Cigarette Smoking and Cardiovascular Diseases

IN 1956, the American Heart Association issued a statement on smoking and cardiovascular diseases. Among other things, this statement indicated that the available evidence at that time was not sufficient to justify conclusions concerning a cause and effect relationship between cigarette smoking and increased death rates from coronary heart disease (Appendix 1). Since then, sufficient additional knowledge has been accumulated to warrant a new report on cigarette smoking and its possible relationship to cardiovascular diseases. (See footnote and Appendices 2, 3, 4 and 5.)

Up to the present, a number of medical studies (Appendix 5) have been made, nearly all demonstrating a statistical association between heavy cigarette smoking and mortality (death) or morbidity (illness) from coronary heart disease. In these studies, death rates from coronary heart disease (heart attacks) in middle-aged men were found to be from 50 to 150 per cent higher among heavy cigarette smokers than among those who do not smoke. This statistical association does not prove that heavy cigarette smoking causes coronary heart disease, but the data strongly suggest that heavy cigarette smoking may contribute to or accelerate the development of coronary heart disease or its complications.

Because coronary heart disease is the leading cause of death and a major cause of disability in the American population, the American Heart Association believes that these studies concerning cigarette smoking and coronary heart disease should be called to the attention of the medical profession, allied health professions, health educators, and the general public. The association recognizes the need for more knowledge and will continue to encourage systematic biological and medical research in order to determine whether a causal relationship exists between cigarette smoking and coronary heart disease and also to determine the effects of smoking in relation to strokes and other important aspects of cardiovascular diseases.

Ad Hoc Committee on Smoking and Cardiovascular Disease:

L. N. Katz, M.D., Chairman, Chicago, Ill.
E. V. Allen, M.D., Rochester, Minn.
M. Cherkasky, M.D., New York, N. Y.
F. W. Davis, M.D., Baltimore, Md.

APPENDIX 1

Statement on Smoking Issued in 1956 by American Heart Association

The text of the report of the Committee on Smoking and Cardiovascular Disease given publicity in 1956 follows:

1. There is evidence supported by clinical observations in a large number of cases, that tobacco smoking is harmful in certain diseases of the peripheral blood vessels of the arms and legs. This harmful effect is demonstrated most clearly in the condition known as thrombo-angitis obliterans (Buerger's disease). It is known that this disease will usually continue to progress if the patient continues to smoke, and that it will usually become stationary, or even improve, if he stops smoking. If smoking is resumed, the disease will usually become active again.

2. It is recognized that a small percentage of persons with known disease of the coronary arteries will develop symptoms and will display signs detectable by laboratory tests when they smoke. Such people may be harmed by smoking.

3. The Committee believes that the available evidence is not sufficient to define the effect of tobacco smoking upon the coronary arteries or upon the heart itself, except in the small group mentioned above who already have coronary artery disease. It is believed that if smoking plays any part in the causation of heart disease, it is only one of many factors.

4. It is the belief of the Committee that much greater knowledge is needed before any
conclusions can be drawn concerning relationships between smoking and increased death rates from coronary heart disease. The acquisition of such knowledge may well require the use of techniques and research methods that have not hitherto been applied to this problem.

5. Consequently, it is recommended that the continuing interest of the American Heart Association be implemented by the appointment of a technical committee representing a wide range of research experience to suggest the lines of investigation that may be most productive.

APPENDIX 2

Summary of Recent Reports on the Biologic Effects of Cigarette Smoking on the Cardiovascular System

By Grace M. Roth, Ph.D., Albuquerque, N. Mex.

Effects of Smoking on the Peripheral Vascular System

Again the question has arisen of the possible allergic activity of tobacco as a cause of certain peripheral vascular diseases. Further work by Fontana and co-workers demonstrated that 33 per cent of the smokers with positive skin reactions to tobacco extracts gave a personal history of allergic manifestations and peripheral vascular symptoms, as compared with 10 per cent of the smokers who did not react to the skin tests. On smoking, 23 per cent of smokers with positive skin tests to tobacco had changes in the peripheral circulation indicated by a fall in skin temperatures of the extremities, as compared with the smokers with negative skin tests, 4 per cent of whom had changes in the skin temperatures.

Previously it had been shown in the rabbit that the constrictor action of nicotine was unaffected by degeneration of all sympathetic fibers to the ear after removal of the stellate and superior cervical ganglia. In contrast, Roth and Shick found no vasoconstriction in the lower extremities of patients during smoking if bilateral lumbar sympathetic ganglionectomy of the first and second lumbar ganglia was complete, but they found a considerable fall in the skin temperatures of the fingers. Thus, after bilateral lumbar sympathetic ganglionectomy, the remainder of the sympathetic nervous system seemed to function in a more than adequate manner.

In 1957, Nordenstam and Adams-Ray described the presence of chromaffin tissue in human skin. Later, Burn and co-workers studied the effects of nicotine on the perfused vessels of rabbits' ears treated with reserpine and found that nicotine no longer produced vasoconstriction because of the depletion of norepinephrine and epinephrine. Therefore, they suggested that peripheral vascular disease could be explained by a hypersensitivity to the action of nicotine in releasing catecholamines from chromaffin tissue located near the blood vessels of the skin.

The controversy in regard to the elevation of the fasting blood sugar by smoking has continued over a period of years. Rehder and Roth found that when 24 normal subjects under basal conditions smoked two thirds of 2 cigarettes, there was no appreciable rise in the levels of the fasting blood sugar and the epinephrine-like substances in the venous blood. However, the blood pressure and pulse rate were significantly raised and the skin temperatures of the fingers and toes were decreased. Thus, this amount of smoking had an effect on the circulation but no significant effect on the fasting blood sugar.

Effects of Tobacco on the Heart

Most investigators agree that the effects of smoking tobacco or of the intravenous injection of nicotine on the heart are an increase in the pulse rate and elevation of the arterial blood pressure and some flattening of the T waves in the electrocardiograph. Two conflicting opinions have developed as to the cause of these effects: (1) that the changes are due solely to the increased work of the heart, or (2) that the changes are due to spasm or constriction of the coronary arteries.

Work on Animals

In 1950 and 1959, Rinzler and co-workers demonstrated that blood flow in the perfused coronary arteries of normal rabbits was increased after the injection of nicotine. On the other hand, when the rabbits had been made atherosclerotic by a high cholesterol diet, nicotine caused a decline in flow through the perfused coronary vessels.

Likewise, West, Guzman and Bellet, working on dogs, catheterized the circumflex and anterior descending branch of the left coronary artery via 1 carotid artery and cannulated the coronary sinus via 1 external jugular vein. They concluded that there was no evidence of coronary constriction following administration of nicotine and that the explanation for the effect was that nicotine influenced the parasympathetic and sympathetic ganglia and chemoreceptors in the heart.

Kien, Lasker and Sherrod determined the effect of cigarette smoke on the open-chest, anesthetized dog by measuring blood pressure, cardiac output,
coronary blood flow, cardiac oxygen consumption, cardiac work and the electrocardiographic effects. A lack of correlation was observed between the onset of the electrocardiographic effects and the changes in cardiac work. Coronary blood flow increased and appeared to follow the changes in blood pressure and cardiac output. The authors suggested that the electrocardiographic disturbances subsequent to the inhalation of cigarette smoke were not due entirely to increased cardiac work or to coronary vasconstriction, but rather to decreased oxygen consumption. They felt that this latter factor was of prime importance in the precipitation of “tobacco angina pectoris.”

In 1959, Armen and Cohen studied the effects of forced inhalation of tobacco smoke on rabbits previously sensitized to tobacco proteins. They concluded that the cardiovascular effects demonstrated by abnormalities of the electrocardiogram were due to anoxia and not to immunologic effects.

A different concept has been introduced by Burn and Rand. They demonstrated that the stimulant action of nicotine on the isolated atria of the heart of rabbits was due to a release of norepinephrine and epinephrine from the stores within the heart. Such stores of these amines could be depleted by giving reserpine; subsequently nicotine did not stimulate the depleted atria. The stores of norepinephrine and epinephrine in the normal heart exert some effect and accelerate the spontaneous rate of the heart. This was shown when the mean rate of the atria in the control animals was 142 beats per minute, while the mean rate of the atria treated with reserpine was 112 beats per minute. From this work, they concluded that smoking can liberate norepinephrine and epinephrine from the stores within the heart, thereby producing acceleration, and may cause or exaggerate ventricular arrhythmias.

Work on Humans

The general consensus is that smoking tests carried out by means of the ballistocardiograph were more discriminating than any other objective method in separating patients with coronary disease from normal controls. Thomas, Bateman, Lindberg, and Bornhold studied the ballistocardiographic effects of smoking on 113 healthy medical students, 103 men and 10 women, who were 21 to 35 years of age. In both smokers and nonsmokers, the systolic and diastolic pressure, pulse pressure, heart rate, stroke volume, cardiac output, and cardiac index showed statistically significant changes on smoking 1 cigarette.

There was quite good correlation between the pattern of response to smoking and the family history regarding hypertension or coronary disease. As a group, subjects with parental hypertension showed a significantly greater rise in cardiac output than expected, while stroke volume and cardiac output were significantly smaller than anticipated among the offspring of parents with coronary disease. No such relationship between familial hypertension and hyperreactivity to smoking had previously been described. The studies indicated that hyperreactivity to smoking is related to hyperreactivity to the cold pressor test and that hypertensive patients react more strongly to smoking than do normotensive subjects; this is in harmony with the hypothesis that hyperreactivity appears particularly frequently in individuals who are the offspring of hypertensive parents and may be a precursor of hypertension in a given individual.

From the above facts, it appears that change in cardiac output after smoking is likely to be the most valuable part of the ballistocardiographic smoking test in screening possible candidates for hypertension or coronary disease.

Again in 1959, Thomas and Murphy, to test the reproducibility of the above ballistocardiographic smoking tests, gave 32 men 4 tests each, 2 before breakfast and 2 before lunch, and 6 subjects 8 tests each, under circumstances kept as standard as possible in every way.

From these findings, it appears that the ballistocardiographic smoking test, in which blood pressure, heart rate, stroke volume, and cardiac output are measured, gives results which are sufficiently reproducible for use as a screening test to classify young adults according to their patterns of circulatory reactivity. The results were materially unchanged by attempts to standardize further the test conditions, except that on the average the response was more marked in the fasting state.

The first studies using direct catheterization of the coronary sinus and a needle in the femoral artery were carried out on 30 human beings by Bargeron and co-workers. They found that smoking a cigarette caused a significant rise in coronary blood flow and heart rate, a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose.

The evidence that cigarette smoking does not reduce coronary flow in normal individuals is in agreement with observations that electrocardiographic or ballistocardiographic changes are absent in individuals without coronary disease. However, from electrocardiographic or ballistocardiographic observations on patients with coronary heart disease, one may suggest that these individuals respond to smoking by a decrease in coronary blood flow and an increase in coronary vascular resistance. This assumption is borne out by Rinzler, who found that nicotine increased the coronary flow through a perfused normal rabbit's heart, but when the animal had been made atherosclerotic by a high
cholesterol diet, nicotine resulted in a decline in flow through the perfused coronary vessels.

Although extensive work has been carried out to determine the cause of the changes in the heart during smoking, the controversy has not been settled. However, with new and more critical instrumentation, the answer may be forthcoming.

References

APPENDIX 3

Summary of Reports Pertaining to Cigarette Smoking and the Cardiovascular System: Clinical Data 1956-60

By Frank W. Davis, M.D., Baltimore, Md.

A review of the English literature of the years 1956-60, inclusive, produced little of primary clinical nature in which the effects of smoking (or nicotine) on the cardiovascular system were considered. Several reports of great interest from the epidemiologic viewpoint were published, but these undoubtedly will be summarized by Dr. Dawber. The much discussed New England, California, and English statistical studies were enlarged during this period.

The most comprehensive report, dealing with most of the known physiologic actions of smoking and touching only briefly on the clinical features, is the excellent review paper of Roth and Shick.1 This doubtless will be included in Dr. Roth’s summary. Of review nature, but in a briefer form, is the paper by Burn,2 in which he outlines his concept of the physiologic and pharmacologic effects of nicotine on the heart. He continues to express the view that smoking triggers the release of a sufficient quantity of vasopressin to elicit coronary vasoconstriction, with the alternative explanation of nicotine effect being direct action on chromaffin tissue and stimulation of epinephrine or norepinephrine release. He suggests abstinence from smoking in patients with clinical coronary disease.

In a rather extensive clinical review, oriented from the allergic point of view, Harkavy3 summarizes the investigations of himself and others, including an evaluation of skin testing of smokers and nonsmokers with and without various vascular disorders, to various tobacco extracts. Approximately 9 per cent of nonsmokers react positively to these extracts, 41 per cent of smokers showing a positive skin test. In patients with thrombo-

Circulation, Volume XXII, July 1960
angiitis obliterans, the incidence of positive tests is 78 per cent. Experimentally, rats can be sensitized to tobacco extracts, and in 33 per cent of such rats, gangrene of the extremities appeared. He concluded from the skin sensitivity studies and from general clinical observation that not only thrombangiitis obliterans, but some arrhythmias and angina, can be related to tobacco allergy.

Thomas and her co-workers have published 3 papers in this period which have potential clinical implication. In the first of these,4 she observed the changes in blood pressure, pulse, and ballistocardiographically determined cardiac output and stroke volume in healthy medical students. There was considerable variability, but each individual seemed to show consistent changes in each parameter studied. Those with a family history of hypertension were hyperreactors (increased output) and those with family histories of coronary disease generally showed a subnormal response. In a subsequent report,5 these effects were shown to be fairly reproducible when studied in the same subjects under various conditions and over a several year period. A third report6 compared these circulatory reactions to smoking with the response to the cold pressor test. Interestingly, these stimuli did not correlate well, and "independent information seems to be gained from each test." The changes resulting from either seemed to be a continuous variable, without clear separation of her subjects into groups, and without definite prognostic information to be gained.

The last group of papers of clinical nature is related to observations on the effect of smoking on the ballistocardiogram. Strober published 2 papers7,8 in which a presumably normal Air Force population was studied with regard to ballistocardiographic pattern change after smoking. He found practically no evidence of ballistocardiographic deterioration in his young males but a rapidly increasing incidence with increasing age, so that 72.7 per cent of those in the 45 to 51 year group responded positively. Obesity likewise seemed to increase the incidence of positive reactions. He concludes that this test may detect asymptomatic coronary artery disease.

Our group published further observations on the ballistocardiograph cigarette test as a diagnostic method in coronary heart disease.9 This represents an extension of previously reported studies in which it was shown that patients with ischemic heart disease react with ballistocardiographic deterioration after smoking much more frequently than do the apparently normal subjects. Filtered or "denicotinized" cigarettes failed to prevent this deterioration. This "test" is presented more as a challenge to the clinical investigator than as a routine clinical procedure.

References


APPENDIX 4

Summary of Recent Literature

Regarding Cigarette Smoking and Coronary Heart Disease

By THOMAS R. DAWBER, M.D., FRAMINGHAM, MASS.

In reviewing the problem of the relationship of tobacco smoking to coronary heart disease, Sigler1 stated: "It has been well established that tobacco smoke induces certain immediate effects on the cardiovascular system. These may consist of an acceleration of the heart rate, a rise in blood pressure, a decrease in the temperature of the fingers and toes, a diminution of the blood

Circulation, Volume XXII, July 1960
flow to the extremities, and minor electrocardio-
vascular changes, such as diminished amplitude
of the T waves.” After considering the physi-
ologic effects of tobacco on the circulatory system,
he concluded that “although the immediate mani-
festations are expressions of physiologic distur-
bances, it is conceivable that accumulative effects
of tobacco intoxication over years may result also
in structural changes. To prove or dis-
prove such an assumption, we must rely mainly
on statistical studies of many cases observed over
a period of years.”

Studies which have been carried out in an en-
deavor to answer this question are of 3 general
types:

Clinical Studies of Persons Who Have Developed
Coronary Heart Disease

Representative of this group of studies is one
by Sigler, who examined the records of
1,520 cases of coronary heart disease and found
that (1) the age at onset of clinical manifesta-
tions of coronary disease in this series occurred
earlier in smokers than in nonsmokers; (2) the
higher the degree of smoking the earlier was the
onset of the clinical manifestations of the dis-
ease; and (3) the age at onset of the first attack
of coronary occlusion also occurred earlier in the
smokers than in nonsmokers in both males and
females. He also found that the age at death was
also younger in smokers than in nonsmokers.

Mortality Data from Large Populations Including
Smokers and Nonsmokers

Although studies of mortality data are open
to the objection that causes of death as attested
to by death certificates and examining physicians
are not completely reliable, there is no reason to
believe that there is a different degree of accuracy
in deaths of smokers as compared to non-
smokers. Comparability of the 2 groups in the
same population is therefore a valid exercise.

The most recent and extensive study of this
type is that of Dorn, who has been following
carefully 198,926 Veterans Administration policy
holders in whom smoking data and cause of death
information could be obtained. According to
Dorn, the death rate from coronary heart disease
was 63 per cent higher for cigarette smokers than
for nonsmokers. This increase did not hold true
for pipe and cigar smokers who had a death rate
“not appreciably higher than nonsmokers.”

Dorn’s report is in agreement with the report
of Hammond and Horn, who state that “death
rates from coronary heart disease were far higher
among men with a history of regular cigarette
smoking than among men who never smoked.”
The death rate was 70 per cent higher in cigarette
smokers than a comparable group of nonsmokers.

On the other hand, Haag and Hanmer, in a
study of workers in the American Tobacco Com-
pany, found that the mortality rates from cardio-
vascular disease were lower in these tobacco
workers, although the number of tobacco smokers
and the average amounts smoked was higher than
in the general population. This study, however,
did not make an internal comparison of smokers
and nonsmokers, but compared the group of
workers in the American Tobacco Company with
the general population. The extent to which gen-
eralizations can be drawn from comparison of
these 2 groups is unknown since they may differ
in a number of characteristics.

Prospective Studies Involving Small Population
Groups in Whom Morbidity Data, as Well as
Mortality Data, Are Available

In these studies, there is more thorough knowl-
edge of the characteristics of the population
studied and its comparability to the general pop-
ulation than in the case of mortality studies;
also, the reliability of the diagnosis of coronary
heart disease is far higher. Nevertheless, due to
the lengthy follow-up necessary to obtain suffi-
cient cases for study, many of the reports are
yet inconclusive. For example: Doyle et al. have
stated that “no clear relation between the inci-
dence of ischemic heart disease and the consump-
tion of tobacco in any form has been demon-
strated. The numbers involved, however, are too
small to permit a reliable estimate.” This con-
clusion was based on a study of 1,913 men fol-
lowed for approximately 4 years. They stated:
“T here appears to be no trend toward an increas-
ing incidence from the light to the heavy smoking
category.” They concluded, however, that a fur-
ther follow-up is needed to establish any rela-
tionship. Similarly, Dawber et al. have reported:
“Study of the relation of smoking to the develop-
ment of all new cases of coronary heart disease
continues to show a lack of association. . . .”
“When, however, a separate analysis is made of
those cases manifesting more severe degrees of
coronary heart disease, excluding those with an-
gina pectoris alone, an association of risk with
cigarette smoking seems to emerge, the risk rising
with the number of cigarettes smoked per day.”

When they considered the mortality experience,
they concluded: “Findings are consistent with
those involving larger populations but based on
too few cases of coronary heart disease to indi-
cate a definite association with smoking.”

Buechley et al., however, after reviewing sev-
eral studies and adding their own study of 3,994
longshoremens, concluded that “the difference in
death rates between nonsmokers and smokers
shows a strong and consistent relationship between
cigarette smoking and coronary heart disease
mortality, at least in men 40 to 70 years of age.”

Circulation, Volume XXII, July 1960
Conclusion

It, therefore, seems possible that when examination of mortality data has been the basis of the study, conclusions have been reached which clearly relate increased cigarette smoking to an increase in death rates from coronary heart disease. In those studies in which morbidity data have been used (i.e., new cases of disease in the living), it has not been possible clearly to link increased cigarette smoking to the occurrence of coronary heart disease. However, such studies have not been carried on for a sufficiently long period of time to demonstrate definitely what the relationship may be. Such studies should ultimately be able better to define the relationship.

References


APPENDIX 5

References

The article by Buechley, R. W., Drake, R. M., and Breslow, L., entitled: 'Relationship of amount of cigarette smoking to coronary heart disease mortality rates in men' (Circulation 18: 1085, 1958), summarizes the studies listed below which support the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases:


The following studies, also supporting the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases, have been reported since the article by Buechley et al. was published:


The following studies question the methods used in studying the statistical association between cigarette smoking and mortality or morbidity from cardiovascular diseases:


Cigarette Smoking and Cardiovascular Diseases: REPORT BY THE AMERICAN HEART ASSOCIATION

Circulation. 1960;22:160-166
doi: 10.1161/01.CIR.22.1.160

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1960 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/22/1/160.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/