

- 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**

## CONTENTS

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Introduction

---

The Relation of Cigarette Smoking to Cardiovascular Risk

---

Factors in Cigarette Smoke Related to Cardiovascular  
Function  
    Nicotine  
    Carbon Monoxide  
    Other Components

---

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

---

The Challenge of Future Research

---

Proposed Future Research  
    Descriptive Studies  
    Cohort Studies  
        Observational Studies  
        Clinical Trials  
    Case-Control Studies  
    Studies of Mechanisms  
    Animal Experimentation  
    Technical Resource Center  
    Behavioral Ramifications

---

Summary

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References

---

## LIST OF TABLES

---

Table 1.—Coronary heart disease—mortality ratios

---

Table 2.—The effect of the cessation of cigarette smoking

on the incidence of coronary heart disease (CHD)—  
morbidity ratios in males

---

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

## 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**

Reference	NS	Number of cigarettes smoked						
		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
Period 2	1.00	0.82
Medium "tar" { Period 1	1.00	0.91
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