health Consequences of Smoking* (*175*). Nicotine readily passes through biological membranes. The level in the breast fluid of smoking women is similar to that found in the plasma (*81*). The heart rate of fetuses of smoking women is elevated, apparently caused by transplacental passage of nicotine (*127, 136*). Thus, nicotine causes widespread effects in the smoker.

An estimate of the relative potency of various cigarettes with respect to the acute cardiovascular effects of nicotine can be determined by direct chemical assay of relative levels of nicotine in the smoke. By measurement of urinary excretion of nicotine and its major

metabolite, cotinine, it is possible to estimate the individual smoker's actual exposure to nicotine.

Nicotine appears to have measurable effects on performance by smokers (*149, 183*). This may account for the apparent role of nicotine in the reported tendency of some individuals to compensate when switched from higher to lower "tar" and nicotine cigarettes (*60, 139, 142, 146, 147*).

Carbon Monoxide

The effects of carbon monoxide in reducing the oxygen-carrying capacity of the blood are well known. More recently a body of evidence has linked carbon monoxide directly to disease states and to early end points that might be predictive of disease (*11, 109*). Aronow has shown that carbon monoxide, along with nicotine, decreased the duration of exercise achieved before angina (*6, 7, 8*). In his studies, a non-nicotine cigarette made of Indian herbal leaves was employed. Smoke from these cigarettes was more active than expected on the basis of its carbon monoxide content. Aronow (*6*) attributed this effect to a "tobacco component" other than nicotine or carbon monoxide. The effect, however, could well have been caused by a specific herb constituent. Models using pigeons, rabbits, pigs, and primates have been employed to study early end points for carbon monoxide effects (*4, 11, 114*). To the extent that carbon monoxide is responsible for cardiovascular disease, determination of the relative potency of various cigarettes in affecting cardiovascular disease can be made by chemical assay of cigarette carbon monoxide yield.

Other Agents

It has been suggested that agents of tobacco smoke other than nicotine and carbon monoxide contribute to its cardiovascular effects (*4, 116*). Until these agents are identified or an alternative explanation for tobacco effects is established, animal models predictive of cardiovascular death in smokers will be important.

Complications of Pregnancy and Early Childhood

A full understanding of the potential effects of smoking on pregnancy and early infancy is still being developed. Most of the current information available was reviewed in the 1980 report, *The Health Consequences of Smoking for Women* (*174*). Maternal smoking causes changes in the vascular structure of the placenta and increased fetal heart rate (*9, 10, 127, 136*). Maternal carboxyhemoglobin (HbCO) is elevated in smokers, leading to an elevated fetal HbCO and thus to a reduced oxygen content of the fetal blood (*108*).

Some, if not all, of the smoking-related complications of pregnancy are attributed to nicotine and carbon monoxide (*108*). The relative

hazards of lower "tar" and nicotine cigarettes with respect to these agents can be determined by chemical assays of carbon monoxide and nicotine. Actual disease risk, however, will be affected by the delivered dose of these constituents, which in turn depends upon the individual's style of smoking. Other constituents of smoke might also contribute to complications of pregnancy. Comparisons of various types of cigarettes should be possible through epidemiological study, coupled perhaps with evaluation of the vasculature of human placenta (*9*, *10*).

Recent reports indicate that cigarette smoke might contain active transplacental carcinogens (*54*, *125*, *140*). The importance of this in human cancer will probably not be determined soon. No animal assays have yet been applied to assess the relative health hazard of varying cigarettes in transplacental carcinogenesis.

Nonspecific End Points of Toxicologic Significance

Cigarette smoke and its components cause several conditions that may relate to human disease in nonspecific ways. Using assays with these end points may provide useful measures of potential risks due to smoking.

Reduction of Lung Defense Mechanisms

Vapor-phase constituents of cigarette smoke inhibit ciliary motility and mucous flow in experimental animals (*13*, *14*). With ciliary paralysis, removal of other toxic materials from the lung will be inhibited. Animal models suffer some limitations in attempts to duplicate the human situation. For example, many of the ciliastatic agents in the gas phase of smoke are absorbed in the upper airways of man and may not reach areas in the lung where they could affect bronchial cilia (*45*). Furthermore, the concentration of ciliatoxic agents in cigarette smoke will depend on the amount of dilution of smoke by air that occurs during inhalation. Accordingly, the interpretation of animal studies requires care. Similar effects occur in humans, however. Clearance of Fe_3O_4 dust from the lungs of smokers is dramatically slower than from the lungs of nonsmokers (*37*).

Induction of Microsomal Oxidase

Cigarette smokers metabolize several compounds more rapidly than nonsmokers (*38*, *39*, *99*, *187*). This effect is believed caused by the induction of microsomal oxidases, which include aryl hydrocarbon hydroxylase (AHH). The level of AHH itself is much higher in placentas from smoking women than from nonsmokers (*130*, *131*, *178*). Activation of these enzymes has also been observed in the lungs of rats, hamsters, and mice exposed to cigarette smoke (*1*, *59*). Guinea pigs, in contrast, showed a reduction in pulmonary AHH after smoke exposure (*18*). Induction of AHH activity appears to result from

systemic exposure to the smoke compounds themselves or to the metabolites of those compounds. Some carcinogens, including PAH, induce AHH (*38*). More important, the AHH system is involved in the metabolic formation of ultimate carcinogens from procarcinogen precursors (*118*). Cigarette smoke may play an indirect role in carcinogenesis among smokers through this mechanism. Assay of the inducibility of AHH as a measure of individual sensitivity to cigarette smoke has not proved useful (*115, 128*); however, screening of enzyme activity in tissues of human or animal smokers of different types of cigarettes might prove useful for indicating the relative potency of the different cigarettes.

Changes in Genetic Status

To the extent that an early step of carcinogenesis involves genetic change, one would expect that exposure to cigarette smoke might cause detectable changes in genetic material. It is reported that heavy smokers have higher incidences of chromosomal aberrations and higher rates of sister chromatid exchange than do nonsmokers (*91*). Animal models with such end points are feasible, but have not been applied to assays of the toxicity of various cigarettes.

Changes in Immune Status

Recent reports suggest that smoking causes changes in immune function (*56, 69, 144*), but the contribution of these effects to major disease states is unclear. Men with malignant melanoma who smoke are more likely to develop metastases than are nonsmokers, perhaps as a consequence of impaired immune systems (*153*).

Composition of Smokes From Various Types of Cigarettes

Smoking-Machine Design

Laboratory smoking-machine parameters historically have been standardized to permit interlaboratory comparisons and to provide reproducible baselines with which modified cigarettes can be compared. Somewhat different parameters are used in different countries (*28*). In the United States, the most widely used standards are those employed by the Federal Trade Commission (*133*). The machines deliver a 35 ml puff from the cigarette over a 2-second period with a bell-shaped puff profile. The cigarettes are puffed once each minute to the defined butt length of 23 mm (nonfiltered cigarettes), or to a butt length 3 mm longer than the filter overwrap (filter-tipped cigarettes). The butt length is different from cigarette to cigarette, according to the length of the overwrap.

These parameters were established in 1967 when the great majority of cigarettes consumed in the United States were nonfiltered and 70 or

85 mm in length. They were based, in part, on observed smoking patterns in a limited number of human smokers. The types of cigarettes smoked today are substantially different with respect to length, paper porosity, pressure drop, "tar" and nicotine yield, and the concentration of gas phase constituents.

Cigarette smoking-machines can be designed, however, to control puff volume, frequency of puffing, duration of puff, the profile of puff pressure over time, butt length, position of cigarette during and between puffs (e.g., horizontal or vertical), and "restricted" or "free" smoking between puffs (i.e., whether the butt end is closed or open). The puff volume can be measured in terms of the air entering the cigarette or the air plus combustion gases leaving the cigarette. Smoking-machines could be designed to change the puff frequency and the nature of the puffs during the course of smoking a single cigarette (*41, 42*).

Human smoking patterns are diverse and span a wide range from one individual to another (*40, 78, 139*). Some individuals compensate for lower yield cigarettes by changing their style of smoking (*80, 139, 142, 146, 180*). These changes can include increasing puff volume, duration, or frequency, or changing the puff pressure profile. In summary, human smoking behavior may be quite different from standard smoking-machine behavior. Furthermore, the average smoker may have a different smoking pattern for each different type of cigarette.

The chemical composition of smoke is affected by smoking-machine parameters. "Tar" yield per puff depends on puff volume, puff frequency, butt length, and the frequency of puffing at different stages of cigarette consumption (*188, 193, 194*). The concentrations of several specific chemical constituents of "tar" are controlled by the puff frequency, volume, and duration (Chortyk, O.T., and Schlotzhauer, W.S.S., personal communication). If the human smoking pattern varies systematically with the type of cigarette, the relative yield of various chemical constituents delivered to the smoker may vary substantially from that measured by machine. Accordingly, evaluation of the toxicological and pharmacologic potential of the smokes from new types of cigarettes will require knowledge of the manner in which those cigarettes are smoked by the consumer and of the effect of smoking patterns on the composition of smoke.

Dependence of Smoke Composition on Cigarette Design

The composition of smokes from different types of cigarettes can be described by absolute yields per cigarette or per puff, or by the concentration of constituents per unit weight of "tar" or per unit volume of smoke. Modifications of cigarette design can affect yield (quantitative change) or composition of the smoke (qualitative change). Information with respect to individual constituents is available for many modifications. However, modifications affecting the

concentration of one substance will also affect the levels of other substances as well.

Because of the complexity of cigarette smoke, the full impact of any cigarette modification on the composition of the smoke in either absolute or relative terms can never be ascertained. For this reason, bioassays with appropriate end points are essential to determine the relative toxicities of new types of cigarettes. Several modifications of cigarettes reduce the mouse skin carcinogenic activity of the smoke condensate. These include choice of leaf variety, use of reconstituted sheet, and use of tobacco substitutes.

Filters

The design characteristic of commercial cigarettes that most affects the cigarette yield is the filter. In 1980, the "tar" yield of cigarettes, as reported by the Federal Trade Commission or by advertisements, ranged from 30 mg for unfiltered, king-size cigarettes to as low as 0.1 mg for some filter-tipped brands (*55*). Filters selectively remove nitrosamines and semivolatile phenols from the smoke (*88, 120, 126, 188*). Thus, not only the absolute delivery of these constituents but also their relative concentration in cigarette "tar" depend on the filter.

Ventilation

A second major influence on the composition of cigarette smoke is ventilation of the cigarette by the use of paper with a high degree of porosity or by the presence of holes in the mouthpiece. When more air is drawn through the paper or through the mouthpiece, the amount of air drawn through the burning coal of the cigarette is reduced. This effect will reduce the quantity of "tar." By altering the burn temperature, it will also change the combustion process and thus the composition of the smoke. Ventilation also dilutes the gas phase of the smoke with air, causing a marked reduction in the concentration of gas phase constituents in the smoke (*66, 83, 126*).

Tobacco Variety

A substantial collection of tobacco lines is available to plant geneticists. These include 63 species related to tobacco and about 1,000 different tobacco varieties (*164*). The wealth of this material permits genetic manipulation of the leaf, which could be used selectively to enhance or to reduce the content of specific constituents. Among flue-cured tobacco lines available at present, the nicotine concentration varies from 0.2 to 4.75 percent (*34*). Among various burley lines the concentration varies from 0.3 to 4.58 percent. The ranges could be extended by agronomists, should that be desired. Changes in yield of many other smoke constituents might be achieved by genetic modification.

Agricultural Practice

The chemical composition of tobacco leaf is also affected by agricultural practice and by curing methods (*161, 163*). High levels of nitrogen fertilizer increase nicotine and nitrate levels of the leaf. Growing plants more closely together reduces the nicotine content of the leaf. Flue-cured tobaccos are harvested, leaf by leaf, as each is ripe, but the entire plant of burley tobacco is harvested at once. Changes associated with leaf maturity depend on the harvesting practice. Enzymatic degradation of leaf constituents is halted by heat during flue curing. In contrast, burley, Maryland, and oriental tobaccos are not heated to this extent, so that more extensive enzymatic changes occur. As a consequence, there is a markedly lower sugar content in burley tobacco along with a markedly higher content of pigment polymers. Homogenized leaf curing (HLC), if commercially developed, could permit better control over these chemical changes. Furthermore, specific leaf constituents such as soluble proteins may be removed during homogenized leaf processing. Cigarettes made with HLC tobacco yielded smoke containing significantly less dimethylnitrosamine and condensate having significantly less sebaceous gland suppression activity (*165, 169*).

Reconstituted Sheet and Modified Tobaccos

The composition of cigarette smoke is also affected by the use of reconstituted tobacco sheet and modified tobaccos (*62, 63, 64, 65*). Reconstituted sheet can contain substantial amounts of the tobacco "stem," which has a different composition from that of the leaf lamina. The stem is noteworthy for having a low nicotine content. In addition, the physical nature of reconstituted sheet can be controlled to change its burning characteristics and hence the composition of the smoke.

In recent years, some cigarette tobacco has been "expanded" or "puffed." Using this material, less tobacco is required to fill the cigarette. The manner in which the tobacco is shredded also affects the burning rate and therefore the composition of the smoke (*47*). Cellulose-based substitutes have been used as a replacement for tobacco (*17, 35*). These materials cause substantial differences in the total yield and chemical composition of the smoke.

Additives

Humectants and flavoring agents have long been used as additives in cigarette manufacture. The advent of reconstituted tobacco sheet (RTS) technology expanded the possibilities for the addition of substances to the sheet during the processing of tobacco for the manufacture of cigarettes (*174, 188*). It is possible to add substances to the tobacco slurry or suspension for extraction of specific constituents, for dilution of the sheet, for burn rate acceleration or retardation, for

ash cohesion, and for enhancement of flavor (smoke aroma and taste) (*65, 151*). Additionally, one process for curing tobacco leaf calls for the addition of exogenous enzymes to tobacco (*169*), and as noted above, artificial tobacco substitutes are also available. In recent years, cigarette manufacturers' advertisements have focused on the flavor of new lower "tar" and nicotine cigarettes, enhanced presumably by the addition of tobacco constituents or by the addition of new flavoring materials, such as natural or synthetic chemicals. The identities and amounts of the additives actually used in the manufacture of U.S. cigarettes are not known. Systematic information has not been published or made available on the influence of these additives on the composition or biological activity of cigarette smoke.

Variations in Human Smoking Behavior

It does not appear possible to fully monitor smoking behavior in humans without the subjects' knowledge. Butt lengths can be measured in a variety of settings, and puff frequency can be observed without distorting smoking behavior. Measurement of puff volume and duration and of intensity of inhalation, however, requires instrumentation that may lead to alteration of usual smoking behavior. Nevertheless, despite these limitations in objectivity, recent studies provide better data than those available in the past.

Smoking measurements reported from England, Germany, and Canada differ from those used for smoking-machines in the United States (*139, 141, 150*). If the average American smoker, as well, is taking larger puffs with a greater frequency than is the machine, the absolute yields of smoke constituents are under-reported in the United States. This is not to say that the relative yield of "tar" between cigarettes is compromised; however, if smokers puff different types of cigarettes in different ways, the relative yields may be grossly distorted. For example, some smokers block the perforations in the mouthpiece of ventilated cigarettes (*102*). These smokers receive substantially more "tar," nicotine, and gas phase constituents than would be predicted from machine-smoked cigarette yields. Because this action would affect the yield only of ventilated filter cigarettes, the relative ranking of cigarettes by yields would be affected. Similarly, smokers' behavioral compensation for low nicotine delivery can affect the relative yields of filter-tipped cigarettes (*80, 142*).

Research Needs

Many gaps in our assessment of the pharmacological properties of cigarette smoke can be filled by a coordinated, well-directed research program. In comparison with the economic and medical costs of cigarette smoking, the size of the required program is modest. Resources sufficient for implementation of a meaningful program are

available. For example, except for assays of "tar," nicotine, and carbon monoxide yield, new types of cigarettes are not being monitored regularly for the delivery of potentially harmful smoke constituents. Scientists currently conducting sophisticated assays of cigarette delivery of various smoke constituents could serve as resource personnel in the design of an appropriate approach to assays of new cigarettes for suspected toxic agents. Other scientists are investigating short-term end points indicative of long-term risk from many diseases. These laboratories could assist in modifying these procedures specifically for cigarette smoke and its constituents.

Surveillance of New Cigarettes

The chief research need for the study of reduced "tar" and nicotine cigarettes is the routine and frequent surveillance of current and new cigarettes for specific chemical constituents and biological activity. The chemical constituents should include nicotine, benzo[a]pyrene, phenols, catechols, nitrosamines, carbon monoxide, nitrogen oxides, volatile aldehydes, and radionuclides. The biological assays should include sebaceous gland suppression assays, mutagenesis assays, studies of the effects of smoke on airway and ciliary function and on the increase of urinary metabolites related to the activity of elastase, and such other biological assays as may appear predictive of human disease in the future.

Inherent in this recommendation is the use of quantitative short-term end points for various conditions associated with human disease. We do not have proven animal models for quantitative evaluation of risks of chronic obstructive pulmonary disease, sudden death due to cardiovascular disease, or complications of pregnancy and infancy. Emphasis should be given to developing short- and long-term bioassays aimed particularly at these diseases.

Determination of Parameters of Human Cigarette Smoking

Smokers may smoke different types of cigarettes differently with respect to puff volume, duration, and frequency, inhalation profiles, and the manner in which the cigarette is held by the fingers and in the mouth. To conduct meaningful assays of cigarette yields and of the biological activity of cigarette smoke, it is important to know how smokers consume each type of commercial cigarette. Only when this information is available can smoking-machines be designed to yield the most accurate estimate of human dose. We must know both the average and the range of variation in smoking pattern.

The available studies compare smokers' behavior with commercial cigarettes found to deliver different amounts of "tar" or nicotine. Other changes that occur in the product are often unknown. A second type of study should use prototype cigarettes specifically designed to deliver a wide range of concentrations of a desired constituent; for

example, with high or low nicotine to "tar" ratios. Such a study would define the behavior of smokers of new types of cigarettes before or as they are marketed. These studies, however, would require a particular resource that is not accessible to most investigators. There are a large number of experimental cigarettes differing widely in several respects (*62, 63, 64, 65*). Unfortunately, they were developed without concern for smoker acceptability and cannot be used to evaluate human response to design changes. A coordinated program should be established to develop a series of clinically acceptable experimental cigarettes that resemble a "reference standard" as closely as possible, differing only in one or two well-defined characteristics. These should then be made available to appropriate investigators for the study of human smoking behavior.

Evaluation of Health Effects of Nicotine

Nicotine has pharmacological significance for man and animals (*92*). The alkaloid is suspected of playing a role in sudden death due to cardiovascular disease, to the complications of pregnancy and infancy, and possibly to chronic obstructive pulmonary disease. Nicotine in cigarettes leads to the formation of tobacco-specific nitrosamines in the smoke. These are potent carcinogens. Nicotine itself is a significant cocarcinogen in mouse skin carcinogenesis assays of smoke condensate.

It is important to determine whether nicotine acts as a cocarcinogen under the conditions of dosage achieved by cigarette smokers and whether the levels of nicotine-derived nitrosamines play a role in human malignant disease. Resources for such study are available and should be employed in a comprehensive evaluation of the potential carcinogenic effects of new types of cigarettes.

Nicotine should be tested alone, and in the presence of other noxious agents such as carbon monoxide, in animal systems designed to serve as models for nonmalignant diseases associated with cigarette smoke.

Experimental cigarettes with a range of nicotine content have been produced for studies of carcinogenesis. Many of these cigarettes are still available. Those experimental cigarettes that might be needed for pharmacological studies of nicotine should be identified and distributed to appropriate laboratories as the need develops.

The Effects of Smoking-Machine Parameters on Relative and Absolute Yields of Smoke Components From Various Types of Cigarettes

Smoking-machine assays of cigarettes fulfill two needs. The FTC ratings of "tar" and nicotine yields measure an implied risk to the smoker. Smoking-machine data guide experimenters in elucidating the mechanisms of induction of smoking-related disease. Absolute levels of smoke constituents may be very important for experiments, so the experimenter must have reliable information about the comparability

of machine and human smoking. The use of machine data to monitor risk has somewhat different requirements. If the *relative* yields of different cigarettes are not greatly affected by smoking conditions, present smoking-machine standards will be adequate to indicate relative risk of new cigarettes. We know, however, that the relative yield of many constituents is affected by butt length, puff frequency, and degree of ventilation. We need to determine how the variations in these smoking parameters affect relative yields of the several substances in smoke that are of toxicological interest.

Influence of Raw Product Modification on the Pharmacology of Cigarette Smoke

The composition of smoke is determined by the physical and chemical properties of leaf tobacco. Modification of the raw product therefore changes the pharmacology of cigarette smoke. The diversity of available tobacco germplasm along with known genetic techniques permits reduction of hazards in cigarettes through plant breeding and selection. Cultural and curing practices are constantly changing in response to market demands and the needs of farmers. Pesticides currently registered for use on tobacco have been tested as contributors to the carcinogenic activity of cigarette smoke condensates. When used as directed, these materials caused no significant change in biological activity (*65*, *166*). However, the pesticides used in tobacco farming change from time to time in response to the occurrence of new plant pests; for example, the recent spread of blue mold in tobacco-growing regions has led to the use of a new pesticide. It is not known whether the use of such materials may result in changes in the hazards of cigarette smoke.

Present tobacco curing processes may vary somewhat from farm to farm. Furthermore, marked differences in agricultural practices such as close spacing of tobacco plants, bulk curing, and homogenized leaf curing might be introduced in the future. We need to determine the consequences of changes (genetic, cultural, and curing methodologies) on both the chemical composition and the biological effect of cigarette smoke.

Physical and Chemical Properties of Smoke From Cigarettes Delivering Less Than 10 mg of "Tar"

In the past few years, cigarettes delivering less than 10 mg of "tar" by FTC test have been placed on the market. These cigarettes apparently employ efficient filters together with various degrees of smoke dilution. The extreme reduction of "tar" and nicotine delivery by these cigarettes suggests significant differences in combustion processes. Substantial differences in the chemical nature of both mainstream and sidestream smoke might result from such changes.

Some or all of the new lower "tar" and nicotine cigarettes are manufactured by processes that involve the use of chemicals or flavor additives to improve consumer acceptability. The nature of these additives, and their combustion products, that are currently used in marketed cigarettes is not available to the public or to the Government. Likewise, there are no published data on the biologic effects of these additives or their combustion products.

Very low yield cigarettes may add to present concerns with respect to sidestream smoke (*5, 157, 184*). While these cigarettes may deliver such low levels of "tar," nicotine, and gas phase constituents that smokers cannot compensate completely, the delivery of sidestream smoke may not be reduced. Indeed, the sidestream smoke might contain more of some substances (e.g., pyrolytic products of flavor additives) than does the sidestream smoke of higher yield cigarettes. For very low yield cigarettes, the risk of the sidestream smoke may equal that of the mainstream smoke. The chemical and physical nature of sidestream smoke should be determined on new cigarettes.

Development and Validation of Analytical Methods

Methods for determining "tar" and nicotine yield were developed before very low yield cigarettes were an important segment of the market. It is questionable whether existing procedures can measure accurately the "tar" delivery of the cigarettes yielding 0.1 mg of "tar." Other techniques giving acceptable results must be developed. Procedures for determining "tar" yields of low magnitude through measurement of fluorescence have been recommended (*159*). These methods must be validated by determining intra- and inter-laboratory reproducibility. Furthermore, fluorescence measurements may be compromised by additives that interfere with fluorescence, either directly or through the behavior of their pyrolytic products. Fluorescence measurements may not be satisfactory for use with new commercial cigarettes.

Analytical procedures must also be validated for a number of chemical constituents in smoke such as aldehydes, nitrogen oxides, phenols and catechols, aromatic hydrocarbons, and nitrosamines. Several laboratories are conducting such assays with favorable results. However, coordinated comparisons among laboratories to measure the degree of intra- and inter-laboratory variability have not been reported.

Other Research Needs

A number of other research needs of lesser priority should be addressed:

1. It is necessary to study the interaction of smoking with occupational and environmental exposure to other noxious materials. The incidence of lung cancer is greatly increased in asbestos workers or uranium miners who smoke cigarettes (*3, 70, 117*). The

risk of using contraceptive hormones is also greater in cigarette smokers (*132, 174*). Laboratory models of cocarcinogenesis should be used to measure the potential effect of combined smoking and exposure to other environmental toxins. Animal models should be developed to investigate the possible synergism of smoking and the environment in causing other diseases.

2. It is necessary to determine the threshold, if any, for carbon monoxide with respect to cardiovascular effects, pregnancy, and psychological performance. Carbon monoxide delivery of cigarettes can be controlled by ventilation (*66, 126*). To determine the carbon monoxide risk of lower "tar" and nicotine cigarettes, we need to know whether thresholds for carbon monoxide activity exist and whether these thresholds vary for individuals of different ages, medical histories, or genetic backgrounds. Evaluation of risk due to carbon monoxide must take environmental exposure into consideration (*152*).
3. It is necessary to define the extent of smoker compensation for differences in nicotine delivery of cigarettes. To the extent that smokers compensate for lower nicotine delivery, they will probably obtain more of other constituents from lower nicotine than from higher nicotine cigarettes. For example, the smoker might take more puffs to obtain the same dose of nicotine, and thus receive a greater dose of carbon monoxide (*80, 145*). It should be determined at what point smokers can no longer compensate for lower nicotine levels and whether compensation is a permanent behavior change of smokers who switch to lower "tar" and nicotine cigarettes. To carry out such studies, standardized noninvasive procedures to indicate smoke uptake from cigarettes yielding various amounts of "tar," nicotine, and carbon monoxide should be validated. Analyses of blood, urine, and expired air have been used for these purposes (*25, 179, 181*). Analysis of saliva for nicotine might also be useful. With any procedure, inter-laboratory comparisons using standardized methods are needed.
4. Many gas phase components of cigarette smoke are ciliatoxic in the experimental setting. They may overcome physiologic defense barriers against pulmonary toxins. To some extent, the ciliatoxic agents are absorbed in the mouth and upper airways and do not reach the deeper portions of the lung. Experimental systems may not be capable of duplicating the anatomic and behavioral factors that may affect human response to ciliatoxic agents. Nevertheless, short-term sequellae of smoking can be measured in human smokers of different types of cigarettes. Further evaluation of these effects in man should be undertaken.
5. Attention to chemical habituation evoked by cigarette smoking is centered on nicotine, which is the most active acute pharmacolog-

ic agent in cigarette smoke. It is necessary to determine whether there may be other chemicals present in cigarette smoke that contribute to cigarette smoking reinforcement.

6. A variety of short-term animal models with quantitative end points predictive of the development of tobacco-associated diseases should be developed. Except for cancer, long-term animal models suitable for quantitative comparisons of disease risk are not adequate. Even if successful long-term animal models are developed, the costs in time and resources may prevent the timely evaluation of new cigarettes.
7. It is necessary to develop methods for dissemination of information regarding the delivery of various noxious agents by cigarettes. The smoke content of "tar," nicotine, carbon monoxide, phenolic constituents, volatile aldehydes, nitrogen oxides, aromatic hydrocarbons, and nitrosamines may all contribute to the risks incurred by smokers. The Federal Trade Commission releases its findings of "tar" and nicotine yields of cigarettes and has announced its intention to assay carbon monoxide delivery. As additional monitoring assays are conducted, it will be necessary to present the new information to the public and to health professionals in a meaningful way.
8. It is necessary to evaluate the health hazard posed by passive inhalation by nonsmokers of the sidestream smoke from new types of cigarettes. Lower "tar" and nicotine cigarettes are designed to reduce the mainstream smoke received by the smoker. There is no evidence that the amount of sidestream smoke or its quality is improved by these design changes. Indeed, if additives are used to insure acceptability of the cigarettes by the smoker, their pyrolytic products may occur in the sidestream smoke. New types of cigarettes should be monitored for the qualitative and quantitative risks they might impose on the nonsmoker.
9. It is necessary to evaluate cigarettes with lower "tar" to nicotine ratios than are currently found in the market place. Compensation by smokers of lower "tar" and nicotine cigarettes appears to be based on nicotine delivery. The "tar" to nicotine ratio may limit the delivery of smoke constituents to the smoker. A low ratio might be a desirable strategy for lower risk cigarettes. It should be determined whether smoke from cigarettes with unusually low "tar" to nicotine ratios has unusual pharmacologic or toxicologic properties.
10. It is necessary to develop a low "tar" and nicotine reference cigarette. Several laboratories will need these reference cigarettes as a standard for comparisons of lower "tar" and nicotine commercial cigarettes. Commercial products cannot serve as a reference because design changes are made without announce-

ment and because the identity of additives is not disclosed. Without a stable reference, intra-laboratory comparisons conducted at different periods of time and many inter-laboratory studies will be compromised. Reference cigarettes are available for a limited range of "tar" and nicotine deliveries. A reference cigarette delivering very low levels of "tar," nicotine, and gas phase constituents is needed. To produce a reference of sufficient quality, large numbers of cigarettes must be made. Because an effort of this magnitude cannot be undertaken by individual researchers, a centralized facility to provide reference cigarettes to appropriate scientists is desirable.

Summary

1. Several thousand constituents have been identified in tobacco and tobacco smoke. Of these, nicotine appears to be the most important acute-acting pharmacologic agent. Nicotine's physiologic effects include increased heart rate and blood pressure. Nicotine also can permit the formation of tobacco-specific nitrosamines, which are potent carcinogens, and nicotine itself may be a significant cocarcinogen. The carcinogenic potency of cigarette smoke condensates appears to depend on the nicotine content of the "tar." This relationship may be due in part to the conversion of nicotine to tobacco-specific nitrosamines or to the coexistence of nicotine and some other unidentified carcinogen. Whether the carcinogenic effects of nicotine as determined in animal studies are directly applicable to humans is not known at present.
2. In an important study to predict the carcinogenic activity of cigarette smoke condensate, the amount of available nicotine delivered to the mice was found to be a factor in every term but one of the predictive model.
3. Polycyclic aromatic hydrocarbons and tobacco-specific nitrosamines are two prominent classes of tumor initiators found in the smoke condensates of commercial cigarettes. Of the polycyclic aromatic hydrocarbons formed during combustion, benzo[a]pyrene (BaP) may be the most important and has been studied the most extensively. A correlation has been found between benzo[a]pyrene levels and the carcinogenic activity of smoke condensates from several types of cigarettes, but other studies have failed to show that carcinogenic potential is significantly dependent on benzo[a]pyrene content. However, the interaction of BaP with nicotine does appear important in carcinogenesis.
4. The tobacco-specific nitrosamines (TSNA) are formed during curing and fermentation of tobacco leaves and combustion of

cigarettes. TSNAs induce cancer in the lungs and trachea of hamsters and may be of particular importance in the induction of human laryngeal cancer. They may be active as contact carcinogens, or their metabolism at distant sites may produce carcinogens that are then transported to a target site.

5. It is not known whether the unidentified mutagens in cigarette smoke are an important cause of lung cancer in humans, but added exposure to any tumor initiators probably carries an increased risk of cancer.
6. Cigarette smoke contains oxidants that have been shown to reduce the activity of alpha$_1$-antitrypsin in animals and man. This inhibitory function is distinct from the effect whole smoke has on increasing levels of elastolytic enzymes released by neutrophils and macrophages.
7. The great variety of tobacco types makes it possible to manipulate the plant genetically to change the content of the constituents of the leaf. The chemical content of the leaf is also affected by agricultural practices and curing methods. The nicotine content of tobacco, for example, is related to the amount of nitrate fertilizer used in cultivation. Modification of tobacco as reconstituted sheet incorporates substantial amounts of tobacco stems that contain less nicotine than the leaf. The physical nature of reconstituted sheets can be controlled to change their burning characteristics and smoke composition.
8. Vapor-phase constituents of cigarette smoke inhibit ciliary motility and mucous flow in experimental animals.
9. Cigarette smokers metabolize several compounds more rapidly than do nonsmokers. This effect is believed to be caused by the induction of microsomal oxidases, which include aryl hydrocarbon hydroxylase (AHH). Induction of AHH activity appears to be caused by systemic exposure to the smoke compounds themselves or to the metabolites of those compounds. The AHH system may be involved in the metabolic formation of ultimate carcinogens from procarcinogen precursors.
10. In recent years, a number of flavoring additives or cellulose-based tobacco substitutes may have been included in manufactured cigarettes. The nature and amounts of such additives as actually used are not known, nor is it known what influence these additives may have on the chemical composition or subsequent biological activity of cigarette smoke.
11. Cigarette design has a major effect on smoke composition. The filter is the design characteristic that has the most impact on "tar" yield; it can also selectively remove nitrosamines and semivolatile phenols from smoke. The porosity of cigarette paper and the presence of holes in the mouthpiece influence smoke

composition because ventilation reduces the quantity of "tar" and dilutes the gas phase of smoke.

12. Because of the complexity of cigarette smoke, the total impact of any cigarette modification on smoke composition will probably never be fully known.
13. Many laboratory studies of the effects of smoke constituents have been carried out using smoking machines that control puff volume, frequency and duration, butt length, and other factors according to standardized parameters. However, the most widely used parameters were established in 1967, and the type of cigarettes generally smoked today are substantially different with respect to length, paper porosity, "tar" and nicotine content, and concentration of gas phase constituents. Evaluation of the toxicological and pharmacological properties of smoke from new types of cigarettes requires detailed knowledge of the manner in which those cigarettes are smoked, as well as of how smoking patterns affect smoke composition.

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Section 3. CANCER

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Introduction

Research indicates that cigarette smoking causes cancer of the lung, larynx, oral cavity, and esophagus, and is significantly associated with pancreas, urinary bladder, and kidney cancer in both men and women (*102, 103, 104*). This conclusion is based on epidemiologic, pathologic, and experimental evidence collected over the past half-century.

A quarter-century ago lung cancer was found to be related quantitatively to cigarette "tar" cumulatively inhaled. This finding, along with much other evidence, led to the production and widespread use of today's lower "tar" and nicotine cigarettes.[2]

The evidence summarized in this section demonstrates that lower "tar" and nicotine cigarettes produce lower rates of lung cancer than do their higher "tar," higher nicotine predecessors, but smokers of lower "tar" and nicotine cigarettes still have much higher cancer morbidity and mortality rates than do nonsmokers, as well as a higher incidence of other diseases associated with smoking.

One important research concern is to identify the human carcinogenic chemical or chemicals in the particulate and gas phases of cigarette smoke. Multiple metabolic transformations are available in the human body for the several thousand chemicals in cigarette smoke, a number of which could lead to carcinogenic activity in model animal systems.

Another important research concern is that changes in cigarette composition to reduce "tar," nicotine, and possibly even total smoke exposure may inadvertently increase, or fail to decrease, those chemical constituents still largely unidentified that contribute to cardiovascular and pulmonary diseases, pregnancy complications, and fetal and perinatal deaths.

A third area of concern is that the animal model systems used to predict human disease from cigarette smoking require additional study and correlation with the human situation, if these models are to serve as a basis for modifying cigarette composition. When disease-producing chemicals are identified, their reduction or elimination should be associated in the animal models with a decrease in the disease(s) predicted and without untoward effects.

This section summarizes data on the human cancers associated with lower "tar" and nicotine cigarettes, as compared with the "standard" cigarette of the 1930s or 1940s. In addition, it compares pathologic (autopsy) studies on bronchi of cigarette smokers of a quarter-century ago with bronchi of lower "tar" and nicotine cigarette smokers. Further, the section describes the identification, metabolism, and possible mechanisms of action of certain carcinogenic chemicals in both the particulate and the gas phases of cigarette smoke. Finally, the

[2] Editor's note: The members of the Working Group preferred the expression filter-tipped, lower "tar," lower nicotine cigarettes. However, the editors have shortened this expression to lower "tar" and nicotine cigarettes because, while all lower "tar" and nicotine cigarettes are filtered, not all filter-tipped cigarettes are lower "tar" and nicotine products.

section presents a series of conclusions and recommendations for research.

Epidemiologic Studies

Background

It has been established that cigarette smoking causes cancer of various organs including the lung, oral cavity, esophagus, and larynx, as well as exhibiting a significant association with cancer of the pancreas, bladder and kidney (*102*). Epidemiological studies, both retrospective and prospective, have shown a dose-response effect; that is, risk increases with the length of time the individual has smoked and with the number of cigarettes consumed. Such studies have demonstrated that, upon cessation of the smoking habit, risk for developing these cancers declines; the slope of the decline depends on the duration and extent of the former habit. For an individual who has smoked more than 20 cigarettes per day for more than 20 years, no reduction in risk of cancer development is noted for at least 3 years; however, the risk decreases thereafter and, after 10 years of cessation, begins to approach that of one who has never smoked.

From these epidemiological observations, it has been predicted that a smoker's cancer risk would be reduced if the "tar" yield of a cigarette were reduced, provided that the individual does not compensate by more frequent and deeper inhalation of lower "tar" cigarettes.

The trend toward cigarettes with lower "tar" and nicotine started more than 25 years ago with the introduction of a number of filter brands. This trend continued over the years with a greater number of filter brands on the market. Since the early 1970s there has been a rapid increase in production of cigarettes with 15 mg or less "tar" and 1.0 mg or less nicotine. By 1980, brands with these characteristics are expected to account for more than 40 percent of total sales (*70*). In 1950, the average cigarette had 40 mg "tar" and 2.2 mg nicotine. Today's filter cigarettes average about 14 mg "tar" and 1.0 mg nicotine. The downward trend, particularly in terms of "tar" in filter cigarettes, is continuing. There are increasing numbers of cigarettes yielding 10 mg "tar" or less, and these have only one-fourth the "tar" yields common 30 years ago. Although total consumption has increased from 365 billion cigarettes in 1950 to 620 billion cigarettes in 1979, consumption per capita by persons 18 years of age and over has decreased by 5 percent in recent years—from 4,148 cigarettes in 1973 to 3,924 cigarettes in 1979 (*101*), reflecting the 30 million smokers who have quit (*75*). On the other hand, the proportion of smokers who reported that they smoke 25 or more cigarettes per day increased from 23 percent in 1970 to 28 percent in 1978.

Epidemiologic Studies

Three epidemiologic studies—by the American Cancer Society, the American Health Foundation, and the National Cancer Institute—have evaluated the effect of lower "tar" and nicotine cigarettes on lung cancer mortality.

The American Cancer Society conducted a prospective study in which more than a million men and women in 25 States were enrolled in 1959 and traced for 13 years. Subjects completed a questionnaire on smoking habits upon enrollment, and the survivors completed another questionnaire in 1965. An analysis of mortality from lung cancer was made for two 6-year periods: July 1960 to June 1966 and July 1966 to June 1972. The analysis included males and females who, in 1959–60 and in 1965, reported either that they had never smoked regularly or that they smoked cigarettes regularly but never smoked cigars or pipes regularly (*36*).

On each questionnaire, subjects reported the brand that they usually smoked. From this information and from various reports of "tar" and nicotine published in the years in which the questionnaires were completed, subjects were classified as high "tar" and nicotine (T/N) smokers, medium T/N smokers, and low T/N smokers. In the first period, high T/N brands were defined as cigarettes with 25.8 or more mg of "tar" and 2.0 or more mg of nicotine. Low T/N was defined as brands with less than 17.6 mg "tar" and less than 1.2 mg nicotine. The medium T/N category was between these two groups. By the time the second questionnaire was distributed, there had been an increase in the number of filter brands on the market and a general lowering of T/N levels. Low T/N was defined in the same way as in the first period, but the high T/N category had to be reset at a somewhat lower level.

Smokers in the three groups were compared by a matched groups analysis. In this procedure, the groups were matched by age and other factors, including number of cigarettes smoked per day, age at which smoking began, race, urban or rural residence, occupational exposures, education, income, and prior history of lung cancer or heart disease.

To be counted in the study, at least one person in each of the three T/N groups had to be matched on all the variables mentioned above. The adjusted number of lung cancer deaths was obtained by dividing the number of deaths in each triad by the lowest number in each of the three groups. The adjusted numbers of deaths were then summarized for each of the three T/N groups.

Table 1 shows the number of subjects and the unadjusted and adjusted number of lung cancer deaths in the high, medium, and low T/N groups by sex and time period. In both sexes, deaths were fewest in the low T/N group.

Figure 1 shows the lung cancer mortality ratios based upon the adjusted number of lung cancer deaths. The number of adjusted deaths for high T/N smokers was set at 1.00, and the adjusted number of lung

TABLE 1.—American Cancer Society Matched Groups Study

Sex	Period	High T/N	Medium T/N	Low T/N
		Number of subjects at start of period		
Male	1960–1966	63,063	54,999	15,360
Male	1966–1972	29,157	40,090	6,832
Female	1960–1966	44,137	59,750	32,708
Female	1966–1972	22,909	49,198	16,803
		Unadjusted number of lung cancer deaths		
Male	1960–1966	567	459	108
Male	1966–1972	437	566	78
Female	1960–1966	65	82	30
Female	1966–1972	89	149	44
		Adjusted number of lung cancer deaths		
Male	1960–1966	122.4	117.4	101.0
Male	1966–1972	89.6	84.5	70.6
Female	1960–1966	48.3	41.4	27.4
Female	1966–1972	58.1	42.2	36.2

SOURCE: Hammond et al. (*56*).

cancer deaths for medium and low T/N smokers was compared with it. The mortality ratio for male low T/N smokers was 0.83 and 0.79 in the two time periods; for females, it was 0.57 and 0.62. The mortality from lung cancer in low T/N cigarette smokers for both sexes over the combined time periods was 26 percent lower than for high T/N smokers. The mortality ratio for smokers of medium T/N cigarettes was lower than for high T/N, but greater than for the low T/N smokers.

Low T/N smokers had mortality ratios considerably higher than men and women who had never smoked. In men, the mortality ratio of nonsmokers for lung cancer was only 9 percent of that of the low T/N smokers; in women, the nonsmoker rate was 43 percent as high in the first 6-year period and 22 percent as high in the second 6-year period.

It is important to note that the T/N level of the brand of cigarettes smoked was not as significant as the number of cigarettes smoked. The adjusted number of deaths in men and women who smoked fewer than 20 high T/N cigarettes per day was compared with those who smoked 20 or more low T/N cigarettes per day. Figure 2 shows the mortality ratios. The less-than-20-cigarettes-per-day high T/N smokers had mortality ratios from 67 percent to 27 percent *lower* than the men and women who smoked 20 or more low T/N cigarettes per day.

A retrospective study of lower "tar" and nicotine cigarettes was conducted by the American Health Foundation (*111*). Data on lung cancer cases in white males and females were collected, and interviews were conducted in hospitals in six U.S. cities between 1969 and 1976. Control cases were selected from patients in the same hospitals on the basis of an absence of a history of tobacco-related diseases.

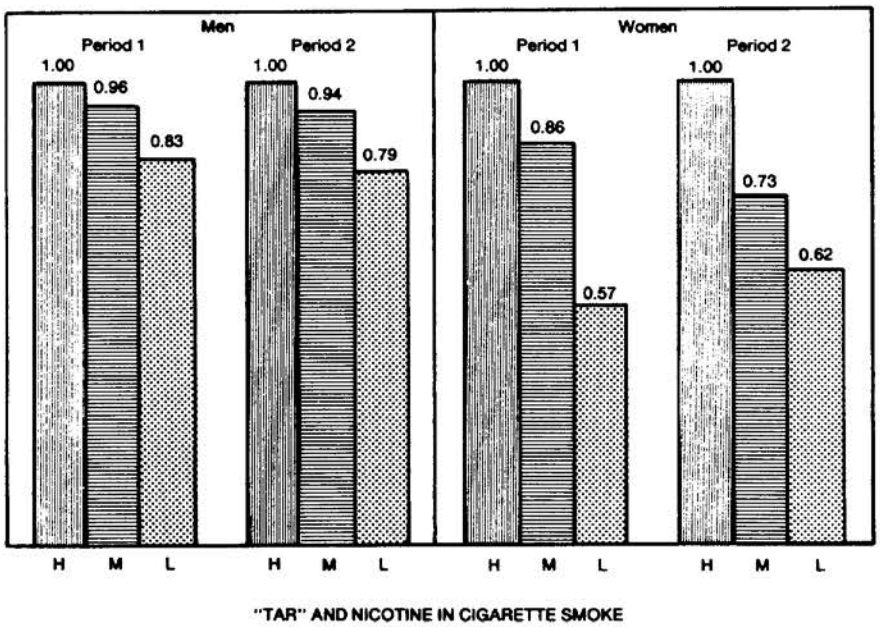

FIGURE 1.—Lung cancer mortality ratios, by amount of "tar" and nicotine in cigarette smoke

NOTE: H = high; M = medium; L = low.
SOURCE: Hammond et al. (*56*).

Cigarette smokers were classified as long-term filter smokers (those who smoked filter cigarettes currently and for at least 10 years) and nonfilter smokers (current smokers of nonfilter brands).

Relative risks for filter smokers and nonfilter smokers were computed by number of cigarettes smoked per day. Figure 3 shows the relative risk of the male filter smokers as a percent of the risk for nonfilter smokers. The percentages ranged from 61 to 89. Females showed the same pattern, with the relative risk for long-term filter smokers ranging from 38 to 79 percent of the nonfilter group. Only in the heaviest smoking category (a small number of cases) were the relative risks the same.

This risk ratio of filter smokers to nonfilter smokers remained low when the data were adjusted for factors such as duration of smoking, amount of cigarette smoking, age, and alcohol consumption.

The American Health Foundation study also analyzed the risk of larynx cancer for long-term filter smokers versus that for nonsmokers. There were many fewer cases of larynx cancer than of lung cancer, but the same general pattern was observed. In men, the relative risk for long-term filter smokers was between 50 percent and 75 percent of the

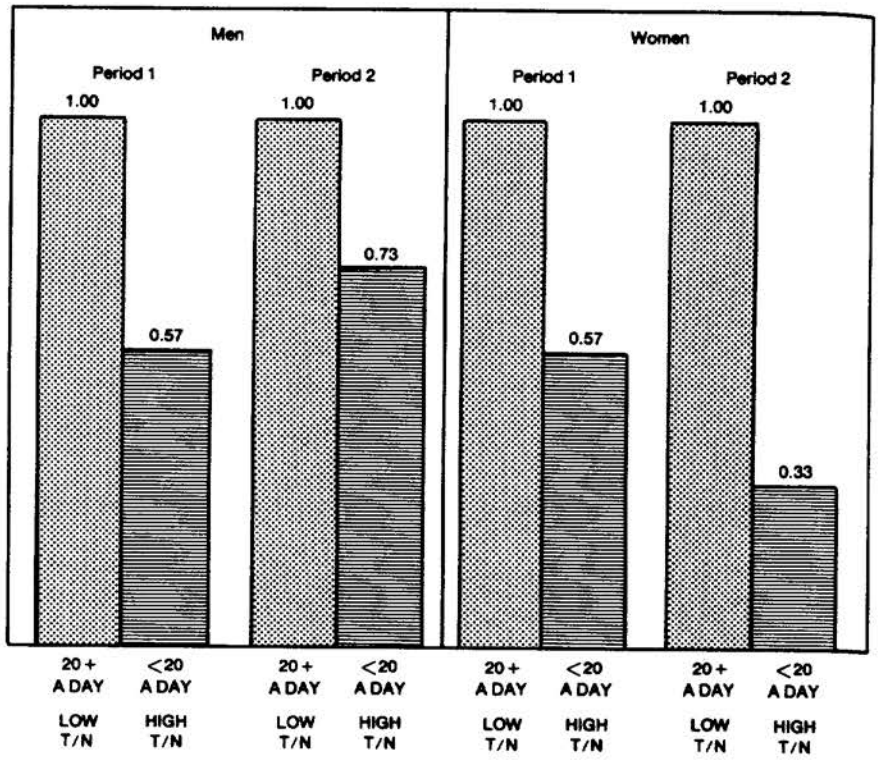

FIGURE 2.—Lung cancer mortality ratios, by number of cigarettes smoked per day and amount of "tar" and nicotine in cigarette smoke

SOURCE: Hammond et al. (*56*).

risk for nonfilter smokers in various number-of-cigarettes-smoked-per-day categories. Women showed the same pattern.

A third epidemiologic study was conducted in Austria (*63*). This project, part of an international study of smoking by the National Cancer Institute, analyzed data on a sample of 414 lung cancer patients and 828 controls. Cigarettes were categorized into three groups by T/N level: Group I, cigarettes with "tar" yields below 15 mg; Group II, 15 to 24 mg "tar"; and Group III, 25 mg or more "tar." These groups were assigned values of 1, 2, and 3, respectively, to indicate average exposure.

The average "tar" exposure in cancer patients (2.596) was significantly higher than for controls (2.026). Scores for total "tar" exposure were computed as the product of the number of cigarettes smoked per day, the number of years smoked, and the "tar" level (1, 2, or 3).

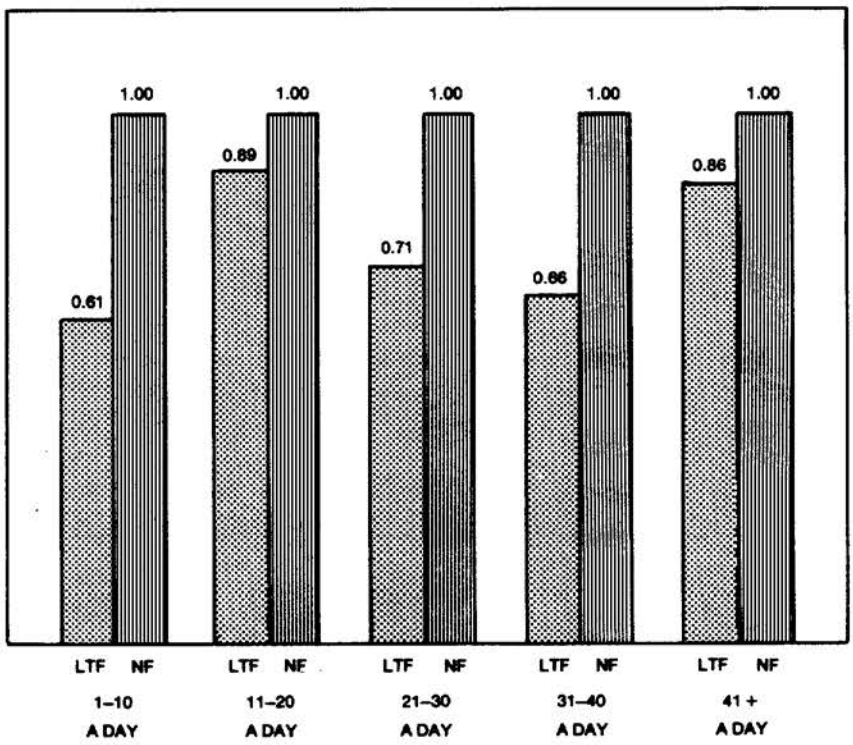

FIGURE 3.—Relative risks of lung cancer in long-term filter smokers (LTF) compared with nonfilter smokers (NF) by number of cigarettes smoked per day, males
SOURCE: Wynder and Stellman (*111*).

Relative risks were then computed by these scores. These risks increased directly with "tar" exposure scores, from 1.6 for scores lower than 500 to a relative risk of 6.1 for scores higher than 5,000.

Discussion

Cigarette smoke condensate of present cigarettes produces fewer tumors on mouse skin than did that of cigarettes tested some 30 years ago (*109*). This difference is probably because today's cigarettes contain more tobacco stems and more reconstituted tobaccos and have cigarette paper with higher porosity, all contributing to smoke condensate that is less tumorigenic to the experimental animal. Changes in chemical composition of the smoke may be a factor. Using just one chemical component as a carcinogenic indicator, researchers have shown that benzo[a]pyrene (BaP) content is significantly lower in today's cigarettes than in cigarettes of 30 years ago (Figure 4) (*49*).

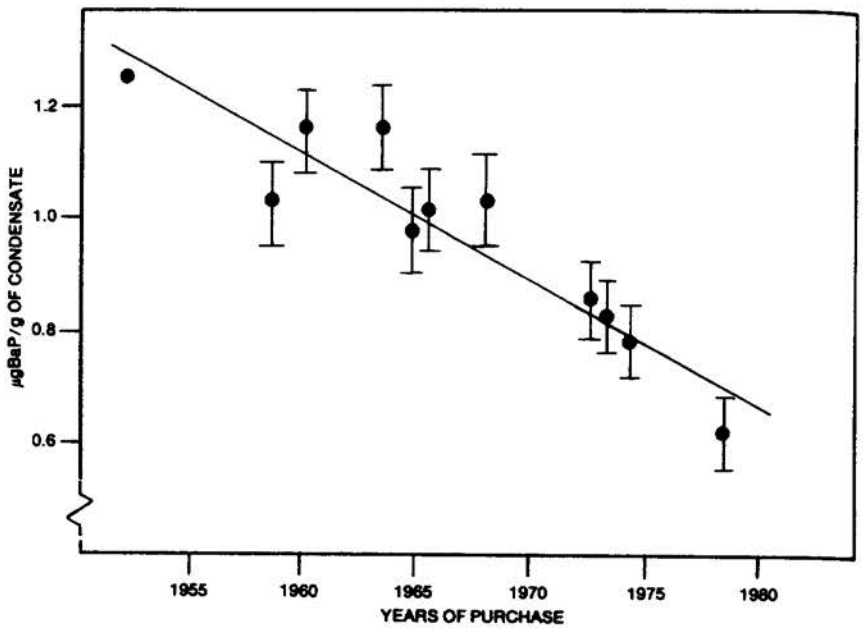

FIGURE 4.—Decrease of benzo[a]pyrene in the smoke of U.S. nonfilter cigarettes (85 mm)
SOURCE: Hoffmann et al. (*49*).

Many brands of cigarettes classified as lower "tar" and nicotine were introduced in the 1970s and had a remarkable growth in sales. The average "tar" in lower "tar" and nicotine brands in 1978 was about 10 mg. Many brands of cigarettes classified as lower "tar" and nicotine in studies reported in the 1960s and early 1970s would be classified as medium "tar" and nicotine cigarettes in the 1980s. Therefore, it might be assumed that cigarettes with lower "tar" and nicotine yields afford even lower cancer risks. But this is not necessarily true. Studies of smoking patterns suggest that smokers of the lower "tar" and nicotine cigarettes tend to inhale more deeply (*44, 98*), have higher amounts of carboxyhemoglobin than predicted (*106*), and have higher than expected carbon monoxide in their exhaled breath (*54*). On the other hand, the lower "tar" and nicotine cigarettes of 1980 have as little as one-fourth the "tar" and nicotine of the cigarettes of 1950, and even if some compensation takes place, actual net smoker exposure is probably much lower.

There is evidence that machines that measure "tar" and nicotine content are not suitable for measurements of smoke from lower "tar" and nicotine cigarettes with perforated filter tips (*62*) and that the

"tar" and nicotine in the inhaled smoke may be more than indicated by the test procedures.

Epidemiological studies thus far have only studied cohorts who began their smoking careers with the old nonfilter, high "tar" and nicotine cigarette. Only in the years to come can we determine the risk of those individuals who began smoking with lower "tar" and nicotine cigarettes, and it is important to study this risk.

As the "tar" yields of cigarettes decrease further, it is probable that flavor additives will be increasingly used. Their potential biologic activities need to be investigated and monitored on an ongoing basis.

Epidemiological data in addition to chemical and biological findings show the reduced risk among lower "tar" and nicotine cigarette smokers, which was predicted because of chemical and biological data previously known. No such clear demonstration of effect exists, however, for cardiovascular disease, chronic obstructive pulmonary disease, or pregnancy. The character and mechanisms of smoke components causing these diseases probably differ significantly from those acting in carcinogenesis.

Pathologic Studies

Histological changes in the tracheobronchial tree in noncancer patients can be observed at autopsy in direct proportion to the number of cigarettes smoked per day during life. Lung cancer patients have the most advanced histological changes in their remaining epithelium (*4, 6*). Ex-smokers who quit for at least 5 years show greatly reduced histologic changes. This finding, together with the observation of cells with disintegrating nuclei in the epithelial lining, suggests that a healing process has taken place in these cases (*5*).

To evaluate the effect of smoking lower "tar" and nicotine cigarettes on histologic changes in bronchial epithelium, male patients who died of causes other than lung cancer in 1970–77 were compared with those who died in 1955–60 (*3*). None of the men who died in the later period could have, in the last 5 to 10 years of their lives, smoked cigarettes that were as high in "tar" and nicotine content as the cigarettes smoked by men who died in the earlier period. Sections from the tracheobronchial tree of 211 men who died in the earlier period and of 234 men who died in the later period were put in random order for microscopic study. A total of 20,424 sections were read, an average of 46 sections per patient. Histologic changes studied included basal cell hyperplasia, loss of cilia, and occurrence of cells with atypical nuclei. Smokers had these changes far more frequently than did nonsmokers, and within each group the percent with these changes increased with the reported number of cigarettes smoked per day. Nonsmokers in both time periods had about the same proportion of these changes. But in each smoking category (adjusted for age), the men who died in 1970–77

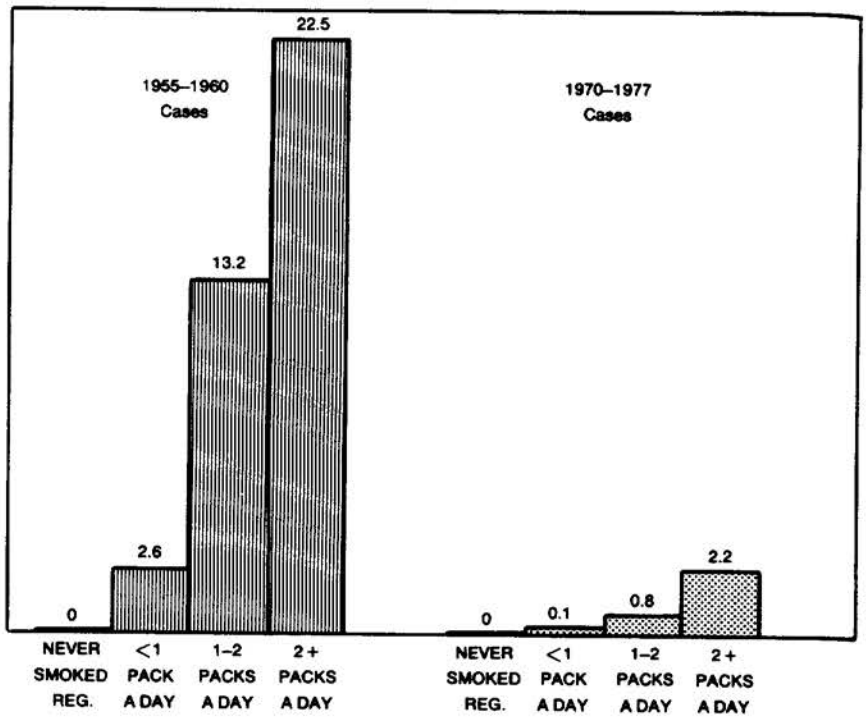

FIGURE 5.—Percent of sections with advanced lesions by smoking habit in two periods
SOURCE: Auerbach et al. (3).

had far fewer histological changes than those who died in 1955–60. Figure 5 shows the percentages with the most advanced histologic change recorded (carcinoma-in-situ) in the 1955–60 and 1970–77 groups. These changes were not found in nonsmokers in either group, and they were found far more frequently in smokers in the 1955–60 cases than in the 1970–77 cases. In two-pack-a-day smokers, 22.5 percent of the 1955–60 group had this advanced change, compared with only 2.2 percent of the two-pack-a-day smokers in the 1970–77 group.

Discussion

Epidemiologic and experimental pathologic studies yield some evidence that filter, lower "tar" and nicotine cigarettes produce fewer neoplasms than the nonfilter cigarettes of 25 to 30 years ago. While it is not always possible to directly extrapolate data on animal experimental carcinogenesis studies to man, the data summarized in this section show the predicted lower mouse skin tumorigenesis of filtered, lower "tar" and nicotine cigarette "tar" on an equal weight basis. Post-

mortem studies of the human lung further support the finding that the filter, lower "tar" and nicotine cigarettes are less oncogenic than the nonfilter cigarettes of 25 to 50 years ago.

Experimental Chemical Carcinogenesis

While epidemiologic, pathologic, and experimental studies all point to polycyclic hydrocarbons within the "tar" moiety of inhaled cigarette smoke as potential carcinogens for man, additional work is needed to determine whether nicotine plays a major role as a cocarcinogen. Further, nicotine and nornicotine give rise to two carcinogenic nitrosamines that are found only in tobacco products. Tables 2, 3, 4, and 5 list known carcinogenic agents in both the particulate and the gas phases of cigarette smoke.

Russell (*90*) recently suggested that a lower "tar," medium nicotine cigarette would be more attractive to smokers and tend to promote their use while minimizing health risk. This action cannot be supported without further research on nicotine's effects in carcinogenesis. Studies should address not only nicotine carcinogenesis, but also the chemical's effects on the cardiovascular, gastrointestinal, endocrine, and central nervous systems. Nicotine has been found to have potent physiologic effects on these systems.

The following discussion briefly considers the probable routes of metabolism and binding to critical cellular components of the chemicals in the particulate and gas phases of cigarette smoke thought most likely to be carcinogenic for man.

Most procarcinogens are metabolized through a mixed function oxidase system, which is composed of the hemoprotein cytochrome P-450, NADPH-dependent cytochrome P-450 reductase, and phospholipid. Various forms of P-450 have been characterized immunologically (*99*), and some have been separated electrophoretically (*78*). The amino acid composition and partial sequences of some forms of P-450 have been elucidated recently (*15*). A treatise on the physicochemical characteristics and physiological function of P-450 has also appeared (*78*). The different forms of P-450 may have differential effects in the production of metabolites (*33, 81, 91*). Metabolic activation of most carcinogens by the P-450 mediated oxygenases is considered to afford structures that are strong electrophiles and thus prone to attach to cellular nucleophiles, including proteins, nucleic acids, and other macromolecules (*21, 72, 73*).

Polycyclic aromatic hydrocarbons present in tobacco smoke are typified by benzo[a]pyrene (BaP). BaP is found in the soil and atmospheric particulates of cities, with relatively high concentrations around highways, airports, factories, and similar installations (*51*). Since it occurs in pyrolysis products, such materials as soot, tar, and charcoal-broiled or thoroughly roasted foods all have measurable

levels. BaP also has been identified in forest soils, in volcano effluents (*50*), in marine sediments, and even in the deeper layers of soil from the permafrost regions of the earth (*52*).

BaP was among the first polycyclic aromatic hydrocarbons isolated from coal tar and has been used for various experimental purposes for 50 years.

On the basis of metabolic studies with phenanthrene, Boyland (*16*) hypothesized that hydrocarbons were metabolized through arene oxide or epoxide intermediates. Such intermediates could account for the identification of phenols, dihydrodiols, premercapturic acids, and mercapturic acids as metabolites of phenanthrene or naphthalene, all depending on whether the epoxide reacted with water or glutathione or rearranged nonenzymatically.

The information gathered from various experiments *in vitro* with metabolites of BaP, DNA adducts, and presumed intermediates led to the conclusion that both the dihydrodiol and epoxide moieties were required for carcinogenic activation of BaP and other polycyclic hydrocarbons. In the case of BaP, the potent carcinogenicity of the 7,8-dihydrodiol indicated that it was probably an intermediate toward the final activated carcinogen (*57*).

A number of studies have substantiated the concept that a "bay" region is involved in transformation of most polycyclic hydrocarbons to the activated intermediate (*74, 96, 108*).

The diol epoxide of BaP thus appears to be the metabolically derived strong electrophile that is capable of reacting with critical constituents in the cell. The reaction of this activated intermediate with nucleic acids has been followed both *in vivo* and *in vitro* (*59, 61, 76*).

P_1-450 is also a component of the enzyme system called aryl hydrocarbon hydroxylase (AHH) (*2*). The major phenolic detoxification product, 3-hydroxybenzo[a]pyrene, results from nonenzymatic rearrangement of the initial 2,3-epoxide formed by the P_1-450 (*112*). The phenols are amenable to conjugation by glucuronyl transferase or sulfotransferase, leading to solubilization and more rapid excretion. The available evidence suggests that in different strains of mice high AHH inducibility leads to increased susceptibility to hydrocarbon-induced tumors. The genetics of AHH inducibility in mice have been thoroughly discussed (*77, 78, 79*). Attempts have been made to extend some aspects of the AHH work to humans, despite the variability in results noted in human populations (*2*).

Although there is currently more emphasis on the reactions of the electrophilic species from carcinogens with nucleic acids, the binding of carcinogens to proteins had been noted many years earlier (*71*). More recent efforts have shown that ligandin, a hepatic protein that binds anionic metabolites of glucocorticoids (*67*), also binds some carcinogens such as polycyclic aromatic hydrocarbons and aminoazo dyes but not aromatic amides (*68*).

Aromatic amines are found in tobacco smoke. These compounds are formed during the burning of tobacco, including toludines, 2-naphthylamine, and unknown aminofluorenes. These compounds are also activated through the P-450 system similar to that for the aromatic hydrocarbons. Ring-hydroxylated products of aromatic amines apparently are detoxification products. For most of the carcinogenic aromatic amines or amides investigated, N-hydroxylation apparently was the activation route.

Further reaction of the N-hydroxy compounds was found necessary to afford forms capable of reacting with nucleic acids or proteins. Acetate, glucuronide, sulfate, or even phosphate esters of the N-hydroxy amide had the required characteristics; the products from *in vitro* reactions with nucleic acid were the same as those isolated from reactions *in vivo*. In some but not all cases, the carcinogenicity of the parent amide or amine roughly correlated with the enzyme levels in a target organ.

One of the most readily obtained of the activated esters, N-acetoxy-N-2-fluorenylacetamide (N-AcO-FAA) has been employed in many model experiments to study effects on the structure and function of nucleic acids. N-AcO-FAA forms a major adduct with DNA where approximately 84 percent of the fluorene residue was linked to the C-8 of guanine by arylamidation, affording N-(deoxyguanosin-8-yl)-2-fluorenylacetamide, which retained the N-acetyl group (*28*).

An additional means for activation and adduct formation of aromatic amine derivatives has been investigated by C.M. King et al. (*58*). An enzyme termed N-O-acyltransferase forms derivatives that are quite reactive and readily form adducts with RNA.

More recent work points toward attachment by the activated aromatic amines and amides to still other positions on the bases of nucleic acids (*10, 55, 56*).

Numerous model studies with N-AcO-FAA modified nucleic acids have shown a change in function of the altered nucleic acid. However, none has shown the exact role in the process of carcinogenesis; this remains an area for further investigation (*94*).

Although the aminoazo dyes and aromatic amines or amides are activated in a similar fashion and both bind to proteins, the proteins involved differed somewhat (*8, 9, 68, 97*).

Relatively less emphasis has been placed recently on carcinogen–protein interactions than on carcinogen–nucleic acid interactions. In view of the essential function of the proteins, it seems their interactions with carcinogens require more investigation.

N-Nitroso compounds found in tobacco smoke include those derived from nicotine, nitrosonornicotine and related compounds, N-nitrosodiethanolamine, and nitrosodimethylamine. Metabolic activation of dialkylnitrosamines is necessary for expression of their toxic and hepatocarcinogenic effects. Oxidative metabolism of dimethylnitrosa-

mine, for example, is accomplished by the liver microsomal P-450 system yielding an unstable (α-hydroxymethyl)methylnitrosamine, which forms formaldehyde and an unstable methylnitrosamine. In turn, this molecular species collapses with release of nitrogen and formation of the methyl carbonium ion, CH_3^+, which alkylates proteins, nucleic acids, and probably other cellular constituents. The intermediacy of the (α-hydroxymethyl)methylnitrosamine is substantiated by the potent mutagenicity and outstanding carcinogenicity of the more stable (α-acetoxymethyl)methylnitrosamine (*11*). More recent studies suggest that other oxidation pathways may also be involved (*66*).

Tobacco and its resultant smoke contain two carcinogenic N-nitrosamines that are formed from nicotine and nornicotine (Table 2) (*46, 47*). N-Nitrosonornicotine (NNN) gives rise to α-hydroxy N-nitrosamines, which are unstable and decompose finally to oxocarbonium ions, the suspected ultimate carcinogenic forms of NNN. Most of the oxocarbonium ions react with water, yielding a keto alcohol and a hydroxyaldehyde (*19*). The other carcinogenic and tobacco specific N-nitrosamine is 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which is also α-hydroxylated. The methyl hydroxylation product gives rise *via* an oxodiazohydroxide to the same carbonium ion as the 2′-hydroxylation of NNN (*42*).

Alkylnitrosoureas afford alkylating moieties without the need for metabolic activation; spontaneous decomposition occurs at alkaline pH values. However, the organs affected by alkylnitrosoureas may vary, depending on the route of administration and the animal model.

Nitrosomethylurea, most widely used in model experiments, can cause tumors in brain, breast, stomach, liver, heart, skin, kidney, intestinal tract, bladder, trachea, and peripheral nervous system (*107*); administration to pregnant animals often leads to tumors of the nervous system in the offspring many months later (*60*).

The alkylating moiety (carbonium ion) formed from a nitroso compound may attach to a variety of positions in the nucleic acids bases, on the phosphate backbone, or on the ribose portion of the RNA.

Environmentally, nitrosamines and related structures represent a problem, since they may be formed endogenously from secondary or tertiary amines, amides, or ureas and nitrite, available from reduction of nitrate by bacteria of the salivary plaque. Nitrate has a widespread distribution in dietary vegetables and grains. Although each individual has therefore the capacity to form nitroso compounds, endogenous nitrosation can sometimes be inhibited by ascorbic acid, propyl gallate, or other compounds that compete with the amine or amide for nitrous acid. This is not a panacea, for ascorbic acid may enhance nitrosation of certain amines (*18*). Furthermore, innocuous nitroso compounds, such as nitrosoproline, or even some aliphatic nitro alcohols, can provide a nitroso group to form carcinogenic nitrosamines or amides by transni-

trosation (*26*, *95*). Although certain bacteria are instrumental in formation of nitrosamines within the organism (*40*), bacteria also degrade nitrosamines (*89*), leading to a balance between endogenous formation and decomposition of nitroso compounds. During the chewing of tobacco, N-nitrosonornicotine is formed in the oral cavity (*41*). Although it has not been demonstrated, it may be assumed that under certain conditions the carcinogens NNN and NNK can also be formed from nicotine in other organs or sites in man.

Another carcinogen, vinyl chloride, has also been identified in tobacco smoke. Metabolically, vinyl chloride is activated through the P-450 system by formation of a halogenated epoxide (*7*, *43*, *113*). Such an epoxide may yield halogenated aldehydes or alcohols through rearrangement (*45*, *113*) or through derivatives of glutathione through S-transferase (*45*).

In summary, most of the identified carcinogens found in tobacco smoke are activated through the P-450 system to electrophilic compounds, which react with proteins, nucleic acids, perhaps lipids, and other cellular constituents. Since there are many constituents of tobacco smoke, only the activation pathways of BaP, typical aromatic amines, nitrosamines, and vinyl chloride have been presented here. The activation pathways of the other carcinogens found in tobacco smoke may be similar.

Although the pathogenesis of several types of cancer, chronic obstructive pulmonary diseases, and cardiovascular diseases is linked to different tobacco smoke constituents, the epidemiologic associations with cigarette smoking are dose related for each of these diseases (*34*, *36*, *37*, *38*, *102*). Thus, the first goal in production of a "less hazardous cigarette" was to reduce total smoke delivery. Because the causal relation between smoking and lung cancer was the first established, primary emphasis was placed on reducing the carcinogenic "tar" of cigarette smoke (*110*).

Tumor Initiation and Cocarcinogens

Inhalation studies with Syrian golden hamsters and bioassays on mouse skin, rabbit ears, and the connective tissue of mice and rats have clearly indicated that the major carcinogenicity of cigarette smoke resides in its particulate phase (*23*, *48*, *109*). Although the presence of volatile carcinogens in the gas phase has been well established (Table 2), the models available at present do not allow detection of a carcinogenic effect of the gas phase because of the low sensitivity of the systems (*23*).

Extensive fractionation studies combined with bioassays have supported the concept that the concentration in cigarette "tar" of certain polynuclear aromatic hydrocarbons (PAH), which are known human carcinogens (*35*, *69*, *86*), is too low to account for their activity

TABLE 2.—Known carcinogenic agents in the gas phase of cigarette smoke*

Agent	Concentration in one cigarette		
	Range reported	Cigarette[a]	Ref.
Dimethylnitrosamine	1 - 200 ng	13 ng	*1,2,4*
Ethylmethylnitrosamine	0.1 - 10 ng	1.8 ng	*1,2,4*
Diethylnitrosamine	0 - 10 ng	1.5 ng	*1,2,4*
Nitrosopyrrolidine	2 - 42 ng	11 ng	*1,2,4*
Other nitrosamines[b]	0 - 20 ng	?	*1,2,4*
Hydrazine	24 - 43 ng	32 ng	*5,6*
Vinyl chloride	1 - 16 ng	12 ng	*3,7*
Acrylonitrile	3.2 - 15 μg	10 μg	*8,9*
2-Nitropropane	0.73 - 1.21 μg	0.92 μg	*10,11*
Urethane	20 - 38 ng	35 ng	*12,13*

*This table is not complete, since the gas phase may also contain such carcinogens as arsine, nickel carbonyl, possible volatile chlorinated olefins, nitro-olefins, and others currently unknown.

[a]Leading U.S. cigarette (85 mm) without filter tip.

[b]The four N-nitrosamines identified on occasion only in the smoke of special cigarettes were di-n-butylnitrosamine, di-n-propyl-nitrosamine, methyl-n-butylnitrosamine, and N-nitrosopiperidine.

as complete carcinogens. These PAH, however, are active as tumor initiators and thus contribute to the induction of tumors by tobacco "tar," which contains an abundance of cocarcinogens (*20, 48*). Tables 3 and 4 list the tumor initiators and cocarcinogens in cigarette smoke known at this time. Large-scale model studies on mouse skin and inhalation studies with Syrian golden hamsters have shown that a significant reduction of "tar" and a selective reduction of tumor initiators and cocarcinogens will lead to a significant reduction of the carcinogenic potential of cigarette smoke (*13, 23, 24, 29, 30, 31, 32, 48*).

Recently, a study has indicated that nicotine (and possibly other tobacco alkaloids) may be active as a cocarcinogen (*14*), while another study did not show acrolein to have cocarcinogenic properties (*27*). Further detailed investigations are required.

Organ-Specific Carcinogens

This approach toward the less hazardous cigarette has been criticized by several groups as one-sided because it has been concerned only with "tar," nicotine, and tumor initiators such as PAH and with cocarcinogens, rather than with organ-specific carcinogens (*85, 88, 102*).

Table 5 lists the known organ-specific carcinogens. In the case of polonium-210, a recent indepth study raises doubts on the significance of ^{210}Po as a factor contributing to lung cancer in smokers. Nevertheless, it may be prudent to reduce the ^{210}Po content of tobacco products (*39*).

Among the aromatic amines, certain individual compounds are known human bladder carcinogens (e.g., 2-naphthylamine, 4-biphenyla-

TABLE 3.—Tumor-initiating agents in the particulate phase of tobacco smoke*

Compound	Relative activity as complete carcinogen[a]	Ng/cigarette
Benzo[*a*]pyrene	+++	10–50
5-Methylchrysene	+++	0.6
Dibenz[*a,h*]anthracene	++	40
Benzo[*b*]fluoranthene	++	30
Benzo[*j*]fluoranthene	++	60
Dibenzo[*a,h*]pyrene	++	pr[b]
Dibenzo[*a,i*]pyrene	++	pr[b]
Dibenz[*a,j*]acridine	++	3–10
Indeno[*1,2,3-c,d*]pyrene	+	4
Benzo[*c*]phenanthrene	+	pr[b]
Benz[*a*]anthracene	+	40–70
Chrysene	+ ?	40–60
Benzo[*e*]pyrene	+ ?	5–40
2-, 3-Methylchrysene	+ ?	7
1-, 6-Methylchrysene	-	10
2-Methylfluoranthene	+	34
3-Methylfluoranthene	?	40
Dibenz[*a,c*]anthracene	(+)	pr[b]
Dibenz[*a,h*]acridine	(+)	0.1
Dibenzo[*c,g*]carbazole	(+)	0.7

*Incomplete list; all listed compounds are active as tumor initiators on mouse skin.

[a]Relative carcinogenic activity on mouse skin as measured in our laboratory on Swiss albino (Ha/ICR/Mil) mice; ?, carcinogenicity unknown; (+), not tested in own laboratory.

[b]Pr stands for present, but no quantitative data given.

SOURCE: Hoffmann et al. (*48*).

mine, and benzidine) (*83*). Doll (*22*) has discussed the aromatic amines as likely contributors to the increased risk of cigarette smokers for bladder cancer. These carcinogenic compounds are primarily pyrosynthesized from the tobacco proteins (*84, 92*). Except for the development of a process to reduce the protein content of tobacco (*100*), no efforts toward the reduction of aromatic amines in cigarette smoke have been reported.

A major group of organ-specific carcinogens in cigarette smoke are the N-nitrosamines. The volatile nitrosamines, for which protein and nitrate are precursors, can be selectively reduced by filtration (*17*). The tobacco-specific N-nitrosamines in tobacco and in smoke are formed during tobacco curing as well as during smoking. So far, N′-nitrosonornicotine (NNN), 4-(N-methyl-N-nitrosamine)-1-(3-pyridyl)-1-butanone (NNK), and N′-nitrosoanatabine (NAT) have been identified. These compounds are formed from the major tobacco alkaloids: nicotine (NNN and NNK), nornicotine (NNN), and anatabine (NAT). The total concentration of these three nitrosamines varies between 0.7 and 10.0 μg/cigarette (*47*). NNN is a moderately active carcinogen in mice, rats, and Syrian golden hamsters, whereas NNK is a strong carcinogen in the respiratory tract of all three species; NAT has so far not been

TABLE 4.—Cocarcinogenic agents in the particulate matter of tobacco smoke*

Compound[a]	Cocarcinogenic activity[b]	Ng/cigarette
I. Neutral fraction		
Pyrene (–)	+	50–200
Methylpyrenes (?)	?	50–300
Fluoranthene (–)	+	100–260
Methylfluoranthenes (+;?)	?	180
Benzo[*g,h,i,*]perylene (–)	+	60
Benzo[*e*]pyrene (+)	+	30
Other PAH's (+)	?	?
Naphthalenes (–)	+	360–6,300
1-Methylindoles (–)	+	880
9-Methylcarbazoles (–)	+	140
4,4'-Dichlorostilbene (–)	+	1,500 (115)[c]
Other neutral compounds (?)	?	?
II. Acidic fraction		
Catechol (–)	+	40,000–350,000
3-Methylcatechol (–)	+	11,000–20,000
4-Methylcatechol (–)	+	15,000–21,000
4-Ethylcatechol (–)	+	10,000–24,000
4-n-Propylcatechol (?)	?	= 5,000
Other catechols and phenols (?)	?	?
Other acidic agents (?)	?	?

*Incomplete list.
[a]In parentheses, complete carcinogenic activity on mouse skin; (?), unknown.
[b]+, active; ?, unknown.
[c]Value from 1968 U.S. cigarettes; today's values would be lower, because DDT and DDD decreased in the U.S. tobaccos.
SOURCE: Hoffmann et al. (*48*).

bioassayed. Although conclusive epidemiologic data are not available, "NNN should be regarded for practical purposes as if it were carcinogenic to humans" (*53*). Research programs on the reduction of these tobacco-specific carcinogens in cigarette smoke and their possible *in vivo* formation in the smoker from nicotine, nornicotine, anatabine, and other tobacco alkaloids need to be undertaken.

A neglected area may be the reduction of other organ-specific carcinogens in cigarette smoke, such as nitro-arenes and pesticides that may give rise to carcinogens such as maleic hydrazide diethanolamine (MH-30).

Carbon Monoxide in Cigarette Smoke

Until a few years ago the reduction of carbon monoxide in cigarette smoke had not been seriously studied. In fact, in 1976 a report from the United Kingdom demonstrated that unperforated filter cigarettes can deliver higher carbon monoxide values (13–18 mg/cig) than nonfilter

TABLE 5.—Organ-specific carcinogens in the particulate matter of cigarette smoke

Carcinogen	Concentration/cigarette	Carcinogenicity*
I. Esophagus	0.1–4.0 μg	+
N'-Nitrosonornicotine	130–5,500 ng	+
4-(N-Methyl-N-nitrosamino)-1-(3-Pyridyl)-1-butanone	0.1–0.4 μg	+
N'-Nitrosoanatabine	0.2–4.6 μg	+
Nitrosopiperidine	0–9 ng	+
Unknown unsymmetrical nitrosamines	?	+
II. Lung		
Polonium-210	0.03–1.3 pCi	+
Nickel compounds	0–600 ng	+
Cadmium compounds	9–70 ng	?
Unknowns	?	?
III. Pancreas		
Nitrosamines	?	+
Unknowns	?	?
IV. Kidney and bladder		
β-Naphthylamine	22 ng	+
χ-Aminofluorene	+	+
χ-Aminostilbene	+	+
o-Toluidine	+	+
Unknown aromatic amines	?	?
o-Nitrotoluene	21 ng	?
Unknown nitro compounds	?	?
Di-n-butylnitrosamine	0–3 ng	+
Other nitrosamines	?	+

*+ Activity confirmed; ? Activity unconfirmed.
SOURCE: Hoffmann et al. (48).

cigarettes (9–16 mg/cig) (*105*). This finding has been confirmed in both Germany and the United States (*49*). An increasing number of the cigarette brands sold in the United States have perforated filter tips, at present amounting to approximately 50 percent. The filter perforation leads to air dilution of the smoke and to changes in the burning profile of the cigarette, and thus, to a significant reduction of the carbon monoxide content of the smoke (Table 6). Filter tip perforation similarly reduces the nitrogen oxides in cigarette smoke (*82*).

Smokers' Compensation

Studies by Russell and his group (*90, 98*) and recently by Hill and Marquardt (*44*) have demonstrated that many smokers who switch to lower "tar" and nicotine cigarettes will compensate for the loss in smoke nicotine (and possibly other agents) by intensifying their smoke intake, puffing more frequently, and drawing larger volumes per puff. In the case of cigarettes with perforated filter tips, the occlusion of the filter vents by the fingertips may be an additional compensation

TABLE 6.—Carbon monoxide in smoke of cigarettes

	Carbon monoxide (mg/cigarette)		
	Nonfilter	Regular filter	Perforated filter
U.S. (90% of av 1977/1978 sales)[a]	11.6–17.0 (N = 8)	14.4–20.0 (N = 23)	2.8–12.8 (N = 9)
U.K. (1975)[b]	9–16 (N = 9)	13–18 (N = 10)	—
Germany (1975)	16–21 (N = 7)	15.5–22.5 (N = 17)	—
Germany (1978)	14.5–19.9 (N = 16)	8.6–18.5 (N = 15)	2.2–13.8 (N = 9)

[a]Average values for nonfilter cigarettes, 14.9 mg; for regular filter cigarettes, 17.1 mg; for perforated filter cigarettes, 8.9 mg.
[b]Average values for nonfilter cigarettes, 12.5 mg; for filter cigarettes, 16.1 mg.
N = number of brands tested.
SOURCE: Hoffmann et al. (*48*).

technique that smokers may develop either intentionally or subconsciously (*62*). These factors of "smoker compensation" must be considered in the evaluation of lower "tar" and nicotine cigarettes. Filtered, lower "tar" and nicotine cigarettes that are less vulnerable to increasing the smoke and nicotine deliveries are needed. Such products are envisioned by scientists in the tobacco health field. Attempting to minimize smoker compensation by selectively reducing "tar" and other smoke compounds while maintaining nicotine yield may carry serious disadvantages. First, maintaining nicotine delivery may reinforce physiologic habituation, and interfere with smoking cessation attempts (*93*). Second, nicotine gives rise to the tobacco-specific carcinogenic N-nitrosamines, NNN and NNK, and nicotine itself may be carcinogenic (see Experimental Chemical Carcinogenesis within this section). Finally, nicotine is suspected to be a major smoke constituent correlated with the increased risk of cardiovascular disease among cigarette smokers.

Transplacental Carcinogenesis

The possible transplacental effect of cigarette smoking on carcinogenesis should be investigated. Recently, it has been shown that cigarette "tar" is an active transplacental carcinogen in Syrian golden hamsters (*80*). Furthermore, a number of smoke constituents are active as transplacental carcinogens in the experimental animal (*25*). These include volatile N-nitrosamines, benzo[a]pyrene, o-toluidine, ethyl carbamate, and vinyl chloride (*87*). Other major tobacco carcinogens including the benzofluoranthenes, NNN, and NNK need to be bioas-

sayed for their transplacental activity and to be considered with respect to lower "tar" cigarettes.

Flavor Additives

The development of lower "tar" and nicotine cigarettes has tended to yield products that lacked the taste components to which the smoker had become accustomed. In order to keep such products acceptable to the consumer, the manufacturers reconstitute aroma or flavor. There are several ways in which this can be achieved. Flavor extracts of tobacco can be added to the lower-yield blends. Other plant extracts can be used to supplement the flavor spectrum, synthetic flavors can be added, or a combination of techniques can be applied (*64*, *65*). Powdered cocoa, one flavoring additive that is probably used in U.S. cigarettes, has been found to increase mouse skin tumorigenicity of the "tar" from a standard experimental cigarette at each of two dose levels (*31*).

The burning of cigarettes with flavor additives produced increased and perhaps novel types of semivolatile agents, including traces of mutagenic compounds. The mutagenic agents were found in the basic fraction of the semivolatile portion obtained from heating the tobacco mixtures. Chemically, the agents thus far identified were substituted pyrazines and other aza-arenes with and without amino groups (*64*).

The exact delineation of the chemical structure of additives, their pyrolytic products, the possible carcinogenic properties, and the quantities found in smoke of lower "tar" cigarettes is urgently needed in order to assure the consumer that the filter, lower "tar" and nicotine cigarette does not carry additional or new health risks.

Conclusions and Recommendations

1. Both retrospective and prospective epidemiologic studies in man have shown a dose-response relationship between cigarette smoking and the occurrence of cancer of the lung, larynx, esophagus, oral cavity, and bladder with a less clear quantitative relationship to cancers of the pancreas and kidney. Smoke dose was measured by various parameters, including numbers of cigarettes (daily or lifetime), duration of habit, depth of inhalation, and number of puffs per cigarette.

   The highest priority in the field of public health is that individuals who have not started smoking should not begin and that those who currently smoke should quit.
2. Those individuals who start smoking with a filter-tipped, lower "tar" and nicotine cigarette, or who switch after a period of time from high "tar" and nicotine cigarettes to the lower "tar" and nicotine cigarettes, will have a lower incidence of lung cancer, but an incidence far in excess of the nonsmoker.

Specifically, high priority should be given to continued and long-term retrospective and prospective epidemiologic studies on *all* tobacco-related diseases, with specific reference to brand of cigarettes smoked, number of cigarettes, manner of smoking, inhalation, etc., along with generation of data on "tar," nicotine, carbon monoxide, and other chemical content, as determined by the most up-to-date scientific methods. This same epidemiologic survey should include studies of individuals in high-risk occupations, of groups such as teenagers, minorities, and people of varying socioeconomic status, of men compared with women, and of different ages at which smoking began. Concern expressed by the group was, because cigarette composition in the United States is changing rapidly, without continued, well-planned, long-term studies, it will be difficult to know what effect the changing composition is having on the health of the American people.

3. An administrative mechanism to focus major interest on tobacco and the diseases caused by smoking tobacco should be established. Such a mechanism should include involvement of basic scientists, epidemiologists, physicians, statisticians, social scientists, and related experts concerned with smoking. There should be a stable source of funding for both new and established investigators to work together on tobacco and health problems over a period of time, since the answers to the questions raised over the past quarter-century will not come quickly, considering the magnitude and duration of the problem in the United States.

   Moreover, institutions and programs should be encouraged to train scientists for smoking research and to maintain a core group of physicians, scientists, and educators to consider various aspects of smoking research issues.

4. Additional work in carcinogenesis should be performed:
   a. It should be determined whether nitrosamines are formed from cigarette smoke in the human body and, if so, whether they are formed in significant concentrations. A key concern is whether nicotine itself forms nitrosamines in biologically significant quantities following reaction with nitrous oxides. The role of nicotine in human carcinogenesis should be identified.
   b. Tobacco additives and flavoring agents should be studied by appropriate methods for carcinogenicity and other toxicities, before their commercial use is permitted, and study data should be made available to the appropriate agencies.
   c. A continuing study of lower "tar" and nicotine cigarettes for carcinogenicity might detect changes resulting from new or different manufacturing practices or from new additives or flavoring agents that might act synergistically.
   d. The gas phase of cigarette smoke should be examined more fully for carcinogenicity.

e. Several carcinogens from cigarette smoke should be studied for synergistic, additive, or antagonistic effects on carcinogenesis because tobacco constituents are inhaled or swallowed as a mixture, not individually.
f. Further investigations of promoters, cocarcinogens, and initiators of cancer in cigarette smoke are necessary.
g. New models for carcinogenicity should be developed with emphasis on *in vitro* or short-term experiments.
h. Nicotine itself should be investigated for carcinogenic or cocarcinogenic action in animals even though it is a very toxic chemical. Similarly, acrolein should be tested for carcinogenic and cocarcinogenic action.
i. Anti-carcinogens or preventive compounds, such as vitamin A, retinoids, or other chemicals that may prevent carcinogenesis deserve further investigation.
j. There should be a registry for listing all the different chemicals identified in cigarette smoke, along with known properties of those chemicals.

5. Cooperative international epidemiologic studies should examine different tobaccos, ethnic groups, diets, and smoking habits. Such studies would describe the differences in development of tobacco-related cancers and elucidate the etiologic roles of differing cigarettes.
6. Genetic markers such as HLA or other indices should be sought to identify high-risk groups prone to tobacco-related diseases if they smoke. Genetically susceptible individuals should be counseled about their high-risk status.

Summary

1. Today's filter-tipped, lower "tar" and nicotine cigarettes produce lower rates of lung cancer than do their higher "tar" and nicotine predecessors. Nonetheless, smokers of lower "tar" and nicotine cigarettes have much higher lung cancer incidence and mortality than do nonsmokers.
2. Smokers of lower "tar" and nicotine cigarettes may tend to smoke larger numbers of cigarettes, to inhale more deeply, to have relatively higher amounts of carboxyhemoglobin than predicted from machine measurements of carbon monoxide yield, and to have higher than predicted carbon monoxide in exhaled air.
3. In attempting to develop a "less hazardous" cigarette, singular emphasis has been placed on reducing the "tar" yield of cigarette smoke because of the early demonstration of a causal relationship between "tar" and lung cancer. Comparable data on changes in

yield of constituents in the gas phase of smoke are not publicly available.

4. The occurrence of laryngeal cancer has been reported to be reduced among smokers who use filtered cigarettes, compared with those who use nonfiltered cigarettes.
5. There is no epidemiologic evidence to prove or to disprove a decreased occurrence of cancers of other sites in humans who smoke lower "tar" and nicotine cigarettes.
6. In evaluating the effect of smoking lower "tar" and nicotine cigarettes on histologic changes in the bronchial epithelium, it was determined in one autopsy study that male smokers who died between 1970 and 1977 had fewer histological changes than those smokers who died between 1950 and 1955.
7. Even among those who do not develop cancer, histologic changes in the tracheobronchial tree are more advanced at autopsy in smokers of cigarettes with higher "tar" and nicotine than among smokers of cigarettes with lower yields.
8. The "tar" content of smoke condensate of today's cigarettes is less tumorigenic to mouse skin than that of cigarettes of 30 years ago. Levels of the known carcinogen benzo[a]pyrene are lower in the smoke of today's cigarettes than in that of cigarettes of 30 years ago. Flavor additives used in lower "tar" and nicotine cigarettes produce traces of mutagenic compounds.
9. Although studies point to polycyclic aromatic hydrocarbons in the "tar" of inhaled cigarette smoke as potential carcinogens for humans, additional work is needed to determine whether nicotine plays a major role as a carcinogen. Definition of the role of nicotine in carcinogenesis is necessary prior to advocacy of cigarettes yielding less "tar" but more nicotine.
10. Animal studies have shown that a significant reduction of "tar" and a selective reduction of tumor initiators and cocarcinogens can markedly reduce the tumorigenic potency of cigarette smoke.

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Section 4. CARDIOVASCULAR DISEASES

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Introduction

The expectation that a lower "tar" and nicotine cigarette would be associated with less cardiovascular disease is based on two well-known epidemiological findings: (1) the strong dose-related association between cigarette use and coronary heart disease (CHD)—the largest component of cardiovascular disease; and (2) the evidence that if one quits smoking, the vascular consequences of smoking diminish. Table 1 shows that the more people smoke per day, the greater their risk of coronary heart disease. Table 2 summarizes several studies indicating that persons who quit have a lower risk of CHD.

These findings have been challenged (*41*) because the sample of smokers who have voluntarily quit may be biased through self-selection. Indeed, even prior to quitting, persons who stop smoking differ from those who continue smoking (*15*); however, their major cardiovascular risk factors do not differ (*18*).

A multivariate analysis of the impact of smoking on CHD that takes into account all the major possible confounders shows smoking's independent effect on CHD risk (*31*). In some studies (*18*), the quitters were more sick than those who continued to smoke, but none of the known major factors involved in CHD risk (disregarding cigarette smoking) explains the difference in CHD rates between smokers and nonsmokers. None of the factors distinguishing quitters from continu-

TABLE 1.—Coronary heart disease—mortality ratios

	Number of cigarettes smoked							
Reference	NS	10	10–20	<20	20	>20	20–40	>40
Hammond and Horn (*23*)	1.00	1.29	1.89				2.20	2.41
Doyle et al. (*14*)	1.00			2.00	1.70	3.50		
Doll and Peto (*13*)	1.00			1.29	1.27	1.43		
Pooling Project (*38*)	1.00	1.65			1.70	3.00		
Kahn (*29*)	1.00	1.39	1.78				1.84	2.00

NOTE: NS = Nonsmokers.

TABLE 2.—The effect of the cessation of cigarette smoking on the incidence of coronary heart disease (CHD)—morbidity ratios in males

Reference	Never smoked	Former smokers	Smokers
Hammond and Garfinkel (*21*)	1.00	1.16	1.62
Jenkins et al. (*27*)	1.00	2.15	2.36
Shapiro et al. (*42*)	1.00	0.76	1.87
Kannel et al. (*30*)	1.00	0.80	1.70

ing smokers clarifies why the risk of cardiovascular disease declines rapidly following smoking cessation.

The effect of smoking on CHD risk fulfills many epidemiological criteria for a causal association: powerful, independent, dose related, and reversible. When the association of smoking with CHD is adjusted by the other major risk factors, the coefficients are strengthened, rather than weakened (*19*).

At present only a few of the several thousand substances found in cigarette smoke have been implicated in cardiovascular risk; others have yet to be fully assessed. In order to facilitate a complete analysis, a study would have to measure the impact of each substance in cigarette smoke and establish its independent contribution. However, testing large fractions of cigarette smoke for cardiovascular risk might allow the elimination of specific constituents.

Currently, one can define only part of the impact of smoking on cardiovascular risk. What factors isolated in cigarette smoke are known to have cardiovascular consequences? What is already known of the cardiovascular impact of smoking cigarettes with some of these factors removed? In view of the rapidly changing variety of cigarettes found in the market, how can one keep pace with studying the cardiovascular impact of each new lower "tar," lower nicotine, lower carbon monoxide cigarette?

The Relation of Cigarette Smoking to Cardiovascular Risk

Many exhaustive reviews of this issue exist, and only a brief account of the essential findings is presented here. The chapter on cardiovascular disease in the 1979 Surgeon General's Report on Smoking and Health amply documents that cigarette smoking is a major, independent coronary heart disease risk factor in Western countries (*46*). There is substantial evidence from autopsies that more atherosclerosis is found in smokers than in nonsmokers (*44*). Hyaline thickening of arterioles in the heart is more prevalent in smokers (*6*). Experiments on atherosclerosis in animals, however, have not produced uniform results.

In those parts of the world where serum cholesterol levels are low, especially below 160 mg%, smoking is not as strong a risk factor as it is in the United States (*33*). After the age of 65, smoking poses less of a cardiovascular risk than it does in younger age groups (*31*). Study results differ on whether smoking is a risk factor in coronary heart disease following a myocardial infarction (*46*). The relationship of smoking to angina pectoris is uncertain (*27, 31*).

It is essential to emphasize these points because one could plan a study of lower "tar" and nicotine cigarettes in developing countries, with older subjects or with people who have already had a myocardial infarction or angina pectoris and find that the excess risk of CHD

among smokers had disappeared. To establish that lower "tar" and nicotine cigarettes cause less risk of CHD than higher yield cigarettes, there should be studies of randomly selected American men, 40 to 60 years of age, for the development of sudden death, first myocardial infarction, or peripheral vascular disease—endpoints with which cigarettes are associated at more than double the normal risk.

All the other factors associated with CHD risk should be measured simultaneously in a multivariate analysis so that any differences caused by quitter self-selection can be eliminated as the explanation of reduced risk. In this way, independent change in risk caused by the change in smoking behavior could be accurately assessed.

In addition to its effect on coronary heart disease, smoking increases the risk of arteriosclerotic peripheral vascular disease. Its impact on cerebrovascular disease is less uniform (*46*).

Factors in Cigarette Smoke Related to Cardiovascular Function

Most of the studies on cardiovascular endpoints associated with cigarette smoke have focused on nicotine and carbon monoxide rather than on "tar," which has not been demonstrated to have a major acute cardiovascular effect. Less is known about the effects of cadmium, zinc, chromium, carbon disulfide, carbon dioxide, tobacco antigens, hydrogen cyanide, nitrous oxide, or polonium-210, among other constituents of cigarette smoke.

Nicotine

Many studies have documented a dose effect of nicotine on cardiovascular function (*2, 45*). Acute studies in humans indicate a rise in heart rate, an elevation of systolic blood pressure, and cutaneous vasoconstriction. Cardiac output generally rises, but not always. Since stroke volume is generally not affected, or may fall, in patients with angina pectoris (*2*), the observed rise in cardiac output has been attributed to an increased heart rate.

Such changes have been attributed to a stimulation of sympathetic ganglia by nicotine. This stimulation results in a rise in catecholamines, which in turn produces variable degrees of positive chronotropic and inotropic cardiac actions. Other effects include generalized peripheral vasoconstriction and transient systemic (primarily systolic) hypertension (*7*).

Levels of free fatty acids rise in nicotine-treated subjects, possibly as another consequence of the catecholamine release (*32*). Whether free fatty acids affect cardiac function adversely, as some researchers have proposed (*37*), or aid in fatty deposition as others have suggested (*10*) has not yet been fully established.

Nicotine increases the diurnal secretion of cortisol (*26*). Plasma cortisol levels have been found to be elevated during myocardial

infarction, but the increase may be an effect rather than a cause of this condition. On the other hand, the cortisol rise has been implicated as a precursor of ventricular arrhythmias (*36*).

Nicotine-stimulated release of catecholamines has also been suggested as a cause of increased platelet stickiness and aggregation (*24*); this and other smoking-related hemostatic effects are potential mechanisms by which smoking may contribute to increased cardiovascular disease.

Although the evidence is meager, some of the acute effects of nicotine on cardiovascular function, such as elevation of heart rate and blood pressure, are dose related and apparently diminish in some lower-nicotine varieties of cigarettes (*2, 45*).

Carbon Monoxide

Carbon monoxide is inhaled in the form of a gas in cigarette smoke. Its affinity for hemoglobin is approximately 210 times greater than that of oxygen. The availability of oxygen to the myocardium is further decreased by the tighter binding of oxygen to hemoglobin in the presence of carboxyhemoglobin. Carbon monoxide also combines with myoglobin, impairing the availability of oxygen to the mitochondria. In addition, carbon monoxide can combine directly with cytochrome oxidase to slow the oxidation of reduced nicotinamide-adenine-dinucleotide (*55*).

Carbon monoxide has a direct impact on cardiac function in patients with angina pectoris, including a negative inotropic effect on the myocardium. Aronow (*1*) demonstrated an increase in left ventricular end-diastolic pressure, with a significant decrease in left ventricular dp/dt and stroke index. Anginal patients with increased carboxyhemoglobin levels also experience significantly shortened exercise time until the onset of angina pectoris (*3*). DeBias and co-workers (*12*) have also shown in monkeys that exposure to carboxyhemoglobin lowers the threshold for ventricular fibrillation.

Myocardial ultrastructural changes have been described in rabbits exposed to carbon monoxide. Among the changes are myofibrillar necrosis and mitochondrial degeneration (*5*).

Astrup (*4*) has proposed that carboxyhemoglobin increases hypoxia of vessel walls. Because this condition may increase the permeability to lipids, including cholesterol-laden lipoproteins, it may promote the process of atherosclerosis. It has been shown that exposure of humans to carbon monoxide increases the rate of disappearance of radioiodinated serum albumin (*43*). Wald and Howard (*49*) have shown that the carboxyhemoglobin level is more closely related to the prevalence of coronary heart disease than is smoking history. They emphasize that smokers who are physically active enhance their mechanisms for releasing carboxyhemoglobin and have a much better CHD prognosis than do sedentary smokers.

Other Components

McMillan (*35*) has reviewed studies on a variety of other factors in cigarette smoke and has concluded that much more data are needed. He noted a possible association of cadmium with hypertension. Smoking generally results in an acute rise in blood pressure, but has not been proved to cause chronic hypertension. Whether tobacco antigens play a role in increased endothelial cell damage is conjectural. Finally, McMillan considered the hypothesis proposed by Benditt and Benditt (*18*) that atherosclerosis is really caused by monoclonal smooth muscle cellular proliferation. If so, one may be persuaded that "tar," which is mutagenic, is atherogenic after all.

Studies of the Impact of Lower "Tar" and Nicotine Cigarettes on Coronary Heart Disease

Not all cigarettes that produce a lower yield of one substance necessarily provide a lower yield of other substances. Indeed, research suggests that cigarettes with unperforated filters ("unventilated"), which yield lower "tar" and nicotine levels than do nonfiltered cigarettes, may increase exposure to carbon monoxide (*53*) and lead to higher levels of carboxyhemoglobin (*52*). Cigarettes with perforated ("ventilated") filters may produce lower carbon monoxide yields (*52*).

People who smoke lower "tar" and nicotine cigarettes do not generally smoke substantially more cigarettes per day than smokers of higher yield cigarettes (*16, 40, 51*); however, their intake of "tar," nicotine, and carbon monoxide is higher than would be predicted by data from machine-smoked cigarettes. This suggests that these cigarettes are smoked more intensively than higher yield cigarettes (*40, 51*).

There is evidence from four studies of the association between cardiovascular disease and the use of lower "tar" and nicotine cigarettes. Hammond et al. (*22*), in their prospective study of volunteers of the American Cancer Society, have shown reductions of 10 to 20 percent in observed coronary deaths among persons smoking lower "tar" and nicotine cigarettes when compared with those who reported smoking similar numbers of regular cigarettes per day. Hawthorne and Fry (*25*), in three prospective surveys of over 18,000 persons in west-central Scotland, showed a slightly increased relative coronary mortality in persons who smoked filtered cigarettes compared with persons who smoked unfiltered cigarettes. Dean et al. (*11*), in a retrospective mortality study in northeast England published by the Tobacco Research Council, showed relative risks of about 0.6 for coronary heart disease and 0.4 for cerebrovascular disease in filter cigarette users versus smokers of unfiltered cigarettes. Unfortunately, smoking habits of cases and controls were obtained from different sources and at different times, confounding the study design. Recent

TABLE 3.—Filter cigarettes and risk of coronary heart disease in men

Reference	Plain	Filter
Hawthorne and Fry (*25*)	1.00	1.04
Hammond et al. (*22*)		
Low "tar" { Period 1	1.00	0.98
Low "tar" { Period 2	1.00	0.82
Medium "tar" { Period 1	1.00	0.91
Medium "tar" { Period 2	1.00	1.08
Dean et al. (*11*)	1.00	0.66
Castelli et al. (*9*)		
< 55	1.00	1.02
55+	1.00	0.85

unpublished data from Framingham (*9*) have failed to show a lower CHD risk among smokers of filter cigarettes, and in younger men there was actually a slightly higher rate of coronary disease among smokers of filtered cigarettes (Table 3).

This study took into account the other major CHD risk factors (cholesterol, blood pressure, and age); the increased risk in filter smokers is independent of effects attributed to these other factors. Overall, use of lower "tar" and nicotine cigarettes has not produced a consistent decrease in risk for cardiovascular disease; indeed, in some studies a slight increase in risk has been seen. Additional studies will be needed to assess the actual impact of any changes in the composition of cigarettes on subsequent CHD rates. Terms like "lower yield" may describe only part of the change; other additives and the overall use of the cigarette might actually increase risk. Wald (*54*) has shown that, in the United Kingdom, while lung cancer mortality fell in men from 1956–60 to 1969–73, with the change to filter cigarettes, CHD mortality increased. The author wondered whether the decrease in "tar" accounted for the lower lung cancer death rates, and whether unchanged levels of carbon monoxide might have contributed to the observed continuing rise in CHD death rates.

The Challenge of Future Research

In the United States, virtually no filtered cigarettes were smoked before 1950; now 90 percent of the cigarettes sold are filtered. The sales-weighted average "tar" composition per cigarette has decreased from over 35 mg of "tar" per cigarette in the early 1950s to under 15 mg in 1979. Currently, nicotine has decreased from over 2.5 mg per cigarette to about 1.0 mg per cigarette. Ultra low nicotine and "tar" cigarettes are now increasingly available, with levels of under 1.0 mg "tar" and 0.1 mg nicotine. Unfortunately, the amount of carbon monoxide delivered by cigarettes has not been studied as intensively as the "tar" and nicotine levels, although a recent United Kingdom

survey of old and current cigarettes indicates that carbon monoxide yields have changed much less than "tar" or nicotine yields. This may be the case in the United States as well. Linking cigarette carbon monoxide yields to possible toxicity is further complicated by the fact that patterns of smoke inhalation for lower "tar" and nicotine cigarettes may differ from patterns for higher "tar" and nicotine cigarettes (*51*).

A technique should be developed to monitor the effect of changes in cigarette composition, particularly in nicotine and carbon monoxide content, on cardiovascular risk.

Proposed Future Research

Descriptive Studies

Continued research into the changes in cigarette smoking is needed. Surveys such as the National Health and Nutrition Examination Survey (NHANES), prospective epidemiological field studies, and prepaid hospital insurance group studies are needed to provide comprehensive information on cardiovascular disease caused by smoking. Such studies should include worldwide data surveillance.

Cohort Studies

Observational Studies

Observational studies are studies of large populations in which a variety of factors related to cardiovascular disease are measured and followed, permitting an independent analysis of variables such as a given cigarette brand.

There are now a number of studies that follow a given population over a period of time to assess prospectively the impact of smoking. Some of these are traditional single-town studies in which a random sample of a given population is followed over varying time intervals, often every 2 to 5 years. Examples of such studies are those in Framingham, Tecumseh, Puerto Rico, Evans County (Georgia), Honolulu, and Goteborg and Stockholm, Sweden, where whole populations or samples thereof are followed on a more or less continuous basis. In addition, there are worksite studies, such as the Albany civil servants, People's Gas Company of Chicago employees, Western Electric workers (Chicago), Minneapolis business executives, California longshoremen, and British doctors, which call for repeated observations. Questionnaire studies, such as the American Cancer Society's 25-State Study or the 9-State Study, the U.S. Veterans Study, the Canadian Veterans Study, the Swedish Study, the Japanese 29 Health Districts Study, and the Study of California Males, can observe as many as a million subjects.

In addition to measuring the risk for cardiovascular disease, most of these studies also assess other consequences of smoking. They allow, better than any other studies, the calculation of the independent effect of smoking.

The shortcoming of these prospective studies has been that the average turnaround time has been approximately 10 years. Occasionally, a 4-year interval produces enough data for a meaningful analysis, but with the rate of change in the composition of cigarettes, the information could be outdated by the time the data are collected and analyzed.

Clinical Trials

Several clinical trials of the effect of smoking intervention on coronary heart disease are in progress. Perhaps the most promising of these is the Multiple Risk Factor Intervention Trial (MRFIT) (*28*), in which high-risk men were randomly assigned to a special-intervention group and a usual-care group. The study, now in its 6th year, avoids self-selection bias by contrasting the overall disease experience of the two randomly assigned groups. Unfortunately, the inferences that may be drawn about lower "tar" and nicotine cigarettes *per se* (which is only a part of the intervention program) are somewhat limited and do involve self-selection. Another problem is that this study directs its intervention to serum cholesterol and blood pressure control as well as to smoking cessation. Nevertheless, long-term studies like the MRFIT are recommended because the followup of cohorts may provide findings that differ qualitatively from those available in strictly observational studies and because the measurement of other major risk factors permits the estimation of the independent effect of smoking behavior changes. All such clinical trials should incorporate the conviction of the medical and public health communities that current smokers ought to quit and that nonsmokers should not begin to smoke.

Case-Control Studies

Case-control studies have the advantage of relatively short turnaround times and usually are less expensive than other studies. Unfortunately, unless very carefully designed, they can suffer from a partial and therefore less accurate assessment of the disease under study. For example, in studying cigarettes, one must assess the death endpoints of coronary disease. The problem in studies of this kind is how to compile an objective smoking history of the deceased. Obtaining information from a spouse or close associate introduces a certain amount of error, but this error may be controlled somewhat by interviewing close associates of the members of the control group.

In studies of nonfatal myocardial infarction, the survival of both the cases and the controls allows more precise measures of the variables under study.

Despite shortcomings, case-control studies represent the major means for assessment of the relative cardiovascular risk of varying cigarettes. Further, serial case-control studies, similarly designed, performed, and analyzed, could provide information on changes in risk over time. In such studies care must be taken to select appropriate controls, to treat cases and controls alike, to avoid hospital-based rosters, and to study well-defined and documented endpoints.

Studies of Mechanisms

In view of the difficulties involved in doing large population-based studies and the need to know more about the mechanisms whereby cigarettes cause damage, more studies are needed on the components in cigarettes that affect cardiovascular risk. It may be that nicotine and carbon monoxide are the chief toxic agents, but until more is learned of the other constituents, judgements are based on scanty information.

Perhaps the main reason to pursue the study of disease mechanisms is to shorten the turnaround time for assessing any new brand of cigarette; studies could be designed to measure particular constituents of the cigarette smoke and characteristics of the subject at risk.

With better noninvasive cardiovascular techniques, studies of how a particular cigarette affects cardiac function could be performed in greater depth. Such studies would provide better measurement of the biological effect of the cigarette smoke components in individual smokers. Measurement of expired carbon monoxide, serum carboxyhemoglobin, thiocyanate, and cotinine would help resolve not only differences in the composition of cigarettes, but also major differences in the ways individuals smoke (*47*, *48*). These more precise measurements of smoke exposure and dosage of smoke constituents could be correlated with a host of biochemical and physiological parameters.

The number of biochemical factors found to be affected by smoking continues to grow. Lower HDL cholesterol levels are found in smokers than in nonsmokers, an effect that is associated with an increased CHD risk (*17*).

A variety of effects could be weighed to produce a multifactorial analysis of how cigarettes produce atherosclerosis, sudden death, and other cardiovascular problems.

Physiological studies using treadmill performance, scintillation scanning—including gated pool studies—and Holter monitoring could provide better clues to the action of cigarettes on cardiovascular function. If such alterations in function could be more certainly tied to later events, they might prove invaluable predictors of smoking-related risk for a given individual.

Animal Experimentation

Most of the animal models used in studies of the effects of cigarette smoke have been designed to test its carcinogenicity on the bronchial epithelium or the skin of small animals, usually rodents. A few models have been developed to examine the effects of inhalation on the respiratory and cardiovascular systems of rodents, dogs, or nonhuman primates (*20*). Very few animal studies have attempted to assess the effects of different cigarette smokes in inhalation studies of experimental atherosclerosis or on the styles of inhalation that may be intervening variables in the pathogenesis of atherosclerosis. It is feasible to induce nonhuman primates to inhale cigarette smoke (*34*). Such primates frequently develop many of the physiologic changes related to the atherosclerosis found in human smokers (*39*). The further utilization of such animal models would permit a comparison of the effects of proposed lower "tar" and nicotine cigarettes with the effects of conventional higher yield cigarettes under controlled conditions. Subjects could be assigned randomly to different types of cigarettes to eliminate the self-selection bias.

The primates could be examined for effects of smoke from different cigarettes on response variables such as serum lipids and lipoproteins. At this time, the augmentation of experimental atherosclerosis by exposure to cigarette smoke has not yet been demonstrated; further development of an animal model must occur before definitive studies in atherogenesis will be practical.

Technical Resource Center

In addition to monitoring research evidence on the impact of smoking on health, further activities should focus on developing tools for the conduct of studies on the impact of smoking on health in several areas. A standard questionnaire on smoking should be refined for use by the various studies in the United States and in foreign countries.

In addition, techniques for measuring actual exposures to carbon monoxide, cotinine, nicotine, and many other substances could be evaluated to determine the most effective analytic techniques. Where debate continues on the merits of one test versus another, studies should be designed to resolve the issue. Control of test quality should be instituted and could be ascertained, even from widely disparate groups. Not only could a hierarchy of useful tests be provided, but a quality-control mechanism should be developed to ensure continued high performance.

Finally, frequent updated ratings of "tar," nicotine, and particularly carbon monoxide yields would permit others to conduct better studies of the impact of cigarette smoke components on cardiovascular functions.

Behavioral Ramifications

It is important to determine the effect of lower "tar" and nicotine cigarettes on cardiovascular disease risk reduction. A key unknown is whether efforts to persuade people to switch to lower "tar" and nicotine cigarettes interfere with other efforts to persuade people not to begin smoking or to quit. Activities to provide a less hazardous cigarette should not interfere with efforts to eliminate cigarette smoking.

Finally, given the limitation in research funds, priorities for research must be drawn. The research proposals outlined above are of high priority. The combination of results from a variety of studies can provide a consensus on the impact of a given innovation in lower "tar" and nicotine cigarette composition. Ultimately, the effect of lower "tar" and nicotine cigarettes will be measured in terms of smoker morbidity and mortality.

Summary

1. Epidemiological studies show that the incidence of coronary heart disease (CHD) increases as the daily number of cigarettes smoked increases and that the incidence of CHD decreases among those who quit smoking. These dose-related effects suggest that lower "tar" and nicotine cigarettes might be associated with lower risks of CHD. However, the overall changes in the composition of cigarettes that have occurred during the last 10 to 15 years have not produced a clearly demonstrated effect on cardiovascular disease, and some studies suggest that a decreased risk of CHD may not have occurred.
2. Of the several thousand substances found in cigarette smoke, only a few have been implicated in cardiovascular risk. A number of substances have not yet been adequately assessed. Further, the changes in smoke constituents that have resulted from changes in the cigarette product have not been documented.
3. Linking cigarette smoke yields to cardiovascular disease is complicated by the evidence that smokers of lower "tar" and nicotine cigarettes may smoke more "intensively," although they may not smoke a substantially greater number of cigarettes daily than do smokers of higher "tar" and nicotine cigarettes. The net result could be to decrease the actual intake of "tar," nicotine, and carbon monoxide less than that expected on the basis of machine measurements.
4. Nicotine stimulates the sympathetic nervous system, producing a rise in catecholamines that in turn increases heart rate, elevates systolic blood pressure, constricts cutaneous blood vessels, and increases levels of free fatty acids. The nicotine-stimulated release of catecholamines has been suggested as the cause of

increased platelet stickiness and aggregation, pointing to a potential role in coronary disease. There is some evidence that these physiological effects may be dose related and somewhat diminished with lower nicotine varieties of cigarettes.

5. Carbon monoxide has a negative inotropic effect on the myocardium of patients with angina pectoris. When combined with hemoglobin in the form of carboxyhemoglobin, carbon monoxide may increase the permeability of the blood vessel walls to lipids, thereby promoting atherosclerosis.
6. Cigarettes with unperforated filters yield lower "tar" and nicotine levels than unfiltered cigarettes, but they yield more carbon monoxide than do unfiltered cigarettes at the same "tar" yield. Carbon monoxide yields are lower in cigarettes with perforated filters, but as the composition of cigarettes has changed, carbon monoxide yields have decreased much less in proportion to the decrease in "tar" and nicotine yields.
7. In studies of patients with angina pectoris, increased carboxyhemoglobin levels significantly shorten exercise time until the onset of angina pectoris.
8. Myocardial ultrastructural changes have been found in rabbits exposed to carbon monoxide.
9. Most cardiovascular studies have focused on nicotine and carbon monoxide rather than on "tar," which has not been shown to have a major acute role in cardiovascular disease. Even less is known about other constituents of cigarette smoke.
10. Not all cigarettes that produce a lower yield of one substance necessarily provide a lower yield of other substances.
11. Evidence on the association between CHD and filter cigarettes is somewhat conflicting. One major study showed a reduction of 10 to 20 percent in coronary deaths among persons smoking lower "tar" and nicotine cigarettes as compared with those who smoked higher yield cigarettes, but other surveys have shown a slightly increased risk of coronary mortality in people who smoked filter cigarettes relative to those who smoked nonfiltered cigarettes. Recent unpublished data from the Framingham Study do not show a lower CHD risk among smokers of filter cigarettes.

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Section 5. CHRONIC OBSTRUCTIVE LUNG DISEASE

CONTENTS

The Research Problem

The causal relationship between cigarette smoking and chronic obstructive lung disease (COLD) (chronic bronchitis and chronic obstructive pulmonary emphysema) is well documented (*34*). However, the possible differences in the effects of higher versus lower "tar" and nicotine cigarette smoke in the pathogenesis of chronic obstructive lung disease are not known. COLD usually progresses slowly; physiologic and pathologic abnormalities may exist for an extended period of time prior to the development of disabling clinical manifestations. The latter are usually associated with severe lung damage or destruction. It is uncertain which of the many ingredients in cigarette smoke has a role in the production of COLD. Lower "tar" and nicotine cigarettes may have no impact, or indeed an untoward impact, on the development of COLD. Therefore, it is urgent that research be carried out to resolve this complex problem.

Cigarette-related chronic lung disease may be subdivided into three major components: (1) uncomplicated chronic bronchitis, a disease of mucous hypersecretion and cough; (2) chronic bronchitis and bronchiolar inflammation, similar to (1) but with airflow limitation caused by intrinsic airway pathology; and (3) emphysema, a disease associated with anatomical hyperinflation of the distal air spaces and destruction of lung parenchyma. Because cigarette smoking is associated with all of these conditions, they commonly coexist. The factors causing one or more of these diseases to develop in response to cigarette smoke in some individuals and not in others are unknown. Cough and mucous hypersecretion are common symptoms among cigarette smokers, while evidence of airflow limitation is significantly less common. Recent evidence suggests that the early stage of emphysema is associated with cigarette smoking-related inflammation in airways less than two millimeters in diameter (*11*).

Research on the response to inhaled irritants is usually focused on one or more of the anatomical components of the lung: the airways, the cellular and biochemical contents of the alveolar spaces, and the contents and structure of the alveolar septa or interstitia. Responses in the airways may consist of alterations in epithelial cell types, mucous gland hyperplasia, hypersecretion of mucus, inflammation, impairment of mucociliary function, abnormalities of immunologic factors or other substances, smooth muscle hyperreactivity and hypertrophy, and intrinsic narrowing fibrosis or destruction of small airways. Physiologic responses reflect airflow limitation, early closure of small airways, and nonuniform distribution of inspired air.

In the alveolar spaces, free cells (including alveolar macrophages and neutrophils), surfactant (a phospholipid secreted by the alveolar lining cells), enzymes released or secreted by macrophages or neutrophils, and protease inhibitors and other proteins that reach the alveolar spaces by transudation from the circulation are all under study. The alveolar

septum or interstitium, consisting of alveolar lining cells, basement membrane, capillary endothelial cells, other alveolar interstitial cells, and the connective tissue framework composed primarily of collagen, elastin, and proteoglycans is the focus of much research. Physiologic alterations reflect decreased surface area for gas exchange and alterations in the elastic recoil of the alveolar structures.

The lung plays an active role in the production and metabolism of various bioactive substances such as angiotensin, prostaglandins, and serotonin. This anatomically, physiologically, and biochemically complex organ is exposed to the external environment and its agents, including cigarette smoke and air pollution. Complicating host factors also affect this system: age; sex; inherent reactivity of the airways; genetic factors that predispose to emphysema, such as alpha$_1$-antitrypsin deficiency; childhood infections; and as yet undefined familial factors.

The design of experiments to determine the short- or long-term effects of cigarettes on smokers is made difficult because the composition of cigarettes and the population of smokers have been changing over the past 10 to 15 years. Further complicating this problem is the large number of tobacco smoke components with varying solubility and interactive capabilities. There is also a lack of knowledge of the topography of cigarette smoking. Individual differences in the mechanics of smoking such as the volume of puff, holding time in the oral cavity, depth of inhalation, time of retention in the lung, and length of butt significantly influence the composition, distribution, penetration, and retention of cigarette smoke components in the lungs. The topography of smoking may vary depending on the nicotine content. The composition and concentration of the gas phase components that reach the small airways and alveoli may have a significant role in the production of emphysema, while the particulate matter that deposits in the larger airways may be more involved in the development of chronic bronchitis. The target tissues, cells, or ultrastructural components may be different in chronic bronchitis and emphysema. Thus it is extremely important to develop a better understanding of the topography of smoking so that appropriate experiments can be designed to determine dose-response relationships of pertinent smoke components and the reactions to them in the different regions of the lung. The problem is that of assessing the effects of continually changing cigarette products on a continually changing population of smokers. The ultimate concern is for the effects on smokers. For chronic lung disease, this effect can best be assessed by the combination of epidemiologic evaluations of populations at risk and laboratory evaluations of the effects of smoke on the mechanism of disease production.

Current Research Findings

Recent advances in research have led to a plausible hypothesis for the etiology of pulmonary emphysema: If an imbalance between endogenous elastolytic enzymes and protease inhibitors in the lungs permits active enzymes to exist in the alveoli or alveolar walls, degradation of the alveolar tissue components, primarily elastin, will occur (*25, 26*). The sources of endogenous elastase are polymorphonuclear leukocytes and alveolar macrophages. The major source of the inhibitor is the serum protein, alpha$_1$-antitrypsin, which reaches the alveolar space by the process of transudation. This hypothesis is reinforced by experimental data from a variety of sources. Humans with a genetically transmitted deficiency of alpha$_1$-antitrypsin are prone to develop emphysema (*29*). The instillation of elastolytic enzymes into the lung, including human neutrophil elastase, will produce experimental emphysema in animals (*33*). Cigarette smoke is implicated in this process by mechanisms that may lead to the development of emphysema.

Alveolar macrophages from smoke-exposed mice increase in number and secrete significantly greater amounts of elastase than macrophages from control mice (*35*). Human alveolar macrophages from cigarette smokers also secrete significantly more elastase than macrophages from nonsmokers (*32*). Alveolar macrophages exposed to cigarette smoke produce a chemotactic substance for polymorphonuclear leukocytes (*17*). Mild exposure to cigarette smoke also increases the release of elastase from human polymorphonuclear leukocytes (*5*).

Cigarette smoke inhalation decreases the alpha$_1$-antitrypsin activity in the rat lung (*22*), and alveolar lavage from human smokers shows a functional antiprotease deficiency (*16*). This effect of cigarette smoke on alpha$_1$-antitrypsin is related to its oxidant effect (*1, 8*). The loss of inhibitory activity of alpha$_1$-antitrypsin is induced by oxidation of methionine residues at the reactive center of the molecule (*23*). A chemical oxidant, chloramine-T, administered to dogs, also induces a reduction in the elastase inhibitory capacity of both the serum and alveolar lavage fluid, and the animals develop morphologic changes of mild emphysema (*13*). This animal model simulates the human alpha$_1$-antitrypsin deficiency state except that the deficiency is functional and not in absolute quantity. Oxidants are also released when polymorphonuclear leukocytes are exposed to exogenous elastase (*27*).

This *in vivo* and *in vitro* experimental evidence indicates that cigarette smoke both increases the amount of elastase in the alveolar tissue or air spaces and simultaneously reduces the functional capacity of the primary elastase inhibitor, alpha$_1$-antitrypsin, and links the action of cigarette smoke to the possible production of disease in humans. Although there is general acceptance of the protease-inhibitor imbalance hypothesis, it has yet to be directly related to human emphysema. There are no available studies in which smoke from

regular and lower "tar" and nicotine cigarettes has been used to determine if there are differences in their effects on elastase or oxidant release or production, or concentrations of cigarette smoke oxidants that could affect the functional capacity of alpha$_1$-antitrypsin.

Small airway inflammation and bronchiolar inflammation develop much more frequently in smokers than in nonsmokers (*11*). Findings in the lungs of individuals 40 years of age or older who died suddenly of nonrespiratory causes revealed inflammation, increased numbers of goblet cells, and muscular hypertrophy in small airways. There was also an increase in airways under 400 microns in diameter and in the occurrence of respiratory bronchiolar inflammation in the smokers. The lungs showing both the largest number of small (under 400 microns) airways and the most airway pathology had the most centrilobular emphysema, the predominant type found in cigarette smokers. The respiratory bronchiolar inflammation was characterized by infiltration with macrophages that extended into adjacent alveolar walls. Previous studies of resected lung from smokers showed that the severity of similar small airway pathology in excised human lungs correlated with impairment in ventilatory function (*10*). The small airway disease and severity of emphysema also correlated with changes in small muscular pulmonary arteries that could be important in the development of pulmonary hypertension (*19*). These studies suggest that cigarette smoke produces small airway pathology, which is a factor in ventilatory function impairment. The respiratory bronchiolar inflammation may initiate an enzyme-inhibitor imbalance in the centrilobular regions. The release of elastase from alveolar macrophages and from neutrophils brought to the alveoli by increased chemotaxis and the impairment of alpha$_1$-antitrypsin function could be stimulated by cigarette smoke in the alveolar spaces. This leads to destruction of alveolar wall elastin and then to the morphologic and physiologic changes observed in emphysema.

The oxides of nitrogen occur at relatively high levels in cigarette smoke and at lower levels as an ambient air pollutant. Exposure of dogs to NO_2 and NO for 68 months resulted in pulmonary function changes characteristic of emphysema (*18*) that continued to progress after cessation of exposure. Long-term exposure to oxides of nitrogen results in airway and alveolar epithelial changes and parenchymal damage that suggest an emphysema-like disease (*14*). Evidence suggests that the damage is induced by an oxidant-type mechanism. In addition, the most severely affected tissues are the terminal bronchioles, alveolar ducts, and adjacent alveoli, which are infiltrated with inflammatory cells. The latter are primarily macrophages with other mononuclear cells and occasional granulocytes. Interruption and thickening of elastic fibers in alveolar walls were observed. These lesions are similar to those induced by cigarette smoke and suggest

that the oxides of nitrogen may be one of the agents responsible for the initiation of the early lesions of human emphysema.

As an outgrowth of the elastase-inhibitor imbalance hypothesis for the etiology of emphysema, new potential markers or indicators of disease are being investigated. Since lung elastin appears to be the target substance for degradation, several laboratories are seeking a method to identify products of elastin breakdown that would serve as markers for the development of emphysema. In one study, peptide breakdown products of lung elastin were identified in the serum of dogs in which experimental emphysema was induced by the administration of elastase (*28*).

Other investigators are measuring the urinary excretion of desmosine, the cross-linking amino acid of elastin that appears as a breakdown product. If it can be demonstrated that elastin degradation products are significantly elevated in the blood or urine of smokers who have early emphysema, undetectable by other means, further development and refinement of such tests may provide a sensitive biochemical marker or screening test for the early detection of emphysema. Such a measurement would simplify cross-sectional and other epidemiologic studies in which the results in subjects who smoke regular cigarettes could be compared with those of subjects who smoke lower "tar" and nicotine cigarettes.

Studies of acute human responses to the different types of cigarettes, which may be important in the pathogenesis of chronic lung disease, are beginning to appear. The type of cigarette and the amount of smoke inhaled into the lungs, measured by changes in blood nicotine level or carboxyhemoglobin level, are not related to the occurrence of acute airway responses to smoke inhalation (*21*). The authors found that individual susceptibility is a factor, but even more important is the smoking pattern. Holding the smoke in the mouth prior to inhalation into the lungs reduced the response, whereas direct inhalation from the cigarette into the lungs caused an increased number of smokers to develop spirometric changes indicative of bronchoconstriction. This was independent of "tar" yield and reinforces the importance of the cigarette smoking pattern in the dose-response relationship. The study showed that the habitual cigarette smoker avoids the direct irritant effect of cigarette smoke by temporarily storing the smoke in the mouth before inhaling it into the lungs and also demonstrated that the smoke inhalation pattern is important in determining the relevant concentration of the constituents of smoke that reach the lungs.

There are few epidemiologic studies, either cross-sectional or longitudinal, that deal with differences relating to the "tar" and nicotine yield of cigarettes smoked. In a survey of over 18,000 civil servants (*20*), the "tar" yield and the number of cigarettes smoked daily were correlated to respiratory symptoms and spirometry. Sputum

production and air flow obstruction increased as cigarette consumption increased. "Tar" yield influenced sputum production, but not the degree of air flow obstruction. When subjects smoking lower "tar" cigarettes smoked over 20 per day, their sputum production was the same as that of the higher "tar" cigarette smokers. In this study of asymptomatic men, the air flow obstruction was related to the daily cigarette consumption. Higher "tar" cigarette smokers did not have a greater air flow obstruction than those using lower "tar" cigarettes. If there was a compensating increase in the number of cigarettes smoked by the smokers of lower "tar" and nicotine cigarettes, the advantage of reduced mucous hypersecretion was lost. Ex-smokers had better lung function than current smokers with comparable total cigarette consumption. The authors conclude that mucous hypersecretion depends on the "tar" fraction of the cigarette's smoke and that the development of air flow obstruction depends on the number of cigarettes smoked. They reason that the gas phase of the smoke, particularly the volatile compounds, was responsible for damage leading to air flow obstruction. They hypothesize that "tar" droplets and soluble gases, such as sulfur dioxide and hydrogen cyanide, are more likely to be deposited or absorbed in the larger bronchi where mucus is produced. The smaller bronchi, which are the site of airway obstruction, and the alveoli are exposed to a lower concentration of "tar," but to a full concentration of insoluble gases, such as the nitrogen oxides and ozone. Higenbottam and co-workers (*20*) did not differentiate between emphysema and chronic bronchitis as a cause of airway obstruction. The authors conclude that smokers of lower "tar" cigarettes who compensate by smoking more cigarettes or inhaling more deeply may increase the risk of obstructive airway disease. They suggest that more information is needed about the nature and concentrations of irritants in the gaseous phase of smoke and their relation to concentrations of "tar" and respiratory damage.

Another British study (*15*) indicates that filter cigarette smokers report less cough. The difference between the groups of smokers was relatively small, however, and the filter cigarettes that were smoked are probably dissimilar to those currently smoked in this country. Dean et al. (*12*) reported the results of two retrospective studies, separated by an interval of 10 years but carried out in the same area, to determine whether the increasing use of filter cigarettes produced less risk of dying of four diseases, including chronic bronchitis. In the second study, relatives of those who had died were interviewed to obtain the information about the smoking habits of the deceased individuals. The cause of death was determined from death certificates. A living population was selected as the control sample. The investigators found that mortality from chronic bronchitis was related to age, to the number of cigarettes smoked, and to the level of inhalation. The estimated risk of mortality from chronic bronchitis of

the population who smoked filter cigarettes since 1954 was about half that of the continuing regular cigarette smokers. Many features of this study could cause bias or misinterpretation: information was collected from relatives of deceased individuals; the information on the living and the deceased populations related to different points in time; and changes in air pollution levels and in the population probably occurred during the period of the study. From the epidemiologic standpoint, firm conclusions cannot be drawn from this study.

In an ongoing study of a healthy population, the rates of decline of pulmonary function in smokers and nonsmokers show only a very small difference (*6*). However, 8 to 12 percent of smokers have a distinctly more rapid decline in the FEV_1. These are primarily male smokers and may represent the group who will ultimately develop symptomatic obstructive lung disease. In the entire population, the tests of "small airway function," such as closing capacity, show no difference in the rate of change between smokers and nonsmokers. These tests tend to be abnormal in those individuals who develop an abnormal FEV_1, but at the same time, a large number of subjects with abnormal tests of small airway function will not develop a rapidly decreasing FEV_1. Data about differences in the type of cigarettes smoked were not obtained, but the extremely small difference between healthy smokers and nonsmokers, except for the small group of rapid decliners, suggests that studies of large populations with this objective may not be revealing.

Another longitudinal study suggests that a study of approximately 8 years is necessary to identify those asymptomatic smokers who will show a significantly accelerated rate of lung function deterioration (*15*). This study also finds that, in spite of frequent smoking-induced cough and expectoration, only a relatively small percentage of smokers show a greater than average decline in respiratory function. The authors report that when a group of asymptomatic middle-aged smokers who had subnormal FEV_1 levels and rapid decline stopped smoking, the rate of deterioration reverted to that of nonsmokers although there was no significant improvement in the initially determined abnormal lung function. This study did not distinguish between the effects of lower "tar" and nicotine and regular cigarettes.

The traditional tests of airflow limitation such as FEV_1 are thought to reflect changes relatively late in the course of disease. Some investigators have demonstrated that flow measurements taken from the near terminal part of the forced vital capacity tracing are more sensitive, but these are not widely used to date (*30*). Newer tests of small airway function such as slope of phase III, closing capacity, and volume of isoflow with helium and oxygen have not been established for their specificity in indicating the development of significant chronic lung disease (*4*).

A study carried out in two successive decades, in which successively autopsied airways from lungs of smokers were studied for bronchial epithelial changes, demonstrated a decrease in changes thought to be related to carcinogenesis (*2*). This favorable change was thought to be related to the increasing use of lower "tar" and nicotine cigarettes. Unfortunately, this study did not examine the lungs for evidence of chronic obstructive lung disease.

Future Research Approaches

Animal models in which emphysema has been induced by elastolytic enzymes have been reported by a number of authors (*24*), but for reasons that may reflect a combination of factors, such as the shorter life span of animals, the method of smoke exposure, and species resistance, there are no published studies that acceptably show in an animal model that the development of emphysema is induced by cigarette smoking. Thus, a successful animal model has not been developed in which the relationship of different types of cigarettes to the development of emphysema can be studied. One study in which dogs received smoke directly through chronic tracheotomies reported the development of emphysema (*3*). The lesions were not conclusive and the results have not been confirmed by others. Therefore, to elucidate more clearly the differences between regular and lower "tar" and nicotine cigarette smoke exposure, it will be necessary to study other aspects of lung function, either biochemical or physiological, that may be altered by the cigarette smoke and that are projected to be important pathogenetic mechanisms in humans.

As suggested in the preceding paragraphs, much new information will be needed before conclusions can be drawn about the effect of lower "tar" and nicotine cigarettes on the development of COLD. Acute and subacute responses could be measured by physiologic studies, although such responses may not be relevant to the development of chronic, irreversible lung disease. The quantity and composition of mucus secreted in the airways in response to different types of cigarettes may be studied in animals or humans. The histology of the bronchial mucosa may be evaluated in human material from lobes or lungs resected for other reasons, from biopsy specimens, or from post mortem findings in which changes related to chronic bronchitis or emphysema are specifically quantitated. In autopsy or resected lungs from smokers of regular and of lower "tar" and nicotine cigarettes, factors in the small airways such as lumen size, number of airways, cell types, goblet cells, muscle hypertrophy, and inflammation may be evaluated. Enzyme inhibitors produced in the tracheobronchial tree could also be evaluated, as could the secretion of immune globulins. Effects of cigarette smoke on the mucociliary function of the bronchial mucosa is another potential measurement.

The response of the alveolar region of the lung could be determined by biochemical, morphologic, and physiological techniques. The cellular content of the air spaces, the functional status of alpha$_1$-antitrypsin, the presence of chemotactic factors, oxidant production by neutrophils or macrophages, elastase production and inhibition, and degradation products of lung elastin may be measured in response to smoke exposure. Human studies would require bronchioalveolar lavage to obtain these data, although the invasive nature of this technique may preclude its use in large populations lacking other indications. Production and turnover rates of lung elastin and collagen, the numbers and types of interstitial cells, and the presence of free or bound elastase may be evaluated in the interstitial tissue. Macrophage and neutrophil responses to the whole smoke and selected fractions can be investigated. These include phagocytosis and elaboration of elastases, chemotactic factors, and oxidants. Surfactant production and alterations might be evaluated. Many of these factors are deemed important in the determination of the protease-antiprotease balance in the lungs. The development of some measurements into standard biologic assays by which the various types of cigarette smoke may be evaluated would be a valuable advance. This research would not only aid in the development of techniques to assess the response to various types of smoke, but also would add important information to our knowledge of the pathogenesis of disabling chronic obstructive lung disease in humans. Physiologic measurements of lung volumes, elastic recoil, and diffusing capacity of the lungs may be studied in humans and animals, although in published studies to date, the observed effect is minimal or negative.

The question of which fraction of cigarette smoke contains the agent(s) that alter the lung defense mechanisms to induce chronic lung disease must be resolved. It is not feasible to evaluate each of the several thousand substances in cigarette smoke, but the major fractions that contain the offending agents and the distribution and penetration of these fractions should be studied. Gas phase constituents should be evaluated by category, and the method of exposure must be related to the actual smoking habits of humans. Cigarette smoking-machines that produce 35 ml puffs and the techniques by which animals inhale cigarette smoke in research models may not be representative of the human situation. Research techniques must be devised by individuals who are knowledgeable in the field of aerosol distribution and deposition, in the chemistry of cigarette smoke, and in the biophysics of the distribution of smoke in the airways. Patterns of inhalation for the average smoker must be studied in more detail. If individuals who switch from regular to lower "tar" and nicotine cigarettes undergo a change in smoking pattern, such as deeper or more frequent puffs, this must be taken into consideration because the contents of the smoke, the size of the particulate matter, and the distribution of smoke in the lung may change with the variations in

inhalation patterns. Such information must be applied to dosimetry in short-term *in vivo* and *in vitro* experiments as well as in epidemiologic or population studies.

Epidemiologic Studies

Studies of populations of smokers with well-defined smoking histories are a major tool in determining whether a real difference exists between smokers of regular cigarettes and smokers of lower "tar" and nicotine cigarettes. If, in well-planned epidemiologic studies, there is no difference found in the human occurrence or severity of chronic obstructive lung disease between smokers of different types of cigarettes, more basic research involving humans, animals, or *in vitro* systems to determine differences between the effects of smoke products would be less useful.

The design of epidemiologic research for this purpose raises a number of issues. Determining the true dose of smoke in cross-sectional, retrospective, or prospective population studies is a difficult problem. Most studies rely on patient histories to obtain dosage information. The accuracy of recall, the design of the questionnaire, and the skills of the interviewer all influence the accuracy of smoking history. The cigarette itself presents a problem in studying the significance of the lower "tar" and nicotine brands because changes in the content and design of cigarettes have continued over the past 10 to 15 years. This "moving target" makes evaluation of the dose-response in populations difficult, especially since a large proportion of current smokers began their smoking careers with regular cigarettes and switched after varying periods of time. The comparison of mortality rates is a commonly used epidemiologic tool. There are well-known problems in obtaining accurate mortality data on chronic lung disease, particularly in retrospective studies in which death certificates obtained 10 or more years ago are utilized. Morbidity, including hospital days and days lost from work because of respiratory illnesses, might also provide useful information but is limited because of the selective nature of populations (*31*).

Population studies that investigate the rate of decline of lung function proportionate to the number of cigarettes smoked have shown variable results. Most of the available data apply to smoking without regard to cigarette yield. Environmental factors such as air pollution may change simultaneously, and corrections must be made for these factors.

The mean differences between the rate of decline of the FEV_1 in populations of nondiseased smokers and nonsmokers are very small. A difference between the smokers of higher and of lower "tar" and nicotine cigarettes may be impossible to detect. However, the subgroup of the smoking population that shows a more rapid decline should

receive special attention, since it is probable that this group of smokers, for reasons yet unknown, is most likely to develop significant disease. Random variations from year to year in the measured FEV_1 in individual patients require an extended period of time before valid data can be obtained (*7*). Biochemical tests that may serve as new markers for chronic lung disease are in the early research stage and should be explored as soon as possible. Under the best of circumstances they could replace the physiologic tests that measure air flow limitation as the earliest practical mechanism to detect lung damage. These measurements should be given high priority to determine their ultimate usefulness. In the meantime, it would be reasonable to collect and store for future use blood and/or urine samples from the screened populations.

The lack of specific, detailed information about the human dose-response to cigarette smoke and the mechanism that causes individual susceptibility to more rapid deterioration of lung function results in difficulty in predicting sample size and the length of time needed for a population study to determine differences between the smokers of higher and of lower "tar" and nicotine cigarettes. Current data suggest that the time and effort required to mount new epidemiologic studies may delay the acquisition of needed information. However, there are several ongoing studies in which epidemiologic data, both cross-sectional and longitudinal, are being collected with relevance to chronic lung disease. It is appropriate to consider the utilization of these current studies where populations are already identified. Data on the history of brands smoked could be added. Available information about the "tar," nicotine, and carbon monoxide yield of the various brands offers one measure of dosage. A recently developed radioimmunoassay for plasma nicotine levels may also be a helpful tool (*9*), although smoking patterns may be as important as the number of cigarettes smoked in determining the actual dosage.

Additional questionnaire material involving brand data and history of morbidity related to respiratory symptoms could be superimposed on ongoing studies. The accuracy of historical data on cigarette smoking must be verified to the best possible extent. If new indicators serving as a screening test, such as blood or urine analysis for lung elastin degradation products, become available, they should be incorporated into the studies. Depending on their diagnostic reliability, it might be possible to study a considerably smaller population than that required for studies of morbidity, mortality, and lung function deterioration. All studies yet to be initiated should include questions on brand history. This would require the revisions in the standard questionnaires of the American Thoracic Society and Medical Research Council of Britain. An ideal longitudinal study will require the enrollment of younger subjects who begin their smoking careers with regular or with lower "tar" and nicotine cigarettes and continue to smoke them. Changes in

other constituents such as additives will have to be considered as will data obtained on patterns of smoking. If population studies enroll subjects who have switched to brands with varying smoke yields one or more times, the probability of detecting differences in FEV_1 or other parameters would be more difficult. Special efforts should focus on observations made of asymptomatic and symptomatic individuals with lung function abnormalities. It will probably be relatively easier to detect differences in the rate of pulmonary function deterioration between the regular and the lower "tar" and nicotine cigarette smokers in this group.

Priorities for Research Recommendations

The primary public health concern is the effect of the lower "tar" and nicotine cigarette on the individual's health. The second concern is the mechanism of the effect, and the third is the specific agent involved in stimulating the mechanism. The first need is to establish whether there is a measurable difference between smokers of regular and of lower "tar" and nicotine cigarettes. The epidemiologic approach to the problem may yield the greatest amount of valuable information in the most rapid manner, but population studies may not show differences in the development of chronic lung disease, since it is not known whether the etiologic component of smoke is altered in the currently marketed lower "tar" and nicotine cigarettes. Therefore, parallel research is necessary to a better understanding of the pathogenesis of COLD and identification of the responsible smoke component. A combination of epidemiologic studies designed to answer broad questions and human, animal, and *in vitro* studies will be required to define the entire problem. The epidemiologic studies will determine whether or not the lower "tar" and nicotine cigarettes have a health benefit or whether a potential benefit is negated either by changes in smoking patterns or by ignoring the agents responsible for inducing COLD. Topographic and dose-response information is required for the human studies. The final and perhaps most beneficial aspect of the research would be the elimination of the offending agents from cigarettes.

Investigation of the distal air spaces or lung parenchyma where the destructive component occurs in emphysema has received recent emphasis with new approaches and measurements. Therefore, investigation of this area may offer a greater possibility for significant new data. To date, studies of air flow characteristics, airway reactivity, and morphology have provided data concerning the chronology of the disease but have not pointed to the mechanism by which lung damage in emphysema is produced. Much of the benefit of basic research hinges on a better predictability of the topography of smoking and dose-response relationships. Information learned in the basic studies

can be translated into or used in epidemiologic studies, while the data obtained from epidemiologic studies can offer directions for the finer tuning of basic research. All of this would provide more information about the pathogenesis of chronic obstructive lung diseases and their potential alteration by lower "tar" and nicotine cigarettes.

The problem of passive exposure to cigarette smoke of different types of cigarettes also needs consideration. However, determination of the impact of lower "tar" and nicotine cigarette smoke on active smoke inhalation presents difficulties significant enough to render to low priority the passive smoking investigation at this time. Future dose-response data, especially determination of thresholds, would offer a lead into the area of passive smoking.

Research Recommendations

1. High priority should be given to a study of the distribution, partitioning, and penetration of regular and lower "tar" and nicotine smoke into the lung, including quantitation of and adjustment for any changes in the pattern of smoking by smokers of lower "tar" and nicotine cigarettes. Individuals in the specialized fields of aerosol physics, pharmacology, and toxicology should be involved in answering this question.
2. Parallel priority should be given to epidemiologic studies, preferably by adding to ongoing longitudinal and cross-sectional studies the data necessary to determine brand-related history. Higher and lower "tar" and nicotine cigarette smokers should be compared for differences in symptoms, morbidity, physiologic measurements, and mortality relating to COLD. Special attention should be given to people with identified disease or whose pulmonary function is deteriorating at an accelerated rate. New studies should be started if it is not possible to supplement the ongoing studies.

   Several ongoing epidemiological studies have been identified: (1) the Tucson Epidemiologic Study of Obstructive Lung Disease at the University of Arizona (Dr. Benjamin Burrows); (2) the Emphysema Screening Center Study of smokers and nonsmokers at the University of Oregon at Portland (Dr. Sonia Buist); (3) the Johns Hopkins University study of risk factors in chronic lung disease in Baltimore (Dr. Harold Menkes and colleagues); (4) the study of smokers in the Kaiser Permanente Health Care Plan (Dr. Diane Petitti); and (5) the Nurses Health Study at Harvard University (Dr. Frank Speizer). Statistical data to be collected by the National Center for Health Statistics, such as the Health and Nutrition Examination Survey, should be oriented to the collection of a detailed history of smoking, and followup studies should include spirometry. Data from the National Health Interview Survey and the National Death Index may also be useful.

3. The rapid clinical evaluation of the recently developed biochemical tests that measure products of lung elastin degradation and that can be detected in the plasma or urine should be carried out. If these prove both specific and sensitive, the time involved in carrying out the human epidemiologic research could be shortened.
4. Human, animal, and *in vitro* research that studies the mechanisms responsible for COLD and their possible alteration by lower "tar" and nicotine smoke should receive emphasis. Although the elastase-inhibitor imbalance hypothesis is well supported by experimental studies, confirmation of this mechanism is required for human disease. Verified animal models of emphysema induced by cigarette smoke exposure are not available at this time, but if such a model can be identified, it should be exploited. Investigation should involve airway factors, parenchymal alterations, and alterations in defense mechanisms that can be studied in short-term or subacute experiments. Biochemical, histological, and ultrastructural studies are required for correlation with exposure to smoke products or components from regular or lower "tar" and nicotine cigarettes. Dosimetry or exposure levels for these studies can be drawn from topographic and epidemiologic studies. Research on both animal and human tissue, cells, and lung lavage fluid is required.

Much progress has been made in recent years in the study of the mechanisms of lung damage relating to cigarette smoke. However, chronic bronchitis and emphysema are potentially devastating illnesses that have no curative treatment. Elimination of cigarette smoking would significantly reduce their public health importance. It is imperative that we define as soon as possible any differences in the effect of currently manufactured lower "tar" and nicotine cigarettes in the pathogenesis of these diseases.

Summary

1. The relationship between cigarette smoking and chronic obstructive lung disease (COLD) is well documented. The constituents of cigarette smoke that are responsible are currently not known. Whether a difference in risk of COLD has occurred with lower "tar" and nicotine cigarettes as compared with higher "tar" and nicotine cigarettes is currently unknown.
2. Cigarette smoking is associated with the release by alveolar macrophages of an increased amount of the elastolytic enzymes, which degrade alveolar tissue, and with reduced activity of alpha$_1$-antitrypsin, the primary elastase inhibitor. This mechanism has not yet been directly related to the development of human emphysema. To date there are no published studies that compare

the effects of higher versus lower "tar" and nicotine cigarettes on elastolytic enzymes and inhibitor activity.

3. Cigarette smoke also contains relatively high levels of oxides of nitrogen. The nitrogen oxides produce lung damage in animals that is similar to that induced in humans by cigarette smoke. The oxides of nitrogen may be responsible for the early lesions of human emphysema.
4. An individual's smoking pattern is one of the most important determinants of the relative concentration of smoke constituents that reach the lungs and of the subsequent response of the airways to smoke inhalation. Holding smoke in the mouth before inhaling it into the lungs produces less response of the airways than direct inhalation, which causes spirometric changes indicative of bronchoconstriction. This effect is independent of the "tar" content of the cigarette.
5. Pulmonary mucous hypersecretion and symptoms of cough and phlegm appear to be affected by the "tar" content of cigarette smoke. The development of airway obstruction is closely related to the number of cigarettes smoked. Smokers of lower "tar" and nicotine cigarettes who compensate by smoking more or inhaling more deeply might thereby increase their risk of developing obstructive airway disease.
6. Population studies that have examined the rate of decline of lung function in relation to the number of cigarettes smoked have shown variable results, and most of the available data do not relate lung function to cigarette yield. Overall, the mean difference between the rate of decline of FEV_1 in asymptomatic smokers and nonsmokers is very small, but there is a subgroup of the smoking population that shows more rapid decline and is apparently more likely to develop significant pulmonary disease.

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Section 6. PREGNANCY AND INFANT HEALTH

CONTENTS

Introduction

Since Simpson (*23*) first reported that the newborn infants of women who smoked during gestation were of significantly lower weight than the infants of comparable nonsmokers, the adverse effects of maternal smoking on pregnancy have been increasingly appreciated. In 1979 the publication *Smoking and Health: A Report of the Surgeon General* (*25*) documented the considerable body of epidemiological, clinical, and laboratory evidence concerning the role of cigarette smoking in complications for the pregnant woman, fetus, newborn infant, and child. Although many of the effects on a pregnant woman and her child of smoking "regular" cigarettes manufactured during the past three or four decades are well known, possible differences between the effects of higher versus lower "tar" and nicotine cigarettes on the incidence and magnitude of these various complications are not known. The relative importance of "tar" and nicotine (commonly assayed in current cigarettes) versus the importance of carbon monoxide and several thousand other constituents of tobacco smoke (usually not measured) is not known. In fact, it is possible that compounds other than "tar" or nicotine are important in producing these effects. It is essential to elucidate these issues.

Evidence on the Effects of Smoking in Pregnancy

The complications of pregnancy ascribed to cigarette smoking may be divided into those that affect (1) the mother, (2) the embryo and fetus, (3) the placenta, and (4) the newborn infant and child. The mother, fetus, and placenta constitute an integrated organic unit rather than separate systems or organs. Thus, although separation of effects into these categories is convenient, it is also somewhat arbitrary. Some effects, such as spontaneous abortion and other reproductive loss, affect both the mother and fetus. Complications in different categories can occur concurrently. Cigarette smoking has been demonstrated to exert effects on each category.

Maternal complications of pregnancy that show a greater incidence among women who smoke cigarettes include placenta previa, abruptio placentae, vaginal bleeding during pregnancy, and, possibly, premature rupture of the membranes (*13, 14*). Lifetime smoking histories also affect the occurrence of placenta previa, abruptio placentae, and bleeding during pregnancy (*17, 19*). The incidence of amnionitis (infection of the amniotic fluid and its membranes) also is increased among women who smoke (*16*). The occurrence of the preceding complications appears to increase with the number of cigarettes smoked. For instance, the risk of placenta previa for mothers who smoke less than one pack per day is 25 percent greater than that of nonsmoking women, but is 92 percent greater in those who smoke one or more packs of cigarettes per day (*14*). Additionally, the risk of

abruptio placentae is increased 23 percent and 86 percent, respectively, in these two smoking-level groups compared with nonsmokers (*14*).

Virtually all of the more than 50 studies published, involving more than half a million births from many countries and ethnic groups, have been consistent in demonstrating that maternal smoking has an adverse effect on birthweight (*25*). These newborn infants weigh on the average 200 grams less than babies born to comparable women who do not smoke, and the decrement in birthweight varies with the number of cigarettes smoked (*25*). In an analysis of data from the Ontario (Canada) Perinatal Mortality Study, the number of newborns weighing less than 2,500 grams was 52 percent greater among women smoking less than one pack per day and 130 percent greater among women who smoked one pack or more per day, when compared with the pregnancies of nonsmoking women (*12, 13*). The contribution of this reduced birthweight to the occurrence of abruptio placentae or placenta previa is not clear (*18*).

Several studies have shown that the placental ratio (placental weight to fetal weight) is higher for the gestations of mothers who smoke (*27*). This increase in the placental ratio results from a decreased newborn birthweight and from a slight increase in absolute placental weight in heavier smokers (*25*). Preliminary results from the Columbia University study fail to show either smaller weight decreases in the newborns of mothers who smoke lower "tar" and nicotine cigarettes or a return to nonsmoker values in the placental to fetal weight ratios.

The risk of spontaneous abortion is 30 to 70 percent higher among pregnant smokers than among nonsmokers and increases with the number of cigarettes smoked (*11*). Rates of fetal deaths (occurring after 20 weeks of gestation) also increase significantly with the level of maternal smoking (*3*). The risk of premature delivery is 36 to 47 percent greater in mothers who smoke during pregnancy than in nonsmoking mothers; about 13 percent of all preterm births can be attributed to smoking (*1, 3, 9, 13*). This is an important factor in the increased risk of neonatal mortality among the infants of smoking mothers. Infants of women who smoke experience a mortality rate ranging from less than 10 percent to almost 100 percent greater than that among offspring of nonsmoking mothers. The excess risk of perinatal mortality varies, depending upon the number of cigarettes smoked and upon the presence of other high-risk factors (e.g., low socioeconomic group, a previous low-weight birth, or anemia) (*15*).

Several abnormalities of infancy and childhood occur more frequently among the offspring of mothers who smoke. Children of women who smoke during and after pregnancy experience higher rates of morbidity and mortality up to the age of 5 years. In Finland, smokers' children had more hospitalizations, more visits to the doctor, and more use of specialized services (*20, 21*). Significantly more infants of smoking parents are hospitalized for pneumonia and bronchitis (*5, 6, 10*). The

sudden infant death syndrome (SIDS) occurs more frequently among the children of parents who smoke (*2, 24*). Other long-term sequelae of maternal smoking during pregnancy are also of concern. Several studies suggest that older children of mothers who smoke have slight but measurable deficits in physical growth, intellectual ability, emotional development, and behavior (*25*). For instance, in Great Britain the physical growth of smokers' children remained less than that of nonsmokers' offspring, at least until age 11 (*4*). Associations have been reported between maternal smoking and deficits in neurological and intellectual development of the child. These include minimal cerebral dysfunction and abnormal or borderline electroencephalograms (*8*), hyperkinesis (*7*), and abnormal infant behavior patterns (*22*). These long-term effects of maternal smoking require attention because of their potential seriousness.

Thus, an excess risk of several disorders or death face the fetus and infant of the mother who smokes.

Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke have been shown to produce various effects, the specific etiologic agents and their mechanism(s) of action are not clearly established for these adverse effects on pregnancy.

Health Effects of Lower "Tar" and Nicotine Cigarettes

Although use of lower "tar" and nicotine cigarettes has grown markedly over the past decade, there are no data available that suggest that the developing fetus, the infant, or the pregnant woman are less harmed by cigarettes with lower levels of these constituents. There has been no demonstration of decreased risk of complications of pregnancy. There is no evidence of a decreased risk among smokers of spontaneous abortion or preterm birth, nor of an increase in the average weights of their babies. Newborn infants of smoking mothers continue to have a mean weight of 200 grams less than those of nonsmokers, a relation that is dose dependent. The risk of preterm delivery remains much greater for smoking mothers. Further, there is no evidence to date that maternal smoking of lower "tar" and nicotine cigarettes decreases the risk of perinatal mortality.

Most research reports to date have considered only the number of cigarettes smoked per day in quantitating smoke exposure, without adjusting for differences in yield of different cigarettes.

Research Approaches

Investigation into the effects of maternal cigarette smoking on pregnancy, the fetus, and the young child should include the following types of studies: (1) prospective epidemiologic studies comparing the course and outcome of pregnancy by maternal smoking habits; (2)

case-control studies of pregnancy complications including laboratory measurements of various body functions and constituents and a prospective study of pregnancy outcome; and (3) clinical and experimental research, often using laboratory animals, in which tobacco smoke or some of its constituents, commonly nicotine and carbon monoxide, are administered to the subject, animal, tissue, cell, or subcellular element, and the response quantified.

With numerous systems to be considered (the pregnant woman, the fetus, the newborn, the young child), and with various organs, tissues, cells, and subcellular elements potentially acted upon by a myriad of tobacco smoke constituents, the selection of appropriate study designs is a complex process. Further, the design of such studies is complicated by continuous changes in the composition of cigarettes over the past two decades. The spectrum of cigarette types, composition, and smoke yield varies enormously. In addition, the individual smoker's lifestyle, habits, and intake of other substances such as alcohol, caffeine, and drugs must be considered.

In view of the multiple variables involved, the recommendations that follow are those most likely to contribute significantly to an understanding of the character and magnitude of adverse effects of smoking cigarettes with varying levels of "tar" and nicotine on pregnancy. Research must define the relative importance of the several constituents, the impact of dose variations, and the mechanisms of action of the toxins in cigarette smoke.

Recommendations for Human Studies

Studies of populations of individuals with defined smoking histories have made an important contribution to elucidating the effects of smoking on various aspects of pregnancy, childbirth, and infant health. To date, no epidemiologic data exist to indicate lower risks of the aforementioned conditions in the pregnant mother, fetus, or infant resulting from the use of a lower "tar" and nicotine cigarette.

Present knowledge is sufficient that new, large prospective studies specifically designed to evaluate smoking effects are not necessary; rather, the approach should be, first, to encourage all prenatal care facilities to record smoking information, preferably with measurement of exhaled carbon monoxide. Second, the major source of information should be centers where continuing prospective evaluation of pregnancy is already being carried out in a systematic way, such as the Kaiser Permanente Cohort Study.

These centers should adopt a uniform practice of keeping detailed records of their patients' smoking habits, recording at each prenatal visit the number of cigarettes smoked, brands, filters, "tar" and nicotine content, and measured exhaled carbon monoxide (to estimate maternal and fetal COHb). Records of other exposures such as alcohol, coffee, and other drugs should also be kept. These and other relevant

personal, medical, and demographic factors should be analyzed or controlled in evaluating the outcome of these pregnancies (spontaneous abortions, later fetal deaths, complications of pregnancy, preterm deliveries, duration of gestation, birthweight, and neonatal and later conditions versus normal, live births).

These comprehensive, continuing studies are needed to elucidate the interrelationships of factors already known to affect pregnancy outcomes. It would be desirable to have several centers with large numbers of births follow a standard protocol for such studies.

Within the context of such a protocol, or possibly separate from it, case-control studies of spontaneous abortions, fetal death, preterm births, and particularly abruptio placentae, placenta previa, and premature rupture of membranes should be carried out. Patients who have not delivered at the time of ascertainment should be followed prospectively to delivery, together with their matched controls. Biochemical tests should be included in these studies to elucidate the mechanism of action of smoking in the increased incidence of these events. Any possible modification of these outcomes that accompany the use of lower "tar" and nicotine cigarettes should be examined.

A variety of other special clinical studies to test for differences in adverse pregnancy outcome by use of different cigarettes during pregnancy could be added to these larger monitoring operations or could be set up independently, using infants of matched smokers and nonsmokers. For example, (a) neonatal behavioral assessment (Brazelton scale), (b) auditory response testing of newborns, (c) neonatal and post-neonatal growth measurement, (d) special studies among very heavy smokers, and (e) placental studies could be performed.

Several epidemiologic studies now in progress might provide answers to some of these questions, for example, the study of spontaneous abortion at Columbia University in New York, or the Oakland Kaiser Permanente Cohort Study, which prospectively links smoking history and cigarette brand to all hospitalizations of approximately 50,000 women, many of childbearing age.

Studies have indicated that maternal smoking during pregnancy may be associated with impairment of physical and intellectual development, hyperkinesis, and changes in the infant's responsiveness (*25, 26*). The hypothesis that alterations in the constituents of cigarette smoke might affect the risk of these conditions needs to be tested. Differences in risk of long-term neurological consequences for a child exposed to maternal smoking should continue to be examined in existing data sets insofar as they contain appropriate information. Data files include (a) the Collaborative Perinatal Project (U.S.), (b) the 1958 and 1970 British Perinatal Studies (U.K.), (c) the Kaiser Permanente Cohort Study (Oakland), (d) the Finnish Perinatal Study (Finland), and possibly (e) the University of Washington Study (Seattle). Such studies must include consideration of possible confound-

ing factors such as socioeconomic status, nutritional status, alcohol use, and exposure to legal and illegal drugs.

In addition to studies documenting the maternal and fetal risks of varying levels of "tar," nicotine, and other constituents in cigarette smoke, there is need for study of the effect of cessation of smoking at different times in gestation on subsequent adverse events of pregnancy, including measures of birthweight, gestational age, perinatal mortality, and long-term sequelae. It will be important also to discriminate the effects of maternal smoking during gestation from those of parental smoking during infancy and childhood.

The combined effect of such studies would be to define any differences by cigarette "tar" or nicotine yield in the incidence of maternal complications or fetal or newborn sequelae, relative to both nonsmokers and smokers of different products.

Recommendations for Behavioral Studies

The factors and influences that lead an individual to start smoking and to maintain the habit despite knowledge that it poses health risks are complex. In view of the absence of evidence that lower "tar" and nicotine products pose less risk to pregnancy outcome, the description of smoking patterns among pregnant women and the investigation of motivational factors in this population are critical to the design of appropriate public health programs.

Some studies indicate that cessation of smoking early in gestation results in a pregnancy and fetus with risks of low birthweight similar to those among nonsmokers (*25*). Clinical studies could be conducted of pregnant women who refuse to quit smoking, in order to define the time intervals during which cessation of smoking results in a risk indistinguishable from those of nonsmokers. In view of the demonstrated effects of nicotine, carbon monoxide, and other tobacco constituents, rapid smoking techniques for cessation are contraindicated in pregnant women. Exhaled carbon monoxide should be measured at each visit, and the results used to explain to the mother that her baby's oxygen supply as well as her own is reduced by carbon monoxide from the cigarettes.

Further, considerable evidence indicates that the majority of women initiate smoking during their teens and pre-teens. Therefore, behavioral studies should focus on the prevention of initiation of smoking in this age group. Adolescents are a high risk group during pregnancy because of many factors, such as inadequate nutrition, anemia, inadequate prenatal care, and the use of illicit drugs. Adolescents who smoke during pregnancy constitute a particularly important group because of the coexistence of smoking and other risk factors. Intervention techniques must be found that effectively illustrate to the pregnant adolescent how smoking affects her body and fetus and that assist in cessation attempts. Such demonstrations might include

measurement of increases in fetal heart rate and decreases in fetal respiratory rate after smoking.

Studies of lifetime smoking experience should describe the role of pregnancy in changing smoking, such as cessation attempts and successes, brand choices, and number of cigarettes smoked daily. A logical extension of this study would define how the techniques of smoking cessation during the course of gestation may differ for pregnant women compared with those directed to smokers in general. The applications of such studies are particularly important for women who smoke heavily as well as for those women at high risk because of other factors.

Recommendations for Clinical Studies

General Studies

The adverse health consequences of cigarette smoking for the individual smoker extend beyond the pregnant smoker. As do the taking of drugs, exposure to workplace chemicals, or voluntary exposures to toxic substances such as alcohol, smoking by pregnant women affects the health of her fetus. The implications of this extended responsibility cannot be overstressed.

The effects of heavy smoking (two or more packs a day) on the pregnant woman, her fetus, and child have not been well defined. If adequate numbers of pregnant women who are very heavy smokers (two or more packs per day) could be identified, a special study should be undertaken to compare them with nonsmokers matched on important factors, e.g., time of registration, age, parity, and socioeconomic status. A prospective study should examine heavy smokers, including users of modified lower "tar" and nicotine cigarettes, as well as nonsmokers. For these heavy smokers as well as for light smokers, maternal blood levels of nicotine, catecholamines, carboxyhemoglobin, thiocyanate, cadmium, and other suspect compounds should be examined during pregnancy. Such a study should monitor several fetal variables including cardiac electrical activity, breathing and other body movements, cerebral electrical activity, and periodic measurements of head growth (biparietal diameter). Following birth, placentas would be examined for morphometric and/or pathologic abnormalities. Newborn infants should be completely examined, including measurement of lung volume and brain size and neonatal behavior assessment using the Brazelton scale. Children should undergo long-term followup for neurologic function (e.g., hearing and visual disorders). Alternatively, certain aspects of neurological dysfunction should be examined by case-control studies in which children with abnormalities are compared with normal neonates, matched by such factors as time of birth, gestational age, and socioeconomic status. Prenatal exposure to smoking by amount, type of cigarette, and yield and exposure to other

substances should then be compared to determine associations between neurological abnormalities and these exposures.

The mechanism(s) by which maternal smoking increases complications of pregnancy, such as spontaneous abortion, abruptio placentae, placenta previa, and premature rupture of the membranes are not clearly defined, despite the fact that these complications account for a significant portion of embryonic and fetal morbidity and mortality. Abruptio placenta will continue to result in anoxic fetal deaths. Preterm deliveries attributable to premature rupture of placental membranes will continue to pose the attendant hazard of neonatal death to the newborn infant.

Therefore, studies ought to test certain hypotheses about the mechanisms of action of cigarette smoke in these events. Instances of complications should be identified (i.e., placenta previa, abruptio placentae, premature rupture of the membranes, and probably spontaneous abortions). Controls should be selected for each case (matched by time of registration, gestational age at occurrence of complication, social status, age, parity, and perhaps other factors), and demographic factors and confounding exposure(s) to other compounds should be examined. A number of variables quantitating smoke exposure should be measured, including the concentrations of blood hemoglobin, carboxyhemoglobin, thiocyanate, copper, and various vitamins (A, B_{12}, C, and folate). The subjects should be followed to delivery, and the influence of measured factors related to outcome. Although at birth one could measure variables such as the biomechanical properties of membranes, tissue collagen concentrations, and cell number and size, such measures are not known to elucidate the mechanism of action of smoke constituents. Biopsies of the cervix from women with premature rupture of the membranes should be examined for concentrations of elastase or other enzymes that might play a role in premature dilation of the cervix. In instances of abruptio placentae and placenta previa (and in matched controls), that organ could be examined for morphometric or morphologic alterations.

Placental Studies

Placental morphology and morphometry are plagued by a lack of information and understanding of the relation of villous structure to the size (generation) of the associated blood vessels. Therefore, such morphometric studies of the placenta should be carried out in a laboratory dedicated to placental structure.

The ratio of placental weight to birthweight increases with numbers of cigarettes smoked daily. Light smokers' placentas may be slightly lighter and heavy smokers' placentas somewhat heavier than those of nonsmokers. The diameter to thickness ratio is also somewhat increased for smokers. Signs of "premature aging" are also seen in smokers' placentas, characterized by early appearance of calcium and

subchorionic fibrin (*27*). The described changes were somewhat smaller in magnitude than those described for high altitude or anemia. These studies did not, however, include consideration of the type of cigarette smoked. The factors that account for these changes and their mechanism of action are unknown.

Morphometric studies should be designed to determine what features of placental architecture are altered by maternal smoking and by the type of cigarette used. These studies would include examination of the trophoblast, blood vessels and their interrelations, relative maturation of the placenta including the presence of calcium and subchorionic fibrin, membrane thickness, relative size of the intervillous space, and evidence of pathologic alterations. In addition, other studies should examine ultrastructural features of the trophoblastic cells and blood vessels. Further studies should examine biopsies of the placental bed, including the decidua and endometrium of women who do and do not smoke.

Studies indicate that the blood of smoking women has lower concentrations of certain amino acids and vitamins A, B_{12}, C, and folic acid, among others, but the mechanism of these changes is unknown. Placentas from smokers of different cigarettes and matched controls should be studied for uptake kinetics and for intracellular to extracellular concentration ratios of amino acids and other compounds.

Autopsy Studies

The fetus of the mother who smokes weighs less than the fetus of a comparable nonsmoking mother, and this effect varies with the number of cigarettes smoked. However, the mechanism(s) whereby this change occurs is unknown. No evidence is available on how different cigarettes affect the occurrence of low birthweights. In an effort to determine whether decreased cell size, or cell number, or both, account for this change, we recommend that studies examine DNA concentrations (cell number) and DNA to protein ratios (cell size) in infants of smoking mothers suffering perinatal death.

One large study, corroborated by others, showed that, among perinatal deaths associated with maternal smoking, the largest categories of cause of death for stillborn infants were "unknown" causes or "hypoxia." The largest number of neonatal deaths were ascribed to "prematurity" alone. In an effort to elucidate specific causes and possible mechanisms of these deaths and the implications for newer cigarettes, dead fetuses and infants who die near the time of delivery, of smoking and nonsmoking mothers, should be subjected to thorough and careful autopsy by an experienced neonatal pathologist. Such studies may help elucidate differences in the smoker's infant who dies.

Fetal lung weight is decreased preferentially in animals exposed prenatally to carbon monoxide. Infants of smoking mothers experience increased risk of respiratory infections and pulmonary disease, and the

lungs may be altered in infants of smoking mothers who expire in the "sudden infant death" syndrome. In an effort to determine the morphologic basis and possible mechanism of these changes, the lungs of stillborns, or of newborn infants who expire, should be examined for morphologic and pathologic changes related to the smoking status of the mother. Some specific indices to be examined include alveolar type II cells, macrophages, and microcirculatory vascularization.

Fetal brain weight is increased (probably from edema) in animals exposed prenatally to carbon monoxide. The infants of smoking mothers experience increased risk of "minimal brain damage," hyperkinesis, and other neurologic disorders. In order to determine the morphologic basis and possible mechanisms of these changes, the brains of the dead fetuses or infants of this group should be examined for morphologic and pathologic changes. Some specific indices to be examined include neuronal and dendritic number and architecture. It may be of special importance to examine the brainstem because of altered respiratory control mechanisms.

Breast-Feeding Studies

Several products of tobacco smoke such as nicotine, cotinine, and thiocyanate are known to be secreted in breast milk. However, little is known about the dose-response relationship of smoking to the concentrations of these compounds. Breast milk of lactating mothers and the blood of their newborns should be examined for concentrations of nicotine, cotinine, thiocyanate, cadmium, and other toxins. In addition, breast milk from smoking mothers should be analyzed for the concentrations of leukocytes, monocytes, immune globulins, and other immunologically important factors, in addition to protein, fat, carbohydrate, and other constituents that affect newborn growth. Again, dose-response relationships should be explored.

Finally, breast-fed infants of smoking mothers should be examined for evidence of nicotine addiction and withdrawal symptoms (irritability, nervousness) at the time of weaning.

Some studies have indicated that maternal smoking suppresses lactation. Milk production and ability to nurse should be studied in smoking and nonsmoking women who want to breast feed their babies, including evaluation of the effects of stopping smoking and the use of lower "tar" and nicotine cigarettes.

Recommendations for Physiologic-Pharmacologic Studies

Laboratory studies in experimental animals have proved useful to test various hypotheses regarding the specific effects of the individual constituents of tobacco smoke, as well as mechanism(s) of action. Such laboratory studies should be carried out in a well-organized and careful

manner, and should consider exposure to tobacco smoke *per se* as well as to its individual constituents.

Tobacco Smoke

The introduction of modified, lower "tar" and nicotine cigarettes raises several questions regarding the effects of these tobacco products on the pregnant woman, fetus, and infant. Although purportedly lower in their yield of "tar" and nicotine, these cigarettes may still deliver a threshold level or more of carbon monoxide or other toxic products. Additionally, smokers may use certain techniques to increase the yield so that the delivery of "tar," nicotine, carbon monoxide, or other constituents is similar to, or perhaps in excess of, that of regular cigarettes.

Further, the possibility exists that there is a systematic difference in the style of smoking depending on "tar" or nicotine level. If smokers of lower "tar" and nicotine products uniformly take more puffs, larger puffs, or inhale more deeply, the actual dose of constituents experienced by the smoker would not be as low as that predicted by machine measurement. In addition, while the relative amounts of smoke absorbed may vary, differences in smoking pattern might also affect the relative proportions of constituents in the smoke inhaled, a fact that might well influence the probability of developing smoking-related health problems. Measurements of smoke constituents and breakdown products in the smokers' exhalations, serum, and other body fluids may provide better estimates of cigarette yield than smoking-machine results. Levels also differ by sex and during pregnancy.

Studies of the effect of tobacco smoke in animals present problems as to the dose of smoke actually received by the animal, the specific compound(s) responsible for the changes observed, and the concentration of these substances in blood or tissue. All such studies should include measurements of blood concentrations of nicotine, carboxyhemoglobin, and perhaps other compounds, as well as tissue concentrations where appropriate.

Numerous animals have been used for studies on the effects of smoking. Ideally such studies should be carried out in subhuman primates, such as baboons trained to smoke. However, the technical difficulties and expense of such studies make this approach unrealistic. Consideration must be given to whether there is, in fact, a particular animal model that is optimal from the standpoint of relevance to human studies, availability, and expense.

As noted previously, an almost universal phenomenon is the decrease in birthweight of infants of smoking mothers. Animal studies must explore which components of cigarette smoke are most important in reducing the rate of fetal growth. Such studies should determine whether it is the rate of mitosis or cell number that is reduced, and

whether the smoking-associated reduction of fetal growth rate is caused by retarded growth of only certain organs or tissues.

Following birth, many children of smoking parents are continuously exposed to tobacco smoke. This may be a factor in the higher incidence of sudden infant death syndrome, hyperkinesis, "minimal brain dysfunction," and respiratory disorders in such children. Animal studies should be performed to examine the effects of passive smoking on newborn or young animals.

Nicotine

Nicotine is an important pharmacologic agent in tobacco smoke. Studies suggest that some smokers titrate their nicotine dose by altering the number of cigarettes smoked, the depth of inhalation, or the degree of occlusion of pores (in the case of low "tar" and nicotine cigarettes). The following major areas of inquiry should be studied:

1. Definition of the role of nicotine exposure during fetal life in birthweight reduction, behavioral development, and childhood growth retardation
2. Examination of the effect of nicotine on individual organ growth, including the fetal brain, adrenal glands, lungs, heart, and kidneys
3. Study of nicotine's contribution to neurologic disorders in children
4. Elucidation of the role of nicotine or its metabolites in carcinogenesis, alone or in combination with benzo[a]pyrene and other carcinogens in smoke
5. Definition of the effect of nicotine on human fetal blood catecholamine concentrations

Carbon Monoxide

Carbon monoxide, a product of incomplete combustion of carbonaceous compounds, is present in tobacco smoke in relatively high concentrations (1 to 6 percent). Hemoglobin avidly binds carbon monoxide as carboxyhemoglobin, decreasing the oxygen transport capacity of blood. Because of the relatively higher affinity of fetal hemoglobin for O_2 and CO, as compared with adult hemoglobin, a given carbon monoxide partial pressure results in a fetal blood carboxyhemoglobin level 10 percent greater than that of the smoking mother, while fetal arterial oxygen tension is only 20 to 30 percent that of the mother. Thus, the fetus experiences higher carboxyhemoglobin levels and a greater carbon monoxide-induced hypoxia than that occurring simultaneously in the mother. Exploration of the following questions should be undertaken:

1. Definition of the major physiological consequences of carbon monoxide exposure on the developing fetus or newborn
2. Elucidation of the dose-response relationship of carbon monoxide in disease occurrence

3. Examination of fetal adaptation to low carbon monoxide concentrations, and the mechanisms of any such adaptation
4. Definition of the patterns of growth, development, and maturation of the central nervous system and other organ systems exposed to chronic low-level carbon monoxide
5. Study of the periods during gestation when the fetus is particularly vulnerable to carbon monoxide

Polycyclic Aromatic Hydrocarbons

Benzo[a]pyrene (BaP) and other polycyclic aromatic hydrocarbons (PAH) are potent carcinogens. Little is known about the transplacental effects of these substances on the developing fetus. Examination of the following questions is needed:

1. Definition of the transplacental passage of BaP and PAH
2. Description of BaP or PAH distribution in the fetal organs and tissues
3. Examination of a possible role of BaP or PAH from maternal smoking in the growth and development of the fetal brain and other organs

It should also be noted that BaP and PAH are known inducers of the cytochrome oxidase (P_{450}) system, including aryl hydrocarbon hydroxylase (AHH). Such enzymes are involved in drug and steroid metabolism, among other functions. Thus, the PAH should be investigated for possible metabolic effects beyond those of carcinogenesis.

Other Substances

Numerous possibly toxic substances are present in cigarette smoke, including cyanide and cadmium. Little is known about the role of these compounds in altering fetal growth and development. Studies should examine the effects and mechanism(s) of action of these substances.

Priorities for Research Recommendations

The preceding discussion has presented many research issues that are major and valid questions. The primary emphasis, however, must be placed upon studies that determine the character and magnitude of the health hazards posed to the individual pregnant smoker and her offspring by the modified lower "tar" and nicotine cigarettes. Research to define the specific etiologic agents and their mechanism(s) of action must take a priority second to that of defining the risks.

It is through epidemiologic research that the answers to the most important questions will be reached. It is apparent that there is a need for refining the measurement of cigarette dosage and the quantitation of cigarette smoke exposure. A more accurate description of dosage must be an intrinsic part of epidemiologic research efforts that deal with smoking exposures. All obstetricians and prenatal clinics should

be strongly urged to record details of their patients' smoking habits at each visit.

Simultaneously, however, laboratory investigation should proceed in parallel to examine the specific compounds involved and their mechanisms of action. Research has contributed some knowledge of tissue, cellular, and subcellular effects. Further studies at these levels hold the promise of elucidating the mechanisms whereby these changes occur. Such studies may lead to a greater understanding of specific cigarette hazards by dosage and thereby suggest directions for epidemiologic studies. Conversely, epidemiologic data will suggest directions and specific questions for laboratory or clinical research. These approaches should proceed in concert for maximal results in understanding the problems of lower "tar" and nicotine cigarettes in the medical, biological, and social environments.

Summary

1. Cigarette smoking during pregnancy has been shown to have adverse effects on the mother, the fetus, the placenta, the newborn infant, and the child in later years. There is no evidence available that lower "tar" and nicotine cigarettes decrease or increase these health risks, relative to those posed by higher "tar" and nicotine cigarettes.
2. Problems that have been linked to smoking during pregnancy include placenta previa, abruptio placentae, vaginal bleeding, and reduced average birthweight of newborn infants.
3. Smoking by pregnant women increases the risk of spontaneous abortion, premature delivery, fetal death, and perinatal death. Parental smoking is associated with the sudden infant death syndrome.
4. The fetuses of smoking mothers have higher blood carboxyhemoglobin levels and lower fetal arterial oxygen levels than do the mothers.
5. Children of smoking mothers appear to show a greater susceptibility to some adverse health effects, such as bronchitis, pneumonia, and respiratory disease, during early childhood. Slight differences in physical growth and other forms of behavioral and intellectual development may be found in children as old as 11 years of age.
6. Although "tar," nicotine, carbon monoxide, and some other constituents of cigarette smoke produce deleterious effects, the specific etiologic agents and their mechanisms of action for adverse effects on pregnancy are not clearly determined. Thus, the relative importance of "tar" and nicotine, or carbon monoxide and other constituents of tobacco smoke in the etiology of adverse gestational and fetal events is not known.

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Section 7. BEHAVIORAL ASPECTS

CONTENTS

This section outlines the future directions that research on lower "tar" and nicotine cigarettes should take. These are: (1) to perform additional laboratory studies under controlled experimental conditions; (2) to conduct additional research on compensatory smoking; and (3) to investigate both the biological and psychological factors involved in smoking.

Research Priorities

Controlled Studies To Determine the Role of Nicotine as a Primary Reinforcer in Cigarette Smoking

Many important questions on the pharmacological importance of nicotine in maintaining cigarette smoking remain unanswered, despite a large number of studies on the topic (*1, 2, 19, 25, 36, 44, 46, 49, 65, 69, 73*).

Nicotine is probably the primary source of the pharmacodynamic appeal of tobacco, but not enough is known about its exact role in smoking to determine whether it is the only source. (For reviews on nicotine and smoking, see *18, 21, 31, 57, 61.*)

Tobacco without nicotine appears not to be sufficiently reinforcing to support sustained use (*18*). There has never been an appropriately designed study with a large number of subjects randomly assigned to smoke flavor-balanced cigarettes of varying nicotine content over a substantial (months) time period. The behavioral aspects of cigarette smoking are of paramount importance in the evaluation of less hazardous cigarettes. Behavior is the interface between cigarette smoking, its pharmacological and physiological effects, and the generation of disease. Compensation for nominally reduced machine-measured "tar" and nicotine yields of cigarettes by increased depth and volume of inhalation as well as proportion of the burning cigarette consumed has been demonstrated. Such a study would be necessary to conclusively support this hypothesis of cigarette habituation.

Instead, we can only look at the distribution of smoking by nicotine yield and the experimental literature. In 1979, the percentage of current regular smokers in the United States who smoked cigarettes low in nicotine content (less than 0.5 mg nicotine and less than 5 mg "tar") was very small, about 4 percent. Research studies using tobacco cigarettes virtually free of nicotine show these to be rated as aversive by smokers (*36, 64*). At the same time, it has been difficult to demonstrate that smokers will use nicotine in a nontobacco medium. In one study, lettuce leaf cigarettes injected with nicotine were smoked for 1-week periods at intake levels only approximately 50 percent the rate of the subject's own brand, and with protest of much reduced satisfaction (*13*). Considered a more direct route of administration, injections of nicotine became a satisfying replacement for cigarettes

after repeated trials, but this early study was not conducted in a "blind" fashion (*38*).

More recent studies of intravenously administered nicotine have contained subjective reports of perceived pleasure (*39*), but also have included reports of an inability to suppress subsequent smoking to a major extent (*39, 46, 49*). Although the results were perceived as only mildly pleasurable, nicotine administered in oral tablet form (*35*) or embedded in chewing gum (*44, 64*) has decreased various measures of smoking in individuals not trying to quit.

The major problem with giving nicotine in other than inhaled form is that it lacks some of the biological as well as many of the behavioral similarities to smoking. The nicotine bolus, when inhaled, reaches the central nervous system in less than 8 seconds (*58*).

More information is needed to understand the pharmacological, psychological, and situational cofactors that may contribute to the reinforcing effects of nicotine. By analyzing the mechanisms whereby nicotine reinforces smoking behavior, it may be possible to design more efficacious treatments for cigarette dependence or to devise techniques for maximizing the rewards of smoking while minimizing the risks to health.

Animal Models of Nicotine Use

Animal models have several advantages over human models in studying the effects of nicotine. In the animal laboratory, environmental variables can be controlled to a much greater extent than they can in the human laboratory. History of exposure to the drug can be manipulated in a true experimental fashion. One of the greatest limitations of much epidemiological and behavioral research on human smoking behavior is that the subjects are self-selected. Consequently, the research is inherently correlational rather than experimental. Correlational research can describe associations between variables, but it is often confounded by unmeasured variables (*30*).

Animal models have been used to study the dependence liability and toxicity of many drugs (*17, 75*). The techniques used in analyzing responses to other drugs should be developed further and applied to the study of nicotine—and perhaps other substances in tobacco.

Methods of administration can have a large effect on the pharmacokinetics of nicotine. Oral, intravenous, and inhalation modes of administration should be employed, but since smokers receive nicotine from inhaled smoke, the inhalation route is particularly important. Unfortunately, animals do not inhale nebulized nicotine or cigarette smoke in ways that are comparable to human inhalation patterns (*53*). Until reliable inhalation methods for animals are perfected, intravenous administration will have to be used in much of this research.

The Self-Administration of Nicotine by Animals

Since people take nicotine on their own, an ideal animal model would be one in which animals take nicotine on their own. Attempts to get animals to administer nicotine to themselves have not been uniformly successful (*17, 21*). Maintained self-administration has been found in the monkey and the rat in some studies (*6, 22, 47, 50*), but not in others (*82*). Recent work has shown that under some schedules of reinforcement, monkeys will self-administer injections of nicotine (*12*). In order to discover precisely what variables are critical to the reinforcing properties of nicotine, further studies are needed.

In addition to studying the parameters of self-administration, toxicity should also be measured. For example, it is important to look at the variables of physical dependence, food and water intake, and morbidity, as well as necropsy findings.

The Study of Tolerance and Physical Dependence

Both tolerance and physical dependence can develop to nicotine or other ingredients in tobacco (*33, 48, 71, 78*). Animal models have been used successfully in research on opioids and alcohol (*70*) and could prove effective in future research on nicotine and smoking.

Appropriate animal models would facilitate the study of the pharmacokinetics of nicotine and would help in the evaluation of pharmacological treatments for dependence. Since tolerance and physical dependence can influence the reinforcing properties of drugs of abuse, animal studies should investigate the extent to which withdrawal phenomena may contribute to the reinforcing properties of cigarette smoke. Methods developed for evaluation of opioid drugs could be adopted for these purposes.

Nicotine Research With Humans

The scientific issues in human and animal research are similar, although not all studies conducted on animals are practically and ethically suitable for research on humans. A great amount of preliminary data already exists on the role of nicotine in human smoking behavior (see the reviews cited above), but the influence of tolerance and dependence on nicotine on the initiation, maintenance, and cessation of smoking behavior are still not resolved (*27, 46, 59, 61, 68*). Clearly, both biological and psychosocial factors influence human cigarette intake (*41*), and it is in the human model of cigarette smoking that the interplay of these factors can best be studied. There is no known analog in animal behavior for future orientation and cognitive factors, such as worrying about the risks of cancer or about weight gain upon giving up smoking.

Progress to date in laboratory studies of smoking dependence has been slowed by the lack of standardized test materials, such as

cigarettes made to research specifications, and of standardized, easily accessible laboratory analyses, such as for plasma levels of nicotine.

Compensatory Behavior in Smoking

If, in the course of a standard assay for the "tar" and nicotine yields of a cigarette (*54*), a smoking-machine derives relatively small amounts of "tar" and nicotine, the cigarette can be called lower "tar" and nicotine. Unfortunately the smoking-machine model is limited in accurately reproducing human smoking behavior. The machines take a 2 second, 35 cc puff each minute until a predetermined butt length is reached. Smokers, however, are able to take larger, more frequent, and higher velocity puffs than the machines do. It appears that such compensatory adjustments often turn nominally lower "tar" and nicotine cigarettes into higher "tar" and nicotine cigarettes (*1, 4, 9, 25, 36, 46, 60, 62*). Even if the compensations made in smoking a single cigarette are small or nonexistent, smokers can increase their intake of "tar" and nicotine by smoking more cigarettes (*66*).

Cigarettes of less than about 6 mg "tar" and 0.5 mg nicotine are also subject to the influences of compensatory smoking. Most of these cigarettes achieve their lower yields as a result of ventilation holes placed in the filters, which cause each puff of smoke to be diluted with air. These air-diluted puffs deliver relatively small amounts of "tar," nicotine, and carbon monoxide to the smoking-machines (*29*). Some smokers have learned to block the ventilation holes with their lips or fingers—or sometimes with tape—and thereby, often unwittingly, defeat the purpose of the holes. If the ventilation holes are blocked, yields of nicotine, "tar," and carbon monoxide can increase by about two, three, and four times, respectively (*42*). In 1979, ventilated-filter cigarettes accounted for about 25 percent of total cigarette sales (*29*).

Many studies have used estimates of nicotine and smoke intake based on direct observations (*44*), measurements of smoking topography by means of special cigarette holders (*24, 36*), or analyses of residual nicotine in cigarette filters (*1, 9, 55*). Only a few studies have measured the levels of nicotine in plasma as a function of the nominal smoking-machine yields (*1, 63*), but research indicates that some smokers do compensate for reduced yields of nicotine.

By smoking more to compensate for lower nicotine intake, lower "tar" and nicotine cigarette smokers can inadvertently increase their exposure to "tar" and carbon monoxide beyond what might be expected from a less intensively smoked higher "tar" and nicotine cigarette (*57, 67*). Because less hazardous cigarettes may require the delivery of moderate levels of nicotine while delivering lower levels of "tar" and carbon monoxide, Russell (*57*) has proposed that lower "tar" to nicotine ratios should be used to indicate less hazardous cigarettes. These ratios may direct smokers to potentially less hazardous cigarettes, but the way in which a cigarette is smoked can affect the ratio

examination of the advisability of encouraging people to switch to milder cigarettes should be undertaken. (See Russell (*60*) for a brief discussion of the possible role of self-selection biases in the epidemiological finding that filter-tipped cigarettes are less hazardous (*3, 81*). See Harris (*23*) for a summary discussion of behavioral and economic factors affecting the promotion of lower "tar" and nicotine cigarettes.)

Controlled Switching

Very few studies on controlled switching have employed measures of plasma nicotine (*1, 28, 60*). No large-scale studies have been conducted that make use of plasma nicotine, carbon monoxide, and physiological measures of smoke exposure.

The relationship between smoker satisfaction and compensatory smoking appears to be complex. One forced switching study (*74*) has shown that, even though the compensation was incomplete and did not change for the few days of the study, satisfaction did improve during the course of the experiment. We do not know if satisfaction with lower "tar" and nicotine cigarettes increases with duration of their use, if it decreases with time if compensation occurs initially, or if nicotine yield alone determines cigarette acceptability.

Additional Comments

As noted earlier, progress in compensatory smoking research has been hindered by the lack of research cigarettes varying systematically in nicotine, "tar," and carbon monoxide, and by the shortage of laboratory facilities in which to do needed analyses.

One byproduct of the proposed research on switching to lower "tar" and nicotine cigarettes might be the development of practical diagnostic techniques. Smokers and physicians have not determined whether lower "tar" and nicotine cigarettes have produced "low-yield" smoking, but simple measures such as expired air carbon monoxide (*11, 26*) might help supply needed information concerning smoke exposure.

Natural History of Smoking Along Both Biological and Psychosocial Dimensions

Since almost nothing is known about the role of lower "tar" and nicotine cigarettes at crucial transition points in a smoker's history, this issue cannot be considered in detail (*7, 20, 40, 52, 56*). One key unanswered question is whether lower "tar" and nicotine cigarettes tend to facilitate taking up the smoking habit. Presumably, initiation of smoking is easier for those who first try lower "tar" and nicotine cigarettes than for those who first try regular cigarettes. Thus, lower "tar" and nicotine cigarettes can reduce aversive physical responses to early smoking episodes that might otherwise deter taking up the habit (*43, 56*).

Teenagers generally prefer moderately high-yield cigarettes (*77*), but 2.5 percent of the boys and 12.3 percent of the girls who smoke use lower "tar" and nicotine brands (here defined as $\leq$ 10 mg "tar"). Research has not addressed the question of what percentage of these smokers may have been helped either in their initiation to smoking or in their shift from casual to habitual smoking by the use of lower "tar" and nicotine cigarettes. The incidence of smoking among teenage girls has increased during the past 10 years (*76*, *77*). Silverstein et al. (*72*) present data supporting the hypothesis that the increasing availability of lower "tar" and nicotine cigarettes has encouraged this increase in smoking. Analysis of a survey of high school students suggests that girls experience greater social pressure to smoke than do boys, and that they also face greater physiological pressure not to smoke because of their higher sensitivity to nicotine. Girls appear to resolve these pressures by becoming lighter smokers than boys and by switching to lower "tar" and nicotine cigarettes. Perhaps if lower "tar" and nicotine cigarettes were less available, some girls would choose not to smoke rather than to experience unpleasant nicotine reactions.

Most research on the initiation of smoking and casual smoking has been psychosocial. No doubt there are practical, if not ethical, constraints on studying biological influences on smoking among teenagers. Whatever the reason, very little is known, for example, about the role of nicotine in early smoking experiences. No one knows how much exposure (days, months, years) to smoking is needed before withdrawal symptoms appear. More balance is needed in research on teenage smoking. Whenever possible, biological factors—both physiological and pharmacological—should be studied along with psychosocial factors (*27*, *41*).

There has been little research on the effects of lower "tar" and nicotine cigarettes on maintenance or cessation of smoking. There are studies on the effects of using decreasing amounts of "tar" and nicotine as a cessation or reduction aid (*10*), but these studies do not include biochemical or physiological measures of change in smoke exposure. It seems plausible that the alternative of a supposedly less-hazardous cigarette might make some smokers less likely to try to abstain completely. By the same token, the example of a satisfied, though perhaps fully compensating, smoker of lower "tar" and nicotine cigarettes might make a former smoker more likely to relapse. The former smoker might view the lower "tar" and nicotine cigarettes as both acceptable and safe (*14*, *15*). Answers to these questions can have immediate implications for smoking treatment. Research in this area should include such crucial variables as gender (*72*). Both experimental and epidemiological data are needed in these studies. Perhaps large-scale smoking surveys can be expanded to include more questions that would help characterize the natural histories of smokers.

Recommendations

Clinical Testing Facilities and Standardized Research Cigarettes

There has been an active research effort in this country on the behavioral aspects of smoking. To further its productivity and to refine the scientific questions that this research can address, especially with regard to lower "tar" and nicotine cigarettes, the facilities and research cigarettes described here are needed.

Clinical Testing Facilities

These facilities should be able to provide biochemical and pharmacological analyses of assays for plasma nicotine, cotinine, carboxyhemoglobin, and salivary thiocyanate. (Jarvik (*34*) reviews the use of these assays.) Each of these assays can be used to measure a smoker's exposure to some of the toxic and/or reinforcing ingredients in tobacco smoke. Plasma assays for nicotine (*8*) are available in a few laboratories; these assays can require special facilities to avoid problems of contamination. For example, a laboratory that is used part of the time by a worker who smokes may be unacceptable for the evaluation of plasma nicotine levels. Few behavioral researchers have access to or sufficient control over the needed laboratory facilities. Laboratories of this nature would be a great boon to behavioral research and would help to standardize assays in this area.

Research Cigarettes

A supply of clinically acceptable cigarettes that vary in nicotine, "tar," and carbon monoxide yield should be made available to behavioral researchers. Although some standardized cigarettes have been available for years from the Tobacco and Health Research Institute of the University of Kentucky, these cigarettes have no filters, and their lack of palatability and acceptability almost completely precludes their use in behavioral research. Cigarette technology has several ways of altering "tar," nicotine, and carbon monoxide yields. Ideally, different strategies would be employed to produce cigarettes with identical machine-smoked yields. Consider two examples. A fast-burning, strong-tobacco cigarette might have the same yields as a slow-burning, mild-tobacco cigarette, but it is not clear how human smoking behavior might change as a function of these modes of yield reduction. A cigarette low in carbon monoxide could be made with either vented cigarette paper or a vented filter. The vented filter can be closed by smokers accidentally or intentionally, thereby increasing the actual yield to the smoker (*42*), but the effect of porous cigarette papers cannot readily be circumvented by the smoker.

Variations in "tar" to nicotine ratios should be of special concern (*57*). It is important to determine the lowest ratios that still produce a satisfying cigarette. Obviously, identical "tar" and nicotine ratios can

occur in cigarettes that have very different standard nicotine yields. Research could show if there is an optimum combination of standard yield and ratio that leads to maximum satisfaction and minimal exposure to toxic products. Cigarettes that vary systematically in "tar" to nicotine ratios are needed for this research.

Machine-Smoked Yields of Lower "Tar" and Nicotine Cigarettes

The standard smoking-machine assay of "tar" and nicotine yields provides inadequate information to the tobacco consumer as well as to the researcher (*16, 45, 74*). The published yields do not indicate how many puffs were taken on a particular brand (*45*); assays at the Oak Ridge National Laboratory (*37*) reveal that from 6.9 to 11.5 puffs are taken on different brands of king-size filter cigarettes during standard assays.

The current smoking-machine standards are meant to represent an average smoker, but it is probable that the standard puff volume (35 cc) is too small (*5, 51*) and that the puff interval (one puff per minute) is too long (*4, 74*). Since compensatory smoking occurs with lower "tar" and nicotine cigarettes, larger and more frequent puffs tend to be taken. Smokers sometimes interfere with ventilation holes on lower "tar" and nicotine cigarettes (*45*); smoking-machines do not.

In addition to the standard assays, there should be maximum-yield assays of "tar," nicotine, and carbon monoxide. These assays would be based on puffing parameters of volume, rate, and duration for the 95th—or even the 75th—percentile of heavy smokers smoking lower "tar" and nicotine ventilated cigarettes up to the tip overwrap. These parameters would be used in smoking-machines, with these same ventilated brands, to derive yields with ventilation holes in both blocked and unblocked conditions. This procedure would produce much higher yields than does the standard assay, and these values would better represent the possible maximum risks of the lower "tar" and nicotine cigarettes to smokers who engage in compensatory smoking. Without access to information about how much the standard yields can change with intensive smoking, there can be only a limited understanding of possible reductions in actual smoking exposure. Using research in the British-American Tobacco Company Laboratories in the United Kingdom, Green (*16*) has argued that intensive smoking can make middle "tar" cigarettes (11 to 16 mg) deliver as much as high "tar" cigarettes (31 to 35 mg). Green could not demonstrate that low "tar" cigarettes (0.4 to 9 mg) can be made to deliver high "tar" levels, but this study did not consider the effect of blocking the ventilation holes on these cigarettes.

Toxicology of Nicotine

A probable outcome of behavioral research will be that nicotine is the primary pharmacological reinforcer for cigarette smoking. If this

prediction is correct, a lower "tar" and nicotine cigarette that will be used by smokers and that will minimize the exposure to other toxic components of smoke may require substantial yields of nicotine (*57, 62*). Consideration of the toxicity of nicotine, then, may become crucial in determining whether the benefits of lower "tar" and nicotine cigarette smoking outweigh the costs.

Summary

1. Nicotine appears to be the primary pharmacological reinforcer in tobacco, but other pharmacological and psychosocial factors may also contribute a reinforcing effect.
2. It appears that some smokers make compensatory adjustments in their smoking behavior with cigarettes of different yields that might increase the amounts of harmful substances entering the body. The frequency and amount of spontaneous compensatory changes in smoking style with different cigarettes require further investigation.
3. Additional information is needed on the role of lower "tar" and nicotine cigarettes in the initiation, maintenance, and cessation of smoking.
4. Rigorous comparative behavioral studies involving animals are needed to provide comprehensive, experimentally valid results on behavioral aspects of smoking.
5. Laboratory techniques developed for study of opioids and alcohol should be adapted for studies of tolerance and dependence on nicotine.
6. Improved laboratory facilities are necessary for more tightly controlled behavioral research. A particular need exists for clinically acceptable cigarettes with standardized ingredients.
7. Smoking-machine measurements that more closely simulate the practices of human smokers must be developed.

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Section 8. LOWER "TAR" AND NICOTINE CIGARETTES: PRODUCT CHOICE AND USE

CONTENTS

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Introduction

This section discusses changes in cigarette smoking over recent years in the United States. Currently available evidence indicates that, while the prevalence of cigarette smoking is at its lowest point in several decades among both adults and adolescents, there are significant differences in the cigarettes being used by those persons who do smoke.

The discussion does not attempt to describe comprehensively the patterns of cigarette smoking; such reviews have been published previously (*25*, *26*). Rather, it focuses on the information that describes the cigarette products currently being used by smokers and the role that such modified products may play in the smoking habit. It includes examination of (1) the growth of the lower "tar" and nicotine cigarette, including social and marketplace activity in recent years, and (2) cigarette product choice and use by the smoking population.

This consideration of changes in the cigarette is restricted to that of "tar" and nicotine yields of various cigarette brands, because of the availability of systematic measures of these constituents through the annual reports of the Federal Trade Commission (FTC). Note should be taken, however, that the extensive discussion of "tar" yields in this Report ought not to be construed as implying a primary or singular role of "tar" in causation of all the adverse health effects associated with cigarette smoking. Rather, "tar" yields are used because they are readily available and correlate closely to nicotine levels. No comparable measurements are available for carbon monoxide or other constituents of cigarette smoke, such as acrolein, hydrogen cyanide, or the nitrogen oxides, which are identified as probable contributors to smoking-related disease. Further, there are no systematic data available regarding the effects of commercially used cigarette additives on the yields of any of these constituents.

Although the data cited here are derived from multiple sources, much of it represents the first analysis of a large, ongoing national survey. At the request of the Office on Smoking and Health, a smoking supplement was added to the continuing National Health Interview Survey (NHIS) by the National Center for Health Statistics. Begun in July 1978 and continued through 1979, the smoking supplement was designed to provide data on the prevalence of smoking, amount smoked, and attempts to quit smoking. Representing a random one-third subsample of the NHIS interviews of noninstitutionalized persons aged 17 or older, the 18-month data included approximately 36,000 individuals interviewed. Unless otherwise indicated, the data cited represent analysis of the approximately 24,000 interviews on smoking conducted during calendar year 1979. Lifetime smoking status (i.e., never, regular, occasional, and former smoker), age at onset, brand choice, amount smoked, and data on the attempt(s) to quit were collected for recent and current smokers. The "tar" and nicotine yields

for the 1978 and 1979 NHIS data sets are based on the FTC listing of cigarette varieties, sampled in 1977 and published in May 1978, and updated to include cigarettes identified by the FTC as marketed in July 1978.

Three major conclusions can be elicited. First, Government and other agency activities in recent decades have led to widespread public recognition of the health hazards of smoking cigarettes. Second, the marked increase in the use of filter-tipped cigarettes in the late 1950s has been followed by a reduction in the "tar" and nicotine content of the cigarette products actually being selected and used by the smoking population. Third, the role of cigarettes of varying levels of "tar" and nicotine in the initiation, maintenance, or cessation of smoking is unknown. The data from the National Center for Health Statistics presented here neither prove nor disprove a role of lower "tar" and nicotine cigarettes in easing initiation, increasing daily consumption among regular smokers, or decreasing the probability of attempting to quit or of succeeding in the attempt. Much further work remains to be done to clarify and define the effects of lower "tar" and nicotine cigarettes on these behaviors, and thus their effect on total lifetime patterns of cigarette smoke exposure.

The Growth in the Use of Lower "Tar" and Nicotine Cigarettes

An Increasing Public Awareness of the Health Hazards of Cigarette Smoking

The decades since the first medical reports of a link between lung cancer and smoking in the 1950s have seen multiple changes in the cigarette products being used by the smoking population (*11, 14, 15, 16, 25*). A number of factors may have encouraged these changes.

The U.S. Public Health Service (PHS) has been active in assessing and attempting to reduce the excess burden of preventable illness related to cigarette smoking. Its first comprehensive review of the evidence linking cigarette smoking and adverse health effects by the Advisory Committee to the Surgeon General of the Public Health Service in 1964 was followed by regularly issued reports from 1966 through 1980, each of which continued and extended the PHS concern. In 1966, the PHS submitted to Congress (*42*) the *Technical Report on "Tar" and Nicotine*. On the basis of the clear demonstration of cigarette dose-dependent risks of several diseases, the PHS concluded:

> The preponderance of scientific evidence strongly suggests that the lower the "tar" and nicotine content of cigarette smoke, the less harmful would be the effect.
>
> We recommend . . . the progressive reduction of the "tar" and nicotine content of cigarette smoke.

At the same time, Secretary of Health, Education, and Welfare John W. Gardner urged the Congress to require "tar" and nicotine levels on packages and advertisements, with provision for adding to the label any ingredients subsequently identified as hazardous (*42*).

The PHS then began transmitting this information to the public. The PHS policy formulated on the evidence available was that there is no safe cigarette; the single best way to avoid the health hazards of smoking is to quit smoking, but for those unable to quit, a lower "tar" and nicotine cigarette would probably pose lower risks.

In 1972, the PHS classified some of the known chemical constituents of cigarette smoke into different risk categories. The compounds classified as "most likely" contributors to health hazards—"tar," nicotine, and carbon monoxide—were recommended as primary targets for reduction (*34*).

In 1974 and again in 1975, Secretary of Health, Education, and Welfare Caspar W. Weinberger formally requested legislation authorizing the regulation of cigarettes by formulation of maximum permissible levels of hazardous ingredients (*38, 39*).

During this time, a number of health professional societies, voluntary health agencies, and concerned citizens' groups also conducted public education activities on the health hazards of cigarette smoking.

The cigarette industry's activities during this period probably also influenced changes in cigarette choice. In 1952 only 1.4 percent of cigarettes sold in the United States were filter tipped; by 1956, 29.9 percent of all cigarettes were filtered (*27*). In 1979, filtered cigarettes represented 89.2 percent of all brands marketed (*24*), and were used by 91.7 percent of regular smokers, according to data from the 1979 Smoking Supplement of the National Health Interview Survey. Advertising probably contributed to this rapid growth of filter-tipped cigarettes. As early as 1954, one brand's advertising slogan read, " . . . filter gives greater protection against nicotine and tars than any other cigarette on the market today. It is the greatest health protection in cigarette history" (*27*). Another brand advertised the "Miracle of the Modern Miracle Tip" (even while the "tar" yield of that product increased 40 percent and the nicotine increased 70 percent over the 2-year period after the filter had been introduced) (*27*).

During the last decade, when systematic data on "tar" and nicotine yields of marketed cigarettes have been available, lower "tar" brands have been marketed in increasing proportions. Federal Trade Commission data show that cigarettes yielding 15 mg or less of "tar" constituted 15 percent of all brands in 1968, 20.4 percent in 1972, 30 percent in 1976, and 58.5 percent in 1979 (*1, 2, 3, 5*). Over the same time period, the proportion of all marketed brands that yielded 10 mg or less of "tar" increased from 4.7 percent in 1968, 9.9 percent in 1972, 12.4 percent in 1976, to 33.0 percent in 1979.

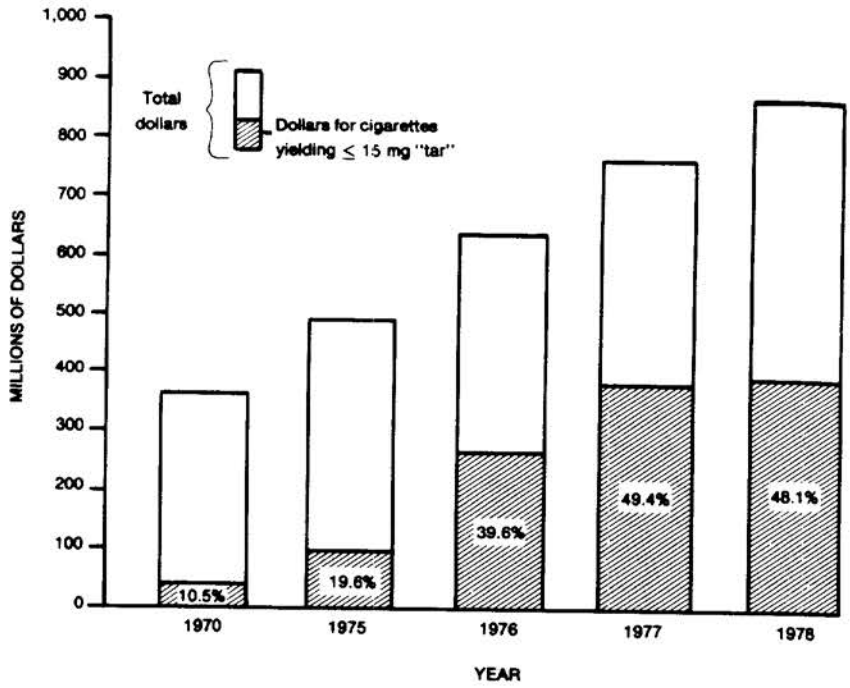

FIGURE 1.—Market share of dollars expended in the U.S. on advertising and promotion of cigarettes yielding ≤15 mg "tar" compared with total domestic cigarette advertising and promotional expenditures for years 1970, 1975, 1976, 1977, and 1978

NOTE: Percentages (shaded areas) refer to percent of each individual bar.
SOURCE: Derived from Federal Trade Commission (*6*).

Further, the marked increase in the last 5 years in the proportion of all cigarette sales accounted for by brands yielding ≤15 mg "tar" coincides with an increased percentage of total dollars spent for advertising and promotion of cigarettes yielding 15 mg or less of "tar" per cigarette. Figure 1 shows this increasing promotional effort. Since 1970, the absolute amount as well as the percent of all advertising dollars spent that went to advertising of "low tar" cigarettes has increased from approximately $37,900,000, or 10.5 percent, in 1970 to $421,300,000, or 48.1 percent, in 1978 (*4*). This increase occurred over the same period as the greatest increase in the lower "tar" brands' proportion of market sales.

Public Attitudes

Several surveys have examined the opinions of the general public about cigarette smoking.

Public surveys conducted by the National Clearinghouse on Smoking and Health examined the beliefs and attitudes of the U.S. public relative to cigarette smoking (*28, 29, 36, 39, 41*). These surveys indicated that the belief that cigarette smoking poses health hazards was increasing, not only among the general public but also among persons who continued to smoke. For example, in response to the statement "Smoking cigarettes is harmful to health," in 1964, 81.3 percent of the persons interviewed agreed and 13.1 disagreed, but in 1975, 84.9 percent agreed and 11.3 percent disagreed, with intermediate figures occurring in 1970 (*29, 35, 39*). Substantial differences were apparent when smoking history was considered. In 1964, former smokers believed smoking to be harmful in 90.5 percent of interviews, while only 69.5 percent of the current smokers believed smoking harmful; only 7.4 percent of former smokers did not agree that smoking is harmful, but 21.9 percent of smokers did not agree (*29*). This difference by smoking status in the percentage of interview subjects who believed smoking to be harmful persisted in 1975, but the difference narrowed (78 percent of current smokers agreed and 91.6 percent of former smokers agreed) (*39*). Very similar results were reported in a large survey in 1978, which found that 90 percent of all persons and 83 percent of smokers believed smoking to be harmful to health (*7*).

The percentage of smokers who agreed that "cigarette smoking frequently causes disease and death" increased from 52.2 percent in 1966 to 70.7 percent in 1975; the proportion of smokers who disagreed declined from 37.6 percent in 1966 to 22.3 percent in 1975. The percentage of the total population who had no opinion on this question and the preceding question declined from 9.1 percent to 5.3 percent and from 4.7 percent to 3.4 percent, respectively. This suggests that educational efforts may have reduced the size of the "undecided" population.

Other questions assessed the personal impact of beliefs about the health hazards of cigarette smoking. Although the percentage of smokers who reported being "slightly" concerned about the possible effects of smoking on their own health remained fairly constant from 1966 (18.1 percent) to 1975 (18.9 percent), the proportion of smokers who were "fairly" or "very" concerned increased from 29.1 percent in 1966 to 47.6 percent in 1975. The number of smokers "not concerned" declined from 52.5 percent in 1966 to 31.5 percent in 1975.

For the entire population, the proportion of interviewees who agreed that "smoking (is) enough of a hazard for something to be done about it" increased from 76.3 percent in 1966 to 84.0 percent in 1975.

Additionally, one question asked of current smokers in 1966, 1970, and 1975 provides information on smokers' perceptions of varying hazards by cigarette type (*29, 36, 40*). The number of smokers who felt that "all cigarettes (are) probably equally hazardous" declined from

57.8 percent in 1966 to 40.6 percent in 1975, while the number of smokers who believed that "some cigarettes (are) more hazardous than others" increased from 29.9 percent in 1966 to 49.1 percent in 1975. Among smokers who believed there was a difference among cigarette brands in health hazard, current smokers who believed their own cigarette brand was *less hazardous* than other kinds declined from 59.9 percent in 1966 to 49.7 percent in 1975, and smokers who believed their cigarette brand was *more hazardous* increased from 12.6 percent to 20.4 percent. Thus in the period from 1966 to 1975, there was an increasing proportion of smokers who believed different cigarettes posed varying health risks, but among these smokers the proportion who felt their cigarette was more dangerous to health than other cigarettes also increased. Unfortunately, identical large surveys to assess subsequent trends either in smokers' beliefs about differences in health risks or about the role of such beliefs in affecting cigarette product choice have not been published since 1975.

The Tobacco Institute, which represents the cigarette manufacturers, has also supported periodic surveys of attitudes. Their most recent survey is publicly available. Conducted in 1978 (*18*), this survey found that more than 90 percent of the U.S. population believed cigarette smoking is hazardous to the health of the smoker. Fully 61 percent believed that any amount of smoking is hazardous, up from 47 percent in 1970. This is in close agreement with surveys performed by the PHS in 1970. Further, in 1970 and 1978, 42 percent and 50 percent, respectively, of the population surveyed believed that smoking "makes a great deal of difference in longevity," a higher percentage than those believing the same thing about fatty diets (43 percent), alcohol consumption (39 percent), lack of exercise (34 percent), and overweight (24 percent).

The proportion of all persons who believe smokers "have" or "probably have" more of "certain illnesses" has increased from 56 percent in 1970 to 62 percent in 1978, when only 11 percent believed that smokers do not suffer more illness. Only 3 percent of people surveyed did not believe that cigarette smoking is a cause of disease, a figure that has not changed appreciably since 1970.

The 1978 Roper Survey found that the proportion of the population who believed others' smoking is hazardous to the nonsmoker's health had increased from 46 percent in 1974 to 58 percent in 1978. In 1978, the number who believed passive or involuntary smoking to be harmful was 69 percent among nonsmokers; while among smokers it was 40 percent. For the first time, the health effect of involuntary smoking was cited most frequently as a reason for legislation to ban cigarette smoking in public places.

The Cigarette Profile

The definition of cigarettes as "lower 'tar' " at $\leq$15 mg is arbitrary. Nonetheless, this breakpoint has gained general acceptance. The separation of $\leq$15 mg "tar" was meaningful when the vast majority of cigarettes were of higher "tar" yields; now, however, more than half of all the cigarettes sold in this country are at or below the level of 15 mg "tar" per cigarette. Many of the following measures use this breakpoint ($\leq$15 mg). Special note should be taken, however, of the fact that both "tar" and nicotine yields vary continuously, and groupings by relative yield measurements do not automatically imply differences either in the type or in the magnitude of their biologic effects.

As discussed previously, the proportion of domestic commercially marketed cigarette brands that yield 15 mg or less of "tar" has increased over the last two decades to 58.5 percent in 1979 (*1*, *5*). These figures, however, reflect industry marketing decisions and do not directly measure the smoking public's selection of a cigarette product. The market share of unit sales, however, reflects both the "tar" yield of each brand marketed and the smoking population's actual use of that product. Figure 2 shows the percentage of all U.S. cigarette sales (the "market share") represented by cigarettes containing 15 mg or less of "tar." Over the last decade the market share of sales accounted for by lower "tar" products has increased consistently since 1971. Cigarettes yielding $<$15 mg "tar" accounted for only 2 percent of the cigarette market sales in 1967, but the comparable figure is projected to approach 50 percent in 1980 (*24*). This represents an almost 23-fold increase over 13 years. There has been a threefold increase over the last 5 years in the proportion of all cigarettes purchased and presumably consumed that are lower in "tar." Thus, cigarettes of 15 mg or less are not only available in the market, but they are also being chosen by the smoking population.

A different measure of cigarette choice is the sales-weighted average of "tar" or nicotine. The sales-weighted average is derived from the "tar" or nicotine yield of each cigarette available in the United States, weighted by the numbers of packages of each brand sold annually. The sales-weighted average values for "tar" and nicotine thus represent a hypothetical "average cigarette" smoked in the United States. Figure 3 shows the trend over time of the sales-weighted average cigarette's "tar" or nicotine content (*43*).

The yield of "tar" declined from 38 mg in 1954 to 19 mg in 1975, while that of nicotine declined from 2.3 to 1.3 mg per cigarette. The decline in both "tar" and nicotine approximated 50 percent over this 20-year period. Data provided from a single source of continuous measurement as shown in Figure 4 indicate that the decline in "tar" has continued in recent years, although at a slower rate than that observed from 1954 to 1965. It is projected that the sales-weighted

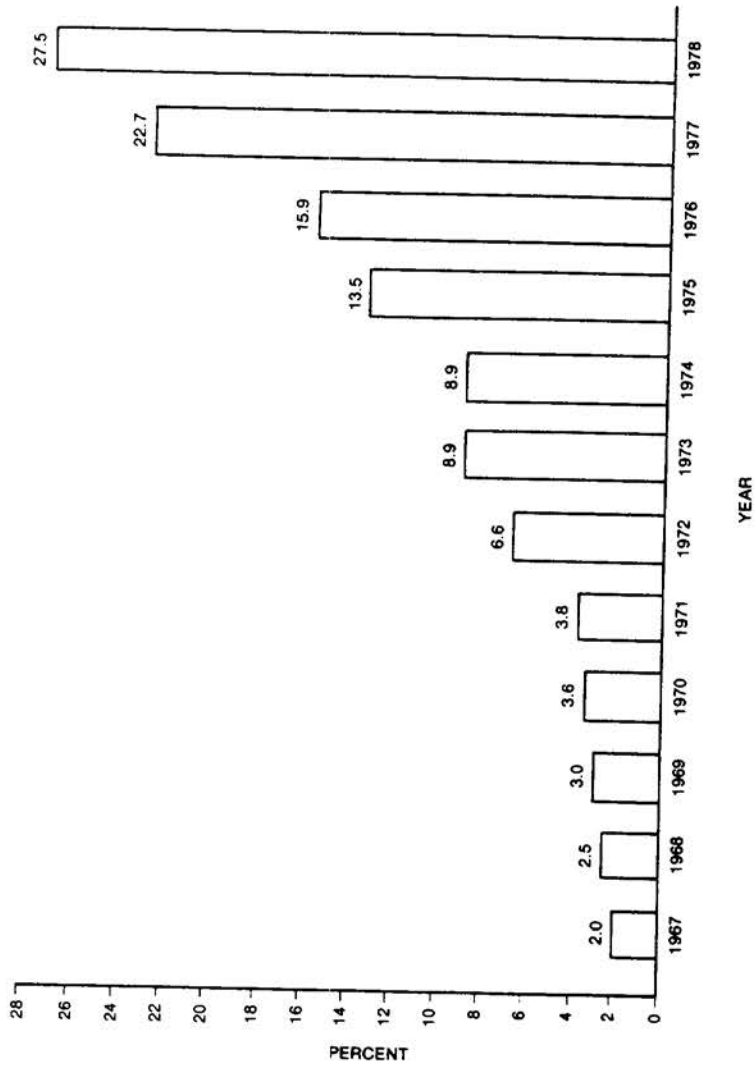

FIGURE 2.—Domestic market share of cigarettes yielding ≤ 15 mg "tar," 1967–1978

NOTE: 1979 data unavailable.
SOURCE: Derived from Federal Trade Commission (*6*).

average "tar" and nicotine in 1980 will be less than 14 mg and 1 mg, respectively.

Examination of the ratio of "tar" yield to nicotine yield per cigarette is interesting in light of the hypothesis that nicotine, perhaps in combination with organoleptic compounds, exhibits a threshold value for acceptability to the consumer. This threshold may have been

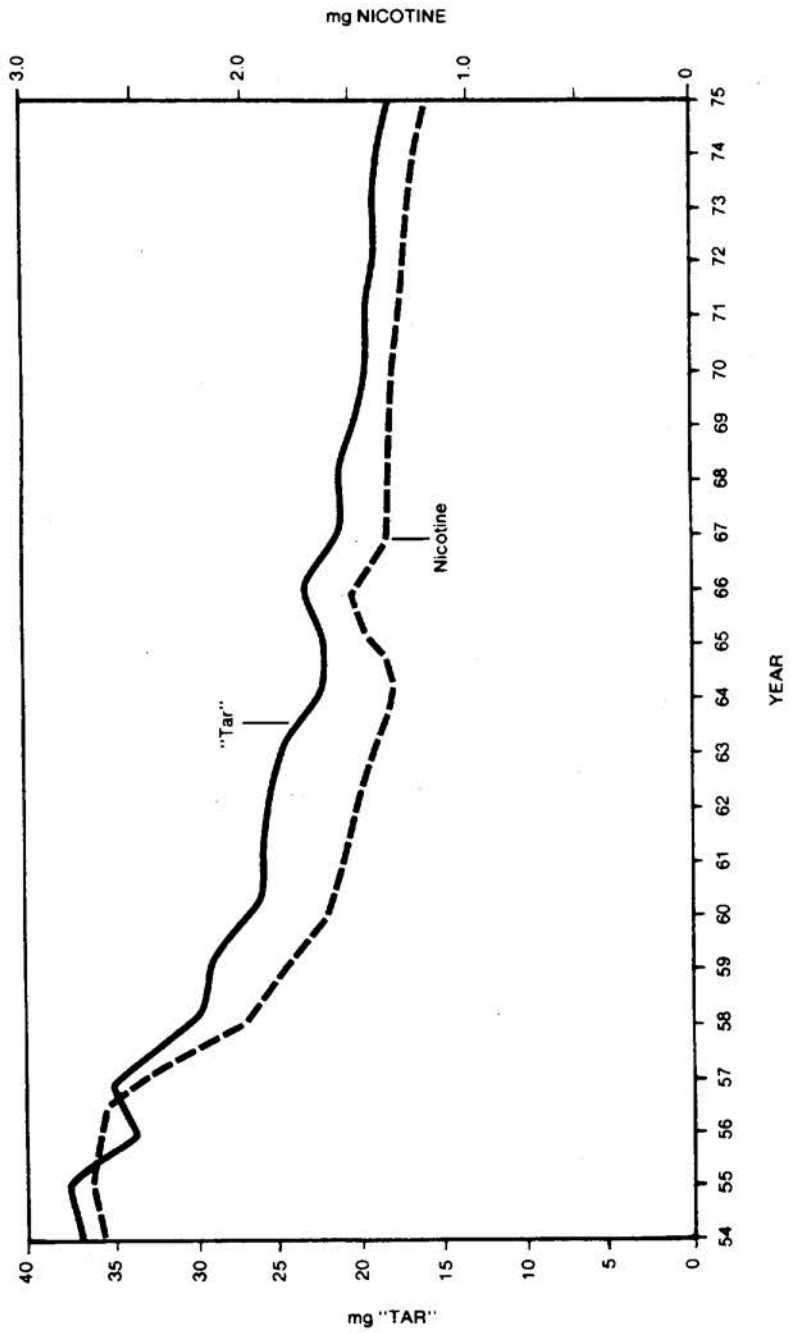

FIGURE 3.—Sales-weighted averages of "tar" and nicotine per cigarette consumed in the U.S., 1954–1975
SOURCE: Wakeham (45).

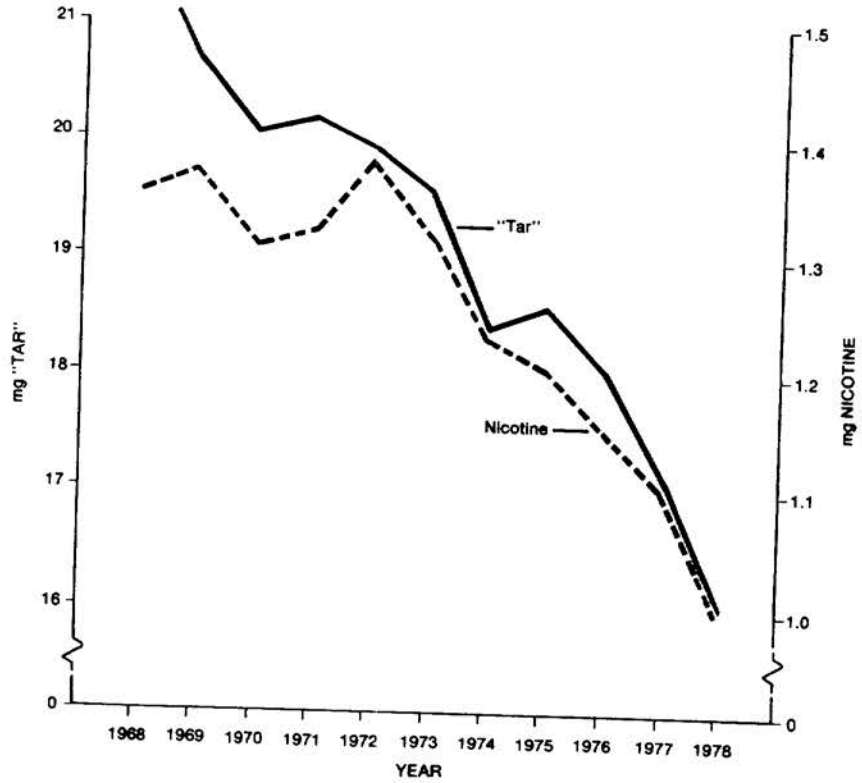

FIGURE 4.—Sales-weighted averages of "tar" and nicotine per cigarette consumed in the U.S., 1968–1978
SOURCE: Derived from Federal Trade Commission (*6*).

reached (at 1.4 mg nicotine) in certain countries (e.g., England) (*19*). In the United States, the sales-weighted average nicotine yield per cigarette has continued to decline below the level of 1.4 mg (Figures 3 and 4). Figure 5 presents the "tar" to nicotine ratio of the sales-weighted "average cigarette" annually from 1968 to 1978. The "tar" to nicotine ratio has ranged from 16 to 14.3, with a maximum variation of less than 10 percent of the ratio's absolute value. There has been no systematic difference observed between the declines of "tar" and nicotine of the average cigarette product over the last decade.

The previous discussion has focused on "tar" yields and, to a lesser extent, on nicotine yields. The relationship between "tar" and nicotine is a direct one, as is shown in Figure 6 (*5*). The correlation coefficient for these two variables is 0.967, based on data from the Federal Trade Commission report (*5*). Similarly, the correlation coefficient reported by the Oak Ridge National Laboratory was 0.917 (*12*). The description

FIGURE 5.—Ratio of "tar" to nicotine based on sales-weighted averages of cigarettes consumed in the U.S., 1968–1978
SOURCE: Derived from Federal Trade Commission (*6*).

of cigarette products by "tar" yield can thus be assumed to approximate closely the pattern that would result from a similar analysis by nicotine yield. There appears to be a similar relationship between "tar" and carbon monoxide yields, as Figure 7 shows. There is, however, a systematic difference between the "tar" and carbon monoxide yields of filtered and nonfiltered cigarettes (*12*). Filtered cigarettes tend to have a higher carbon monoxide yield than do nonfiltered cigarettes of the same "tar" yield. Nonetheless, there appears to be a strong association between "tar" and carbon monoxide yield by cigarette variety, with a correlation coefficient for "tar" and carbon monoxide of 0.803.

Data from the Department of Agriculture describe tobacco weight per cigarette over time (*24*). Figure 8 shows tobacco weight per cigarette in relation to "tar" yield, with both values shown as a percent of its value in calendar year 1967. While "tar" content per cigarette declined by 32.2 percent and nicotine declined by 25.6 percent since 1968, the weight of tobacco per cigarette declined by 23.8 percent over the same period (*24*). This suggests that a significant portion of the

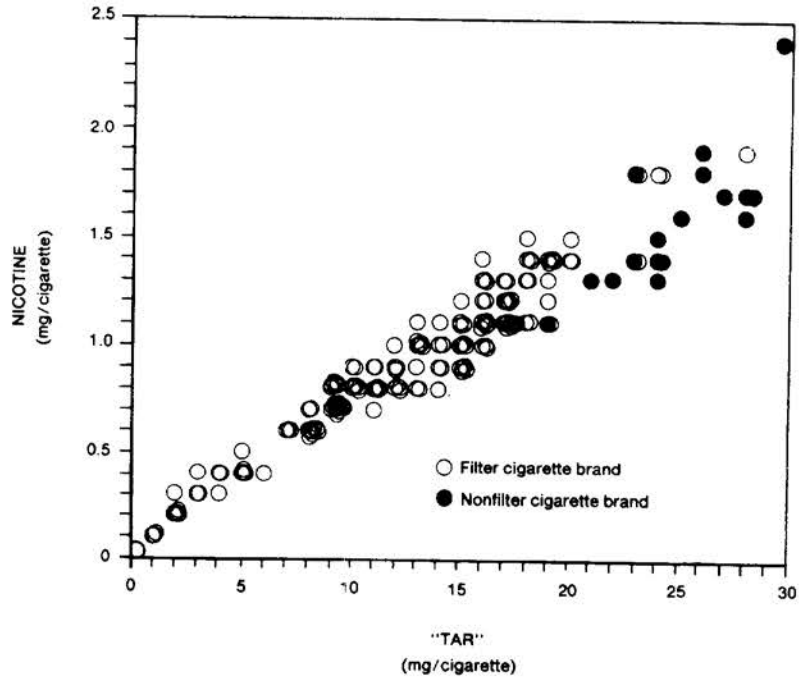

FIGURE 6.—Delivery of nicotine as a function of "tar" of commercial cigarettes, U.S.
SOURCE: Federal Trade Commission (*5*).

decline in the "tar" and nicotine yield in recent decades may have resulted directly from a decrease in the amount of organic material (tobacco) available to be burned in the cigarette.

Data available from Canada suggest that the observed decline in that country's officially measured "tar" and nicotine yields per cigarette at least in part results from a decline in the total number of puffs taken per cigarette during machine measurements of smoke yield (*13*). Although detailed information on the number of puffs taken per cigarette is not available for U.S. cigarettes, the FTC reports on "tar" and nicotine yields of U.S. cigarette brands suggest a similar factor may be operating in the decline of "tar" and nicotine yield measurements. The FTC testing method specifies that cigarette "tar" and nicotine yields be determined by smoking the cigarette to a minimum butt length of 23 mm, or to the filter and overwrap length plus 3 mm if in excess of 23 mm, while holding constant the puff volume, duration, and interval. Since 1967, the filter and overwrap length of U.S. cigarettes appears to have increased. In 1967, the proportion of cigarette brands that were smoked down to a butt length

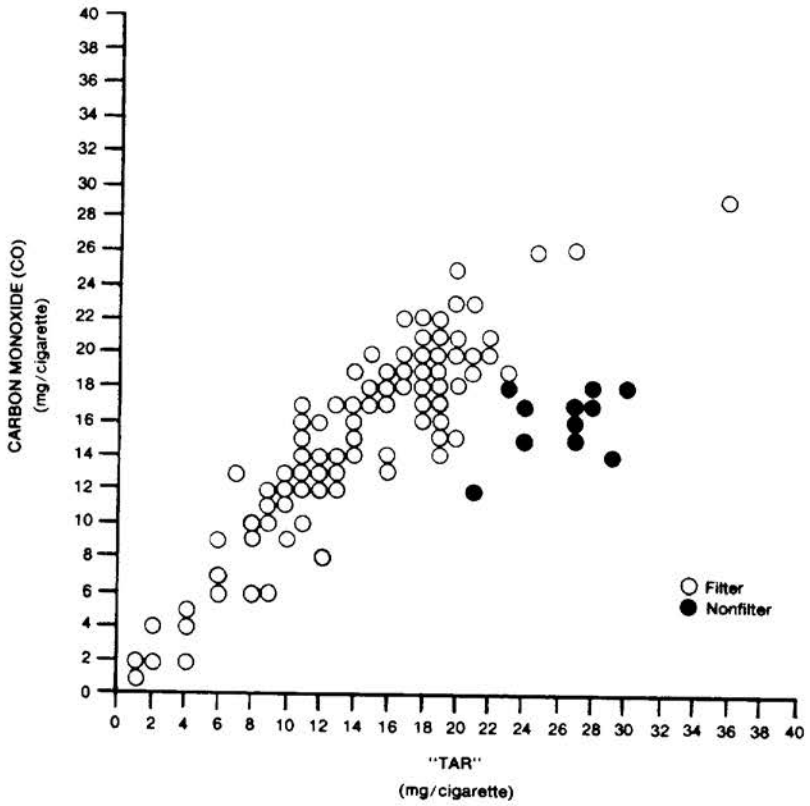

FIGURE 7.—Delivery of carbon monoxide as a function of "tar" of selected U.S. commercial cigarettes
SOURCE: Derived from Jenkins (*12*).

of 23 mm was 26 percent, but in 1979 the comparable figure was only 10 percent. Conversely, the number of all brands tested that were smoked to a butt length 30 mm or longer increased from 21 percent in 1967 to 77 percent in 1979. Thus, the butt and overwrap lengths of U.S. brands appear to have increased. The absolute contribution of this factor in the total decline in "tar" and nicotine yields over recent years, however, is undetermined.

Cigarette Choice and Smoking Behavior

Overview

Previous examinations of many parameters measuring the patterns of cigarette smoking in the United States have been published (*25, 26*). They documented the continuing decline over the last several decades

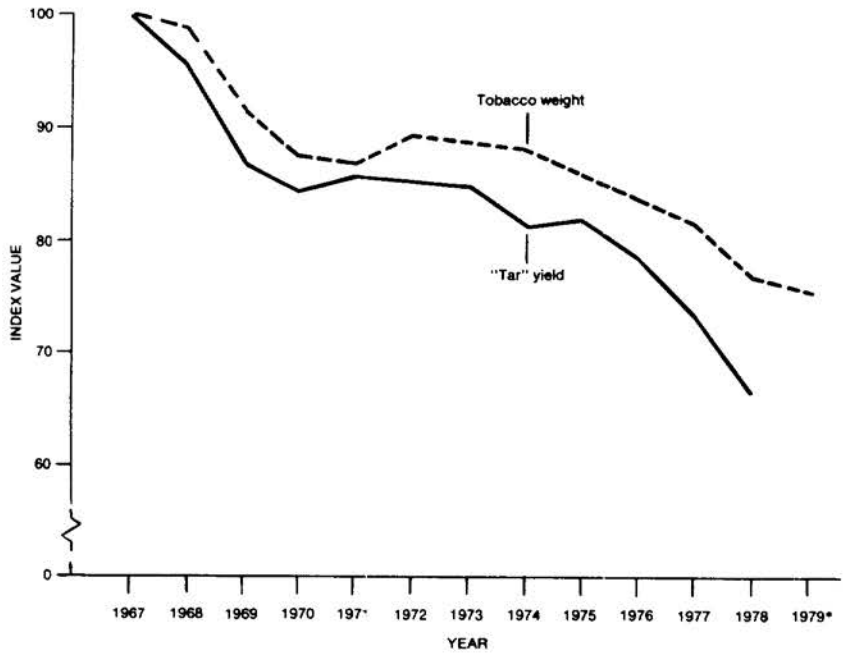

FIGURE 8.—Index of average "tar" and tobacco per cigarette, annually, 1967–1979

* Data estimated or unavailable.
NOTE: Base year 1967 = 100.
SOURCE: U.S. Department of Agriculture (*24*).

in the proportion of men who were regular cigarette smokers, from 52.6 percent in 1955 to 37.0 percent in 1978. These publications also reported a similar but smaller decline since 1965 in the proportion of women who were current regular smokers, varying between 32 and 33 percent from 1965 to 1976, but declining to less than 30 percent in 1978. These trends continued through 1979, with a total prevalence of smoking at 32.5 percent of all adults, or 36.1 percent for males and 29.4

percent for females, according to data from the 1979 Smoking Supplement of the National Health Interview Survey. Interpretation of these cross-sectional data is difficult since changes in prevalence figures represent the net effect of several variables, including the entry of new smokers, the removal of smokers who quit, the reentry of "relapsing" smokers, and the removal of smokers by death or emigration. The data show an increasing proportion of former smokers among the population, suggesting a significant role of cessation of smoking in the observed decline in the prevalence of adult smoking, particularly among males (*25*). The 1979 prevalence of regular smoking at 32.5 percent of all adults represents the lowest total figure in more than four decades.

Accompanying this decline in the prevalence of smoking among adults has been a decrease in the per capita consumption of cigarettes in recent years (Figure 9) and in the per capita consumption of pounds of tobacco in any form or as cigarettes (Figure 10). After peaking at 4,336 in 1963, the consumption of cigarettes per adult decreased (Figure 11) and is estimated to be 3,880 in 1980, its lowest point since 1950 (*24*). The decrease in per capita consumption of pounds of tobacco began in the 1940s and continues to the present. The relatively greater decrease in total pounds of tobacco consumed per capita in the form of cigarettes than in tobacco consumed per capita in any form since 1978 may result from an increasing use of tobacco in other forms, such as snuff or chewing tobacco, in addition to the previously mentioned decline in the estimated weight of tobacco per cigarette.

The preceding parameters are aggregate measurements. Other more detailed sources of evidence, however, suggest that the average number of cigarettes smoked daily by regular smokers may, in fact, be increasing. These data include evidence suggesting that the proportionate decrease in percentage of the adult population who smoke exceeds the reported decrease in per capita cigarette consumption for the total population (*25*). Further, when figures on total annual per capita cigarette consumption are divided by the estimated number of smokers in the United States as derived from reported prevalence figures, the estimated average daily intake for regular adult smokers was 11.5 cigarettes in 1935, 26.2 cigarettes in 1955, and 33.3 cigarettes in 1979 (*26*). These data should be interpreted in light of a strong tendency for smokers to round off their reported number of cigarettes smoked to one pack per day. Of the approximately 24,000 persons surveyed for the Smoking Supplement of the National Health Insurance Survey, fully 35.2 percent of all regular smokers reported smoking one pack, or exactly 20 cigarettes per day. Nonetheless, the proportion of all current regular smokers who consume 25 or more cigarettes per day has increased for both sexes (*26*). These findings could result from a higher rate of quitting by light smokers, from an actual increase in the number of cigarettes consumed by continuing

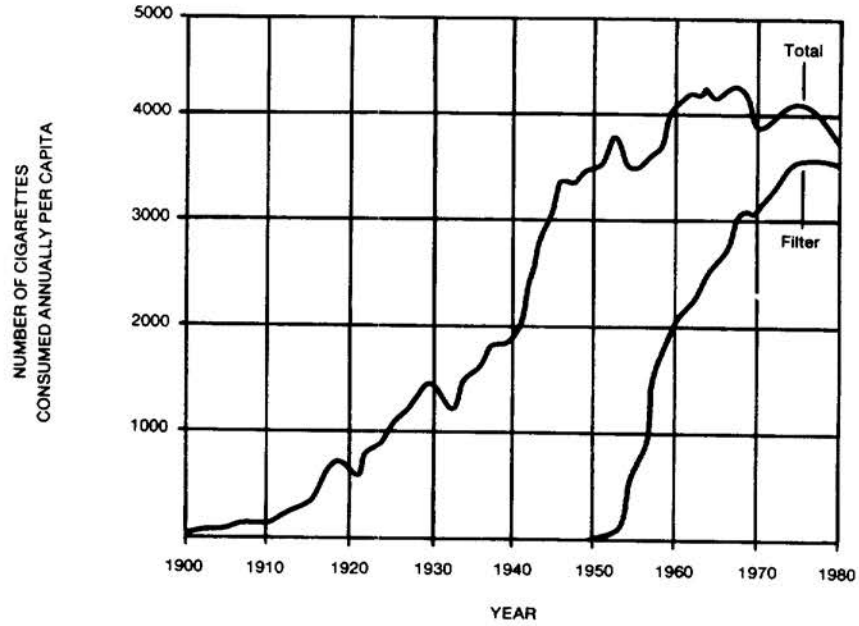

FIGURE 9.—Annual per capita consumption of total cigarettes and filter-tipped cigarettes in the U.S., for persons aged 18 and older, 1900–1979

SOURCE: U.S. Department of Health, Education, and Welfare (*26*).

smokers, from the entry of new smokers who consume more cigarettes per day, or from some combination of these factors. A number of sources of information exist on the issue of the role of nicotine as the major pharmacologic agent in maintenance of smoking, including prospective studies (*8, 9, 10*) and short-term experimental studies (*20, 21*), A more detailed discussion of the possible role of lower nicotine yields in increasing the daily number of cigarettes smoked can be found in the Behavioral Aspects section of this Report. To summarize, the available evidence is consistent with the conclusion that the average daily number of cigarettes smoked by current regular smokers has increased. Although a role for "tar" or nicotine yields in this change has been postulated, whether the role is primary and by what mode of action are not clearly understood.

Several surveys in the 1970s examined the percentages of recent smokers who recently attempted to quit and of those who succeeded. Data from the National Center for Health Statistics indicate that men and women were not only similar in the probability of attempting to quit but also indistinguishable in the probability of quitting successfully (*26*).

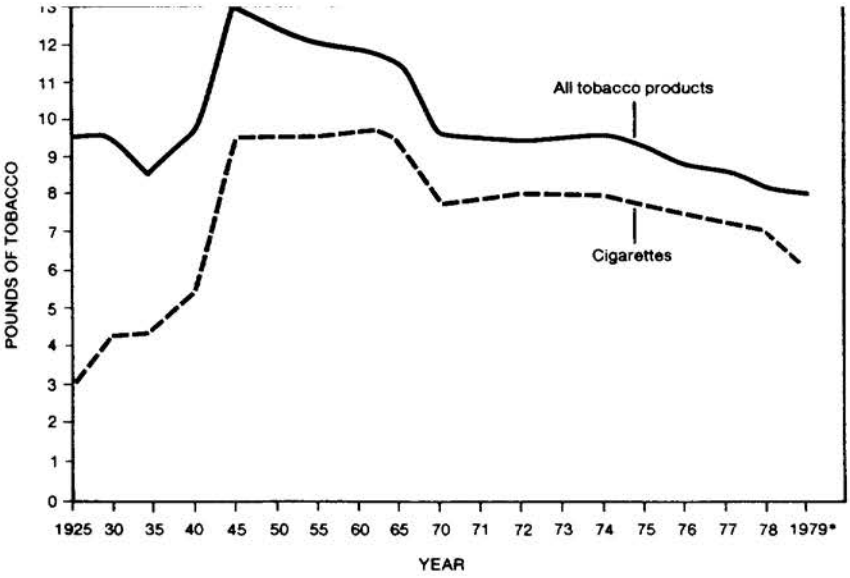

FIGURE 10.—Annual per capita consumption of tobacco products in the U.S. (including overseas forces) for persons aged 18 and older, 1925–1979

* 1979 data subject to revision.

SOURCE: U.S. Department of Agriculture (*22, 23, 24*).

Relationship of "Tar" and Nicotine Yields to Smoking Behavior

As indicated previously, this section focuses upon the currently available "tar" and nicotine data for adults. The discussion presents (1) a description by demographic characteristics of the current use of cigarettes of different yields, as well as changes over time where available; (2) data on the effect of varying "tar" or nicotine yields on consumption patterns; and (3) data defining the role of varying yields of "tar" and nicotine in cessation of smoking. The following data are from the National Center for Health Statistics' Smoking Supplement to the Health Interview Survey and include discussion of the information on "tar" and nicotine levels of the cigarettes smoked by adolescents, as collected by the National Institute of Education (*17*).

As noted previously, the selection of categories of "tar" or nicotine yields is arbitrary; in fact, both are continuous variables. The categories of yield used in the following analysis do not imply that the cigarettes within those categories differ either qualitatively or quantitatively from the cigarettes in other categories. Rather, the groupings permit convenient presentation of data on a cigarette's yield of "tar" and nicotine relative to other available cigarettes.

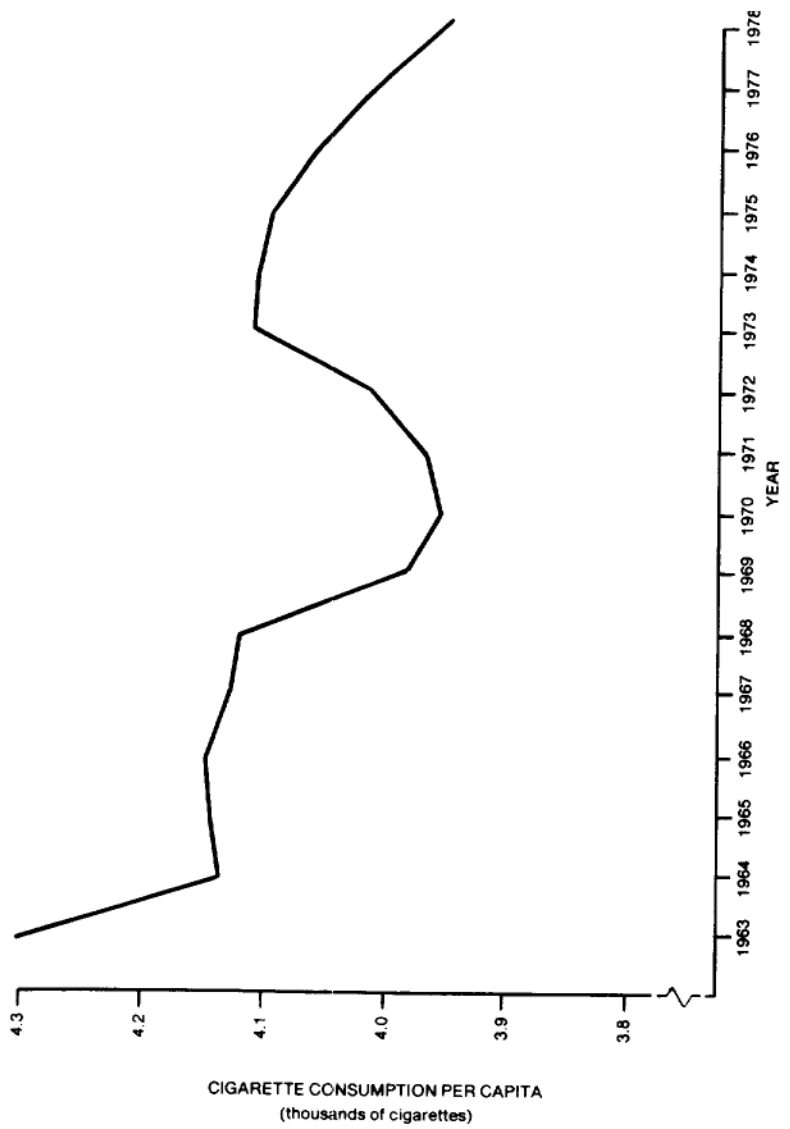

FIGURE 11.—Annual per capita consumption of cigarettes in the U.S. (including overseas forces) for persons aged 18 and older, 1963–1978

SOURCE: U.S. Department of Agriculture (*24*).

TABLE 1.—Estimated percentage distribution of current regular smokers by "tar" yield of primary brand of cigarette, by sex, race, age, and education, adults, U.S., 1979

	"Tar" yield of primary brand			
	<10 mg	10–14 mg	15–19 mg	>20 mg
Total	13.0	20.3	57.3	9.4
Sex				
Males	11.1	17.3	59.1	12.5
Females	15.0	23.6	55.4	6.0
Sex and race				
Males, white	12.2	18.0	57.4	12.5
Males, black	3.2	12.1	71.5	13.2
Females, white	16.0	24.5	53.6	5.9
Females, black	7.6	15.0	69.8	7.6
Age in years				
17–24	9.6	22.6	66.9	1.0
25–44	13.5	20.8	58.9	6.9
45–64	13.9	18.2	50.0	17.8
≥65	15.6	19.4	50.0	15.0
Years of education				
0–8	7.0	16.0	61.0	16.0
9–11	8.6	16.3	65.4	9.6
12	12.6	21.2	57.8	8.4
13–15	18.3	24.8	49.4	7.4
≥16	23.9	24.7	45.0	6.4

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

The percentage distribution of current regular smokers by "tar" level of their primary brand of cigarettes is presented in Table 1. Although not shown, the same patterns are observed among five arbitrary categories of nicotine yield (based on data from the 1979 Smoking Supplement of the National Health Interview Survey).

As noted previously, both 1978 and 1979 data on brands were coded to 1978 FTC values for "tar" and nicotine yield. For this reason, and because the cigarette samples tested in 1978 were obtained in 1977, the data that follow probably report slightly higher values of "tar" and nicotine yields than were actually being used during these periods. A further discussion of the differences in "tar" and nicotine yields of cigarette varieties reported by the FTC in 1978 and 1979 appears in the addendum to this section. Overall, 33.3 percent of current smokers use lower "tar" cigarettes (yielding less than 15 mg of "tar") and 66.7 percent use higher "tar" cigarettes. Females smoke lower "tar"

cigarettes in higher proportions than do males. This difference in choice of product by "tar" or nicotine level also persists when examined by race. Whites smoke lower "tar" products in greater proportions than do blacks, regardless of sex. For both sexes, white smokers choose lower "tar" products approximately twice as frequently as do black smokers of the same sex. While the percentage of all smokers using cigarettes yielding <10 mg of "tar" increases within age cohorts, there is no clear relationship of age cohort to those smoking cigarettes yielding 10 to 14 mg of "tar." Among smokers of the two highest "tar" categories, there is a clear difference by age; the proportion of smokers choosing cigarettes yielding 15 to 19 mg of "tar" decreases with age, but the percentage using the highest "tar" (≥ 20 mg) cigarettes increases with age. The trend to increasing use of highest yield products among older cohorts is clearer than the corresponding trend to higher proportions using the lowest "tar" yield products. The correlation of older ages and more frequent use of the highest "tar" products could result from a cohort effect among older smokers who continue to use the higher "tar" cigarettes that they used when they first began to smoke.

Educational level, as measured in years of education completed, is strongly associated with the percentage of smokers who use low "tar" products. In considering products of 15 to 19 mg "tar" yield, an inverse relationship with educational level in the proportion of smokers using that product is observed, and a similar pattern is observed for the extremely high "tar" products, yielding 20 mg or more of "tar" per cigarette. (This inverse relationship persists even when age is controlled, although the data are not shown in the table.) A similar though less clear trend is observed with an increasing proportion of smokers choosing lower "tar" products among higher income groups (data are not shown).

The lack of correlated health endpoint information or detailed data on knowledge and beliefs precludes interpretation of these data as cause or effect, but the data do provide a description of the observed differences in product choice by "tar" or nicotine yields.

The percentage of adults of both sexes who use lower "tar" products has increased over time. These increases are observed in both races for the time period shown. This is consistent with the previously cited market data on the sales of lower "tar" products. The finding that only 33.3 percent of adult smokers in 1979 used cigarettes yielding less than 15 mg "tar," although these products accounted for almost 40 percent of the market, does not establish a greater daily number of cigarettes smoked by users of the lower "tar" products, because gross sales figures include purchases by smokers not included in this analysis (e.g., institutionalized persons including the military forces, adolescent smokers, occasional smokers, and interviewees whose smoking status is unknown).

Comparison of changes in the "tar" level of chosen brand is possible for the years 1970 and 1979. The proportion of male smokers choosing cigarettes yielding less than 10 mg "tar" increased from 1.1 to 11.1 percent and females choosing these brands increased from 2.7 to 15 percent. The use of high "tar" ($\geq$15 mg) declined from 1970 to 1979 from 89.4 to 71.6 percent for males and from 90.5 to 61.4 percent for females (based on data from the 1979 Smoking Supplement of the National Health Interview Survey and from U.S. Public Health Service (*37*)).

Analysis of cigarette choice by nicotine yield shows the same patterns by demographic variables, with the proportion of current regular smokers who use lower nicotine products increasing with increasing age and the proportion of smokers using products with higher nicotine yields also increasing with increasing age. Whites use lower nicotine products in greater proportions than do blacks.

A further measure of consumption suggests that the actual toxic exposure of smokers by age, race, and sex may, however, differ significantly from that implied by consideration only of cigarette "tar" or nicotine yield. Table 2 shows the estimated mean daily "tar" or nicotine dose derived from combining the reported yield per cigarette and the number of cigarettes smoked daily by each individual in that group. There is a consistent trend toward higher dose with increasing age of smokers for race and sex groups. Although these figures do not consider possible systematic differences in the style of smoking (e.g., butt length unsmoked, frequency and depth of inhalation, etc.), they do illustrate marked differences in an estimate of mean dose of "tar" or nicotine by age, sex, and race. It shows that if all smokers smoked in the same manner, blacks would nonetheless experience a lower daily dose of "tar" and nicotine than whites. Thus, although blacks smoke higher "tar" products in higher proportions, the lower numbers of cigarettes they smoke daily may result in a lower average daily dose of smoke constituents.

More recent data on cigarette brand choice reveal changes. Table 3 presents data on the percentage distribution of smokers by "tar" and nicotine yield of cigarettes in the period July through December 1978 versus 1979. These two surveys, each of which represents approximately 12,000 interviews, showed a shift in the percentage of persons using lower "tar" ($<$15 mg) cigarettes from 28.8 percent in 1978 to 33.7 percent only a year later; a similar downward shift was observed at nicotine yields below the highest category. Such a shift might be caused by either an actual brand change or an involuntary downward "creep" due to reduction in the "tar" or nicotine yield of the product by the manufacturer. As noted previously, however, the cigarette brands reported were coded in both 1978 and 1979 by the 1978 FTC "tar" and nicotine yield values. Thus, the downward shift observed over this 1-

TABLE 2.—Mean daily dose* of "tar" or nicotine for current regular smokers by race, sex, and age, U.S., 1979**

		Mean daily dose (mg/day)	
		"Tar"	Nicotine
Males		406	26.3
White	All ages ≥ 17	417	26.9
	17–24	309	20.2
	25–44	416	27.1
	45–64	482	31.3
	65+	424	25.1
Black	All ages ≥ 17	308	21.1
	17–24	234	17.4
	25–44	294	20.7
	45–64	387	26.5
	65+	299	14.1
Females		316	21.0
White	All ages ≥ 17	324	21.4
	17–24	286	19.1
	25–44	326	22.0
	45–64	359	23.3
	65+	289	17.8
Black	All ages ≥ 17	244	16.9
	17–24	204	14.6
	25–44	243	17.0
	45–64	262	17.5
	65+	392	28.0

*Number of cigarettes consumed multiplied by the level of "tar" or nicotine.
**Last two calendar quarters only.
SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

year interval in cigarette "tar" and nicotine yield represents an actual change in the brand of cigarettes used by smokers.

Similar patterns have been observed in smoking among adolescents. In a 1979 national telephone interview survey of 2,639 adolescents, the percentage of all adolescent smokers who selected brands of lower "tar" ($\leq$15 mg) had increased from 6.7 percent observed in 1974 for both sexes (Table 4) to 33.5 percent in 1979. Direct comparison of the percentage distribution of "tar" yield among adolescents with that observed among adults is complicated by different groupings of "tar" level and by different definitions of "regular" smokers in the two surveys (after having smoked 100 cigarettes, "regular" smokers were defined for adolescents as "smoking regularly each week"; for adults, as any positive response to "when did you start smoking regularly?"). Nonetheless, a similar trend toward increasing use of lower "tar" products is observed among adolescents and adults.

Table 5 presents data on brand choice by "tar" level among adolescents of different ages from the largest recent smoking survey of adolescents. The small numbers of smokers, and the relatively large numbers of individuals who are unclassifiable, make interpretation of

TABLE 3.—Estimated percentage distribution of current regular smokers by "tar" and nicotine yield of primary cigarette used, U.S., 1978* and 1979*

"Tar" yield	Percentage in 1978	Percentage in 1979
≤5 mg	4.2	4.0
5–9 mg	7.5	9.0
10–14 mg	17.1	20.7
15–19 mg	61.4	56.8
≥20 mg	9.8	9.6

Nicotine yield	Percentage in 1978	Percentage in 1979
<0.5 mg	4.3	4.2
0.5–0.9 mg	26.7	31.7
1.0–1.2 mg	41.1	37.7
1.3–1.6 mg	26.7	25.3
≥1.7 mg	1.2	1.2

*Last 2 calendar quarters only.
SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

TABLE 4.—Estimated percentage distribution of regular smokers by "tar" yield, adolescents aged 12–18, U.S., 1974 and 1979

	Percentage boys		Percentage girls		Percentage both sexes	
"Tar" yield	1974	1979	1974	1979	1974	1979
≤10 mg	0.5	2.5	0.5	12.3	0.5	7.8
11–14 mg	5.6	29.5	6.8	22.6	6.2	25.7
15–19 mg	73.7	60.8	74.4	59.5	74.0	60.1
≥20 mg	20.3	7.4	18.2	5.5	19.3	6.3

SOURCE: National Institute of Education (*17*).

product choice among adolescents by age group difficult. Thus, a clear definition of the relationship of the adolescent smoker's age to choice of cigarette smoked is not possible from this series.

In Table 6, the mean age of onset of smoking cigarettes for all current regular smokers is 18.2 years. Although most of the data in the National Health Interview Survey Smoking Supplement involves recall, the mean age at onset is perhaps the most subject to bias, whether in remembrance or in reporting preference. Nonetheless, the reported age at onset of smoking is higher among older age groups. This might reflect (1) a real change in recent years in the age at which younger cohorts start to smoke, (2) the addition of a few late-starting smokers during the extra years "at risk," causing a higher reported age at onset among older cohorts, or (3) an effect of different mortality rates for early versus late beginning smokers. The demonstration that the average age at onset of smoking among females has declined from 35 years among women born prior to 1900 to 16 years among women

TABLE 5.—Percent distribution of adolescent regular smokers by "tar" yield of primary brand, by sex and age, U.S., 1979

	"Tar" yield of primary brand							
	≤15 mg		>15 mg		Unspecified		Don't know	
Boys age group	%	n	%	n	%	n	%	n
12–14	11.1	2	55.6	10	27.8	5	5.6	1
15–16	29.4	15	62.7	32	7.8	4		
17–18	26.4	19	58.3	42	15.3	11		
19	23.6	13	63.6	35	12.7	7		
	Nicotine yield of primary brand							
	≤15 mg		>15 mg		Unspecified		Don't know	
Girls age group	%	n	%	n	%	n	%	n
12–14	25.0	6	70.8	17	4.2	1		
15–16	23.9	11	56.5	26	13.0	6	6.5	3
17–18	34.7	34	52.0	51	12.2	12	1.0	1
19	30.5	18	50.8	30	18.6	11		

SOURCE: National Institute of Education (*17*).

born between 1951 and 1960 (*26*) explains a portion of the observed differences in age at onset by cohort. Older cohorts may not fit the assumption that the survivors within that cohort are representative of all individuals within the original cohort. The amount and direction of the effects of (1), (2), and (3) remain to be defined. However, there is a general trend that, for each age cohort, the higher the "tar" level of the cigarette currently smoked, the younger the reported age of onset of smoking. The same observation is also found in the relationship between nicotine yield and age of onset, except that an older age of onset is indicated for those smoking the highest nicotine yield (>1.7 mg) cigarettes, which value is based on a small sample size.

Consumption Patterns

In attempting to define the role of "tar" or nicotine yield on the daily number of cigarettes smoked, adult regular smokers were divided into three levels of daily consumption by approximate quintiles of "tar" and nicotine yield of primary brand (Table 7). This Table shows that the percentage distribution of smokers by number of cigarettes per day does not exhibit an association with "tar" or nicotine level of cigarette used. This Table provides evidence that there is not a significantly greater proportion of "heavy" smokers among smokers of the lowest "tar" and nicotine cigarettes than there is among smokers of the highest "tar" and nicotine cigarettes. It does not, however, disprove the theory that individual smokers may increase their daily number of cigarettes smoked when they switch to a cigarette with lower "tar" or nicotine yield. That is, the absolute number of cigarettes

TABLE 6.—Mean age at onset of regular smoking by "tar" or nicotine yield of primary brand, by age at interview, current regular smokers, U.S., 1979

"Tar" yield	Total	Age at interview					
		17–24	25–34	35–44	45–54	55–64	65+
<5 mg	19.6	16.6	18.3	19.5	20.3	19.2	23.8
5–9 mg	18.8	16.3	17.8	18.8	19.6	20.7	24.1
10–14 mg	18.5	16.2	18.1	18.7	19.3	20.6	22.4
15–19 mg	18.0	15.6	17.3	18.3	19.0	19.8	23.9
≥20 mg	17.0	15.7	17.1	17.0	17.1	18.1	21.3
Total	18.2	15.8	17.5	18.4	18.8	19.7	23.2
Nicotine yield							
<0.5 mg	19.7	16.5	18.3	19.8	20.5	19.2	24.1
0.5–0.9 mg	18.7	16.3	18.1	18.9	19.5	20.7	23.3
1.0–1.2 mg	18.0	15.7	17.2	18.2	19.1	19.7	23.7
1.3–1.6 mg	17.7	15.2	17.0	17.8	17.6	18.7	22.6
≥1.7 mg	19.3	18.0	17.5	17.3	19.4	21.6	20.3
Total	18.2	15.8	17.5	18.4	18.8	19.7	23.2

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

smoked by individuals at low "tar" and nicotine yields may, in fact, be higher than the number of cigarettes the *same individuals* smoked at high yield levels, even though there is no cross-sectional difference.

The relationship of "tar" or nicotine yield to the number of cigarettes smoked daily can also be examined by the average number of cigarettes smoked in various age groups, as presented in Table 8. After grouping smokers by age at interview, it is still observed that neither the level of "tar" nor that of nicotine demonstrates a definite association with the mean number of cigarettes smoked daily.

Cessation

The role played by cigarettes of varying "tar" and nicotine yields in cessation has been widely discussed (*25*, *26*). Present survey data have not sufficed to define the role for varying "tar" and nicotine yields in cessation, largely because of the lack of longitudinal surveys of cigarette consumption prior to attempting to quit or after an unsuccessful attempt. A longitudinal study of smoking patterns by both cigarette product choice and number smoked daily to determine their relationship to cessation is being conducted by the NCHS for the Office on Smoking and Health during 1980 and 1981.

Table 9 examines by cigarette "tar" or nicotine yield the percent of current smokers who report ever having seriously tried to quit smoking. Overall, there is a clear inverse relationship between the "tar" or nicotine yield of the cigarette and the percent of smokers who have ever tried to quit. The group of lowest yield smokers shows a

TABLE 7.—Estimated percentage distribution of current regular smokers by number of cigarettes smoked daily by approximate quintiles of "tar" or nicotine yield, adults, U.S., 1979

	"Tar" yield per cigarette (quintiles)				
	≤10 mg	11–15 mg	16–17 mg	17–18 mg	≥19 mg
Percent of total population	19.1	18.1	23.5	19.4	19.8
Daily number of cigarettes					
<15	29.9	27.5	31.2	27.6	25.9
15–24	42.7	45.5	42.4	43.3	43.9
≥25	27.5	26.9	26.3	29.2	30.2
Totals	100.1	99.9	99.9	100.1	100.0

	Nicotine yield per cigarette (quintiles)				
	≤0.7 mg	0.8–1.01 mg	1.02–1.09 mg	1.10–1.31 mg	≥1.32 mg
Percent of total population	20.3	20.3	19.7	21.3	18.4
Daily number of cigarettes					
<15	29.2	29.0	28.2	27.5	31.0
15–24	42.3	46.5	41.4	43.3	43.1
≥25	28.5	24.5	30.4	29.2	25.9
Totals	100.0	100.0	100.0	100.0	100.0

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

higher proportion of persons who have ever tried than those groups smoking higher yield products. This relationship was found for both "tar" and nicotine yields for all age groups except those 65 or more years of age, where the sample size was considerably smaller and the pattern was less clear.

The finding that greater proportions of current smokers of lower "tar" or nicotine products report ever attempting to quit than do smokers of higher "tar" products could result from (1) a higher rate of attempting to quit (but with a similar failure rate) for more health-conscious individuals who may also therefore choose lower yield cigarettes; (2) a difference in the addictive qualities of lower "tar" or nicotine products, causing a higher probability of relapsing after attempting to quit; or (3) the choice of a lower "tar" and nicotine cigarette product after failing to stop smoking. Selection between these alternatives would require comprehensive data on brand choice both prior to and following an attempt to quit smoking, as well as health status measurements that might affect brand switching or quit attempts. Such information is not available from this data set.

TABLE 8.—Mean number of cigarettes smoked daily by "tar" or nicotine yield, by age groups, current regular smokers, adults, U.S., 1979

Tar yield	Age at interview						
	Total	17–24	25–34	35–44	45–54	55–64	65+
<5 mg	21.5	16.0	19.5	23.3	26.3	21.8	18.9
5–9 mg	20.7	17.0	20.7	21.9	23.3	22.0	18.9
10–14 mg	20.2	16.2	20.2	23.1	23.7	19.5	16.4
15–19 mg	20.6	17.5	21.0	22.7	23.3	22.1	16.4
≥20 mg	22.5	15.2	23.0	24.9	23.9	21.6	16.9
Total	20.7	17.1	20.8	22.9	23.4	21.5	17.2
Nicotine yield							
<0.5 mg	21.4	16.9	19.8	22.9	25.6	21.5	18.7
0.5–0.9 mg	20.2	16.2	20.3	22.4	23.7	20.5	18.4
1.0–1.2 mg	21.0	17.7	21.9	23.1	23.5	22.0	15.9
1.3–1.6 mg	21.2	17.6	20.1	23.4	23.7	22.3	17.3
≥1.7 mg	18.5	5.5	18.3	21.4	18.8	18.3	17.0
Total	20.7	17.1	20.8	22.9	23.4	21.5	17.2

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

TABLE 9.—Estimated percent of current regular smokers who have tried seriously at least once to quit, by "tar" or nicotine level and age, U.S., 1979

Age group	"Tar" level of primary variety				
	<5 mg	5–9 mg	10–14 mg	15–19 mg	≥20 mg
17–24	62.9	57.1	57.6	52.3	43.3
25–44	72.9	68.8	63.5	59.8	50.0
45–64	71.5	64.0	59.1	58.5	51.0
≥65	50.8	60.0	61.6	58.4	49.7
All ages	69.8	65.3	61.8	58.8	51.5

Age group	Nicotine level of primary variety				
	<0.5 mg	0.5–0.9 mg	1.0–1.2 mg	1.3–1.6 mg	≥1.7 mg
17–24	60.7	58.0	53.6	47.1	50.4
25–44	73.3	65.1	61.2	55.1	49.2
45–64	70.7	60.6	58.4	55.0	48.3
≥65	53.3	60.8	57.5	54.3	58.6
All ages	68.8	62.1	58.4	53.8	50.0

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

Table 10 shows a comparison of the frequency distributions of recent smokers by "tar" or nicotine level of the primary cigarette brand smoked by those who either did not try to quit, those who tried but failed to quit, and those who succeeded in quitting smoking within the

12 months prior to interview. In this analysis, "success" in quitting was arbitrarily defined as persons who had recently been regular smokers who had attempted to quit within 12 months and who had not smoked for at least 6 months prior to interview. Persons who smoked regularly within 1 year prior to the interview and who had attempted to quit during the last year but had been off cigarettes less than 6 months are excluded from consideration in this analysis. Unsuccessful quitters were defined as regular smokers at the time of interview who reported having attempted seriously to quit at least once within the 12 months prior to interview date. Interpretation of these data is complicated by the fact that the primary brand reported for successful quitters represents the brand smoked prior to a quit attempt, while unsuccessful quitters' brands are those smoked after a quit attempt. Thus, clear distinction cannot be made between the possible explanations. The data show that higher proportions of smokers who use the two lowest "tar" or nicotine cigarette products are found among the unsuccessful quitters than among successful quitters. The proportion of recent regular smokers who use cigarettes yielding <5 mg of "tar" is lowest for persons who did not attempt to quit (3.8 percent), intermediate among those who succeeded in quitting (4.6 percent), and highest among those who failed at an attempt to quit (4.9 percent).

Grouping these smokers into larger categories by "tar" level (e.g., the percent smoking cigarettes yielding <10 mg or those smoking cigarettes yielding <15 mg "tar") shows that a lower proportion of recent smokers who successfully quit used lower "tar" products than do recent smokers who did not attempt to quit, while smokers who failed in an attempt to quit reported smoking lower "tar" products in the highest proportions. Conversely, a lower proportion of unsuccessful attempters currently smoke higher "tar" products (65.3 percent) than is found among either nonattempters (69.0 percent) or successful quitters (72.2 percent). A similar relationship was observed by nicotine yield: the proportion of persons choosing the lower yield products (<1.0 mg) was highest for unsuccessful quitters, intermediate for nonattempters, and lowest among successful quitters.

Thus, these data are consistent with the postulated tendency of smokers to switch to lower "tar" and nicotine cigarettes following an unsuccessful attempt to quit smoking.

The relationship between number of serious attempts to quit smoking and the "tar" or nicotine yield of the primary cigarette smoked is shown in Table 11. Note should be taken that the table includes only current regular smokers who have tried at least once to quit. For the lowest categories of "tar" and nicotine yields, there is a suggestion of a shift in the population toward a greater number of cessation attempts. No significant difference is observed in the frequency distributions of smokers of other "tar" and nicotine products.

TABLE 10.—Estimated percentage distribution of recent smokers by status of recent attempt to quit, by "tar" or nicotine yield of primary brand, July 1978 through December 1979*

Status of recent attempt to quit smoking	"Tar" yield of primary brand					
	<5 mg % (n)	5–9 mg % (n)	10–14 mg % (n)	15–19 mg % (n)	≥20 mg % (n)	Total % (n)
Successful	4.6 (13)	5.6 (16)	17.6 (50)	63.4 (180)	8.8 (25)	2.3 284
Unsuccessful	4.9 (152)	9.2 (286)	20.5 (636)	59.7 (1849)	5.6 (175)	25.6 3098
No attempt	3.8 (355)	8.3 (721)	19.0 (1655)	58.1 (5070)	10.9 (950)	72.1 8731
Total	4.1 (500)	8.4 (1023)	19.3 (2341)	58.6 (7099)	9.5 (1150)	100.0 12113
	Nicotine yield of primary brand					
	<0.5 mg % (n)	0.5–0.9 mg % (n)	1.0–1.2 mg % (n)	1.3–1.6 mg % (n)	≥1.7 mg % (n)	
Successful	4.6 (13)	26.8 (76)	43.0 (122)	25.0 (71)	0.7 (2)	2.3 284
Unsuccessful	5.0 (155)	32.2 (999)	39.7 (1229)	22.3 (692)	0.7 (23)	25.6 3098
No attempt	4.0 (351)	29.2 (2553)	38.3 (3340)	27.1 (2368)	1.4 (119)	72.1 8731
Total	4.3 (519)	30.0 (3628)	38.7 (4691)	25.8 (3131)	1.2 (144)	100.0 12113

*Unweighted data.

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

TABLE 11.—Estimated percentage distribution of current regular smokers by number of serious attempts to quit smoking, by "tar" or nicotine level, U.S., 1979

"Tar" level (mg)	Number of serious attempts to quit				
	1	2	3	4	≥5
<5	27.3	29.1	10.6	6.0	27.1
5–9	35.7	28.9	15.8	4.4	15.2
10–14	36.9	29.1	14.6	5.5	13.9
15–19	38.6	26.3	14.7	5.3	15.0
≥20	37.6	23.7	14.9	5.4	18.5
Total	37.3	27.1	14.6	5.3	15.7
Nicotine level (mg)					
<0.5	26.8	29.4	10.2	5.7	27.8
0.5–0.9	37.4	28.6	14.9	5.1	14.1
1.0–1.2	39.5	26.7	14.1	5.0	14.7
1.3–1.6	35.9	25.2	15.7	6.2	17.0
≥1.7	38.6	25.1	21.1	2.3	12.9
Total	37.3	27.1	14.6	5.3	15.7

SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

The relationship of cigarette choice to the duration of the most recent unsuccessful quit attempt is shown in Table 12 for current regular smokers. Although there are large variations in the individual durations within each "tar" or nicotine grouping, the mean durations

TABLE 12.—Mean duration of most recent attempt to quit, by "tar" or nicotine yield of current primary brand, current regular smokers, 1979*

	Mean number of days	
"Tar" yield		(n)
<5 mg	3.4	(132)
5–9 mg	3.1	(247)
10–14 mg	3.8	(566)
15–19 mg	3.5	(1647)
≥20 mg	4.7	(144)
Total	3.6	(2736)
Nicotine yield		
<0.5 mg	3.4	(133)
0.5–0.9 mg	3.7	(885)
1.0–1.2 mg	3.3	(1080)
1.3–1.6 mg	3.9	(622)
≥1.7 mg	6.8	(16)
Total	3.6	(2736)

*Unweighted data.
SOURCE: Based on data from the 1979 Smoking Supplement of the National Health Interview Survey.

do not exhibit a relationship to either "tar" or nicotine yield. The higher mean duration of quit attempt among the smokers of highest yield products must be interpreted in light of the small numbers of individuals within those yield groupings.

Summary

1. Public awareness of the dangers of smoking has steadily increased since 1965. In 1978, more than 90 percent of all Americans believed cigarette smoking to be hazardous to health.
2. Cigarette product choice has shifted dramatically since the 1950s. In 1979, 91.7 percent of U.S. smokers used filter-tipped cigarettes, compared with 1.4 percent in the early 1950s.
3. Lower "tar" cigarettes conventionally have been defined as yielding 15 mg of "tar" or less per cigarette. The proportion of all cigarettes consumed in the United States that are lower "tar" has increased from 3.6 percent in 1970 to almost 50 percent in 1979. In 1979, 58.5 percent of all cigarette brands marketed in the United States yielded 15 or fewer mg of "tar."
4. Since 1968, the "tar" content of the "average cigarette" in the United States has declined by 32.2 percent, and nicotine content has fallen by 25.6 percent. These declines may be partially accounted for by lower tobacco weight per cigarette—down 23.8 percent from 1968 to 1978—and by the greater length of the filter and overwrap of the average cigarette, which could result in a declining number of machine puffs per cigarette.

5. The prevalence of smoking in the U.S. adult and adolescent populations has continued to decline. In 1979, 32.5 percent of the adult population smoked cigarettes (36.1 percent of men and 29.4 percent of women). However, evidence suggests that the average daily number of cigarettes consumed by those adults who continue to smoke has increased over several decades. The availability and use of lower "tar" cigarettes have increased over recent years.
6. In 1979, 33.3 percent of adult regular smokers used cigarettes yielding 15 mg "tar" or less. Studies show that women smokers are more likely to use lower yield cigarettes than men are, and white smokers use lower yield cigarettes in greater proportions than do blacks. Smokers of higher income and education also select lower yield cigarettes in a higher percent of cases.
7. A large national survey found that smokers in older aged cohorts choose both the lowest and highest yield cigarettes in higher proportions than do younger cohorts.
8. Although black smokers choose cigarettes of higher "tar" and nicotine in greater proportions than do whites, the lower daily number of cigarettes smoked by blacks suggests that their average daily intake of "tar" and nicotine may be lower than that of white smokers.
9. In 1979, 33.5 percent of adolescent smokers (age 12 to 18) used lower "tar" cigarettes, compared with 6.7 percent in 1974. Boys and girls smoke cigarettes of about the same level of "tar" content.
10. Adult smokers started smoking regularly at the average age of 18 years. One survey showed that the higher the "tar" level of the cigarette currently smoked, the younger the reported age of beginning smoking.
11. Evidence from a large national survey does not support a correlation between a greater mean number of cigarettes smoked per day by users of lower "tar" and nicotine cigarettes than by higher "tar" users.
12. In a national survey, smokers of lower "tar" and nicotine cigarettes more frequently reported having attempted to quit at least once, and among these smokers, a higher proportion report having attempted unsuccessfully to quit multiple times. The applicability of these data to defining of the role of "tar" or nicotine yields of cigarettes in quitting behavior is not clear in the absence of more detailed longitudinal data.
13. Although a greater proportion of unsuccessful quitters reported smoking the lowest "tar" and nicotine products than did recent successful quitters in one large survey, interpretation of these data is made difficult by the noncomparability of brand reported

(i.e., unsuccessful quitters reported the brand smoked after an attempt, successful quitters reported the brand smoked prior to the attempt).

14. In a large national survey, the mean duration of the latest unsuccessful attempt to quit shows no clear relationship to "tar" or nicotine yields.

Addendum: Comparison of "Tar" and Nicotine Yields of Cigarettes in 1978 and 1979

The Federal Trade Commission (FTC) has conducted tests of commercially available cigarettes in the United States since 1968. The FTC measures "tar" and nicotine yields of approximately 99.5 percent of the brands available in the United States and issues annual reports on these measurements.

This discussion examines the changes in cigarette yields from 1978 to 1979 as published by the FTC. The following should be helpful in estimating to what extent the coding of NHIS brand data for 1979 by the "tar" yields measured in 1978 might influence the results presented above in this section.

Yields of "Tar" and Nicotine

The cigarettes tested in 1978 (sample collected in 1977) had a mean "tar" yield of 15.4 mg and in 1979 (sample collected in 1979) the mean "tar" yield was 13.6. The corresponding mean yields of nicotine were 1.02 and 0.97 mg in the 1978 and 1979 FTC reports (Table 13). These reductions in yields occurred regardless of the different parameters of cigarette type (length, menthol/plain, package type, and filter/nonfilter). If only filter-tipped cigarettes are considered, the mean nicotine yield declined from 0.95 to 0.90 mg. For all 1979 varieties, there was a significant difference in "tar" yield between filter and nonfilter cigarettes, and between menthol and nonmenthol varieties of cigarettes. Examining filtered cigarettes only, the length of cigarette was the only parameter that showed a significant difference in mean "tar" level.

Correlation of Varieties Reported in 1978 and 1979

There were 144 varieties of cigarettes marketed in both years (1978 and 1979) that were unchanged, as defined by exact variety name, length, menthol and filter status, and package type. Despite the identity of all five parameters, the mean "tar" level of varieties declined over the period mentioned (Table 14). The mean "tar" level declined from 15.3 mg in 1978 to 14.8 in 1979; for filter-tipped cigarettes only, the mean "tar" level declined from 13.8 to 13.3 mg. These decreases, although slight in absolute terms, are statistically significant. The change in nicotine yields for these same brands of cigarettes over the same period is negligible.

TABLE 13.—Mean yield of "tar" and nicotine of cigarettes, by type of modifier, all and filtertip varieties, U.S., 1978 and 1979

	All varieties						Filtertip varieties					
	"Tar" (mg)		Nicotine (mg)		No. of varieties		"Tar" (mg)		Nicotine (mg)		No. of varieties	
Type of modifier	1978	1979	1978	1979	1978	1979	1978	1979	1978	1979	1978	1979
Soft	15.9	13.4	1.03	0.96	138	149	14.0	12.2	0.97	0.90	119	134
Hard	15.1	14.7	1.00	1.04	29	27	13.4	13.3	0.88	0.91	26	24
Filter	13.9	12.4**	0.95	0.90**	145	158	-	-	-	-	-	-
Nonfilter	25.1	24.7	1.48	1.58	22	18	-	-	-	-	-	-
<100 mm	15.4	13.4	0.99	0.93	99	100	12.6	10.9**	0.85	0.80**	77	82
≥100 mm	15.3	14.0	1.06	1.01	68	76	15.3	14.0	1.06	1.01	68	76
Menthol	14.0	12.2*	0.97	0.90	58	64	13.8	12.2	0.96	0.90	57	64
Regular	16.1	14.4	1.05	1.01	109	112	13.9	12.5	0.96	0.90	88	94
Total	15.4	13.6	1.02	0.97	167	176	13.9	12.4	0.95	0.90	145	158

**P <.001.
*P <.05.
SOURCE: Federal Trade Commission (*4*, *5*).

TABLE 14.—Mean yield of "tar" and nicotine of the varieties of cigarette marketed in both 1978 and 1979, by type of modifier, all and filtertip varieties, U.S.

	All varieties					Filtertip varieties				
	"Tar" (mg)		Nicotine (mg)			"Tar" (mg)		Nicotine (mg)		
Type of modifier	1978	1979	1978	1979	No. of varieties	1978	1979	1978	1979	No. of varieties
Soft	15.2	14.7**	1.03	1.03	119	13.9	13.3**	0.96	0.97	104
Hard	15.5	15.0	1.03	1.05	25	13.5	13.4	0.89	0.92	22
Filter	13.8	13.3**	0.95	0.96	126	-	-	-	-	-
Nonfilter	25.6	24.7	1.58	1.58	18	-	-	-	-	-
<100 mm	15.3	14.8*	1.01	1.02	83	12.5	12.1*	0.85	0.86	65
≥100 mm	15.2	14.7*	1. 05	1.06	61	15.2	14.7*	1.05	1.06	61
Menthol	14.0	13.4*	0.97	0.97	54	13.9	13.3*	0.97	0.96	53
Regular	16.0	15.6*	1.06	1.08	90	13.8	13.4*	0.94	0.95	73
Total	15.3	14.8**	1.03	1.03	144	13.8	13.3**	0.95	0.96	126

**P <.001.
*P <.05.
SOURCE: Federal Trade Commission (*4, 5*)

TABLE 15.—Comparison of "tar" and nicotine yield on the varieties of cigarette marketed in both 1978 and 1979, U.S.

"Tar" yield in year	Mean "tar" difference (mg)	Mean nicotine difference (mg)	No. of varieties
1978 = 1979	-	-0.0157	7
1978 < 1979	-0.6945	-0.0829	55
1978 > 1979	1.3366	0.0478	82
Total	0.4958	-0.0052	144

SOURCE: Federal Trade Commission (*4, 5*).

Further examination of the changes in the "tar" and nicotine yield occurring in the same varieties of cigarettes over this period is presented in Table 15. Of the 144 brands reported on in both periods, only 7 showed no difference in mean "tar" level. Fifty-five brands showed a slight increase, with the mean difference being less than 1 mg. Eighty-two brands, however, showed a decline from the 1978 reported yields to the 1979 yield. Once again, however, the mean decrease was small, only 1.3 mg.

"Tar" and Nicotine Yields of New Brands in 1979

There were 32 varieties of cigarettes defined as new in the 1979 FTC report (Tables 16 and 17). A "new" variety was defined as a different name (such as a varietal name change by addition of the word "lights"), or by a change in one of the other four varietal parameters of filter, length, package type, or menthol status (e.g., a nonfiltered cigarette changing to filtered). The average "tar" and nicotine yields for these 32 new brands in 1979 were 8.5 and 0.67 mg, respectively. Except for a single new variety, the new varieties yielded less than 15 mg of "tar," with two-thirds of them yielding less than 10 mg "tar." A similar examination of new 1979 varieties by nicotine yield showed a similar trend toward lower yields, with 81 percent of them yielding less than 0.9 mg of nicotine.

Applications to the Discussion

As noted in the body of this Report, all NHIS variety data on the Smoking Supplement collected in interviews during 1978 and 1979 were coded to the FTC 1978 "tar" and nicotine yields. Since the cigarettes reported on in 1978 were collected in 1977, and since the updated measures of yield for 1979 were not available in time for their use in coding the 1979 smoking data, the described distribution of smokers by "tar" and nicotine yields of their cigarettes is conservative and underestimates to some extent the proportion of smokers who use lower yield products.

TABLE 16.—Mean yield of "tar" and nicotine of the new varieties of cigarette marketed in 1979, by type of modifier, U.S.

Type of modifier	"Tar" (mg)	Nicotine (mg)	No. of varieties
Soft	8.3	0.66	30
Hard	11.7	0.82	2
Filter	8.5	0.67	32
Nonfilter	-	-	-
<100 mm	6.5	0.54	17
≥100 mm	10.8	0.82	15
Menthol	7.0	0.57	11
Regular	9.4	0.72	21
Total	8.5	0.67	32

SOURCE: Federal Trade Commission (*4, 5*).

TABLE 17.—Distribution of "tar" and nicotine yield of the new varieties of cigarette marketed in 1979, U.S.

	"Tar" yield (mg)				
	<5	5–9.9	10.0–14.9	15.0–19.9	Total
N	7	14	10	1	32
%	21.9	43.8	31.3	3.1	100.0

	Nicotine yield (mg)					
	<0.49	0.50–0.69	0.70–0.89	0.90–1.09	1.10–1.29	Total
N	9	4	13	4	2	32
%	28.1	12.5	40.6	12.5	6.3	100.0

SOURCE: Federal Trade Commission (*4, 5*).

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