Smoking and Health

Joint Report of the Study Group on Smoking and Health

The Study Group on Smoking and Health was organized in June 1956, at the suggestion of the American Cancer Society, the American Heart Association, the National Cancer Institute, and the National Heart Institute, to review the problem of the effects of tobacco smoking on health and to recommend further needed research to the sponsoring organizations.

The study group has held six 2-day conferences, has examined the pertinent literature and more recent unpublished reports, and has consulted with scientists representing specialized areas of research concerned with the subject.

The study group, cognizant of the implications of its conclusions and recommendations, now submits the following joint report.

Lung Cancer

At least 16 independent studies carried on in five countries during the past 18 years have shown that there is a statistical association between smoking and the occurrence of lung cancer (appendix A). (As used in this report, the term *lung cancer* refers to epidermoid and undifferentiated types of carcinoma of the lung, but not to adenocarcinoma.) These retrospective studies have been reinforced by two investigations in which large male populations have been followed prospectively. Lung cancer occurs much more frequently (5 to 15 times) among cigarette smokers than among nonsmokers, and there is a direct relationship between the incidence of lung cancer and the amount smoked. It is estimated that on a lifetime basis, one of every ten men who smoke more than two packs a day will die of lung cancer. The comparable risk among nonsmokers is estimated at one out of 275 (appendix B). Self-selection and sampling bias have been mentioned as possible sources of error. Examination of the evidence shows that any distortion resulting from these sources does not invalidate the conclusions (appendix C).

Epidemiologic studies also indicate that cigarette smoking cannot account for all cases of epidermoid cancer of the lung. There are other causative environmental factors, the most important of which are probably various atmospheric pollutants. As in other diseases, various other influences, such as sex, nutrition, and heredity, may modify its occurrence (appendix D).

The two prospective studies further suggest that cessation of smoking by chronic smokers decreases the probability that such individuals will develop lung cancer.

The epidemiologic evidence is supported by laboratory studies on animals. At least five independent investigators have produced malignant neoplasms by tobacco smoke condensates. Although the active material has not been identified chemically, some progress has been made in localizing the activity in purified fractions (appendix E). Although the demonstration of carcinogenic activity in animals does not constitute proof of carcinogenicity in the lungs of human beings, this is important contributory evidence that strengthens the concept of causal relationship.

Studies on pathogenesis of human lung cancer are also compatible with the causal relationship. Physiologic observations indicate that foreign material is trapped in the tracheobronchial tree, particularly where ciliary action is inhibited or the ciliated epithelium is destroyed (appendix F).

Fluorescent substances present in cigarette smoke have been shown to enter the cells of the buccal mucosa (appendix G). Detailed histologic studies of the tracheobronchial tree indicate that basal cell hyperplasia, atypical hyperplasia, squamous metaplasia, and areas of morphologic alteration with all characteristics of carcinoma *in situ* are encountered more frequently among cigarette smokers than among nonsmokers (appendix H). Thus, every morphologic stage of carcinogenesis, as it is understood at present, has been observed and related to the smoking habit.

The sum total of scientific evidence establishes beyond reasonable doubt that cigarette smoking is a causative factor in the rapidly increasing incidence of human epidermoid carcinoma of the lung.

The evidence of a cause-effect relationship is adequate for considering the initiation of public health measures. Nevertheless, additional research is needed to clarify many details and to aid in the most effective development of a program of lung cancer control. The need for information in the following areas appears to be very important: (i) the isolation, identification, and possible elimination from tobacco smoke of chemicals that produce cancer in animals (appendix I); (ii) the role of atmospheric pollutants and additional environmental factors other than cigarette smoking in the causation of lung cancer in man; (iii) the effect of cessation of smoking on the occurrence of lung cancer in man (appendix J); (iv) measurement of possible physiologic, sociologic, and psychologic differences between smokers and nonsmokers and the relation of host differences to the occurrence of lung cancer (appendix K).

Longevity and Cardiovascular Diseases

At least three statistical investigations show an association of tobacco smoking with a decrease in longevity, probably referable to a higher risk, for male smokers, of dying from cardiovascular disease. The mortality among smokers in certain age groups is reported to be approximately double that of the nonsmokers (appendix L).

The study group is of the opinion that the significance of this observation requires further research before its meaning can be determined. Cardiovascular diseases account for well over half of all adult male deaths. Even a relatively small proportionate excess in the cardiovascular death rate could, therefore, contribute a larger number of deaths than a much larger excess in the lung cancer death rate.

In the few reports available, there is no convincing biological or clinical evidence to indicate that smoking per se has a causative role in cardiovascular disease. Many physicians have the clinical impression that patients with coronary artery disease should not smoke, on

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the basis that smoking may be detrimental to previously damaged coronary arteries. A few studies have provided some validating evidence for this hypothesis. However, further systematic investigation is essential (appendix M).

The study group strongly urges a research program of wide scope that will clarify the relationship and association between smoking and cardiovascular diseases. The following areas are considered to be of particular importance: (i) epidemiologic studies, with appropriate consideration of the roles of other factors such as diet, physical activity, and blood lipides (appendix N); (ii) the chronic effects of tobacco and nicotine in animals, with and without experimental atherosclerosis; (iii) further physiologic studies of man, particularly of the effect of smoking on coronary artery blood flow in normal individuals and in individuals with coronary insufficiency.

Other Diseases

The study group considered reports of association of smoking with a number of other disease entities, including carcinoma of the larynx, oral cavity, esophagus, bladder, and stomach; peptic ulcer; bronchitis and tuberculosis; and thromboangiitis obliterans (appendix O).

The evidence that relates smoking directly to thromboangiitis obliterans is based on repeated, well-confirmed demonstrations that the disease is materially ameliorated by cessation of smoking and strikingly aggravated by continued smoking (appendix P).

For the other conditions mentioned, the relationships have been studied only to a degree that indicates statistical association. Further research on the individual conditions is necessary before valid conclusions can be drawn.

Conclusions

The study group concludes that the smoking of tobacco, particularly in the form of cigarettes, is an important health hazard. The implications of this statement are clear in terms of the need for thorough consideration of appropriate control measures on the part of the official and voluntary agencies that are concerned with the health of the people. The lack of specific recommendations in this regard reflects no lack of interest. Rather, it reflects the desire of the study group to limit its recommendations to the area of research needs in accordance with the instructions it received.

The study group recommends that further research on smoking and health be vigorously pursued. The recommendations made in the section on "Lung cancer" are for research into means of coping with lung cancer hazard, which has been established for cigarette smoking. The recommendations of the sections on "Longevity and cardiovascular diseases" and "Other diseases" are directed primarily at establishing whether smoking is one of the contributory factors in other diseases, particularly in coronary artery disease. Many of these answers can best be obtained by a cooperative research effort.

The Study Group on Smoking and Health approves dissemination of this report as desired by the sponsoring agencies and hereby terminates its activities.

Appendixes

A) Fourteen (*1–14*) of the retrospective studies have been reviewed by Cutler (*15*). Stocks and Campbell (*16*) have studied the association between smoking and lung cancer in terms of place of residence. An additional recent retrospective study by Wynder (*17*) is concerned with the occurrence of lung cancer in women.

B) Doll and Hill (*18*) in England and Hammond and Horn (*19*) in this country reported their first results in 1954. Since then, Doll and Hill have published a follow-up report (*20*), and Hammond has reported additional data (*21*).

Although the statistical evidence has often been quoted as indicating an association between *heavy* smoking and lung cancer, there is no evidence of a threshold level below which the risk disappears. The best available estimates for both the United States and England indicate that the lung cancer risk is statistically significant for half-pack-a-day smokers and that there is a correlation of risk with amount smoked (*16, 20, 21*).

C) By numerical illustration, Berkson (*22*) has indicated that, in epidemiologic studies similar to the one conducted by Hammond and Horn (*19*), it is possible to obtain a spurious statistical association between smoking and a disease as a result of sampling bias, even though no real association exists. It has been pointed out by Cornfield (*23*), Korteweg (*24*), Levin (*25*), and Lilienfeld (*26*) that, in order for the degree of association between cigarette smoking and lung cancer observed by Hammond and Horn to be a result of sampling bias, it would be necessary to assume an unreasonably large degree of such bias. Furthermore, a study of smoking habits of a probability sample of the United States population reported by Haenszel and associates (*27*) indicates that the necessary degree of sampling bias was not present in the Hammond-Horn study. Berkson also indicated that the influence of sampling bias would disappear with the passage of time. Doll and Hill (*20*) have recently reported that, over a 4-year period of observation, the gradient of lung cancer mortality in relation to the amount smoked has remained remarkably constant during each of the 4 years.

The issue of self-selection is raised as an argument against interpreting the statistical association of cigarette smoking and lung cancer as a causal relationship. Self-selection assumes that there is a factor that both causes a person to smoke and causes lung cancer; thus, individuals are selected for both smoking and lung cancer by a third mutually related factor. Such a hypothesis does not appear likely. Doll and Hill (*20*) and Levin (*25*) have indicated that such a hypothesis would be inconsistent with the marked increase of lung cancer mortality in recent years. The likelihood of this hypothesis is diminished further by the biological and pathogenetic evidence discussed in this statement. However, information concerning the characteristics of smokers and nonsmokers would be valuable for further evaluation of this theoretical possibility.

D) Epidemiologic studies indicate that cigarette smoking cannot account for all cases of lung cancer; nonsmokers do develop lung cancer, and variations in frequency of lung cancer in different population groups are not completely related to variations in frequency of cigarette smoking. The most significant observation on this point is the higher death rate from lung cancer in urban, as compared with rural, areas (*28, 29*). This excess urban death rate has been attributed by most investigators (*16, 30, 31*) to the probable influence of air pollution. As has been indicated by Hammond (*29*) and by Haenszel and Shimkin (*28*), part of this urban excess may be attributed to the higher proportion of cigarette smokers among urban populations, but they have also pointed out that even after adjustment has been made for differences in smoking habits, the urban rate is still higher than the rural rate. Estimates have been made of the relative contribution that cigarette smoking and the "urban factor" (probably air pollution) make to the lung cancer deaths. From studies in Liverpool, Stocks and Campbell (*16*) have estimated that 50 percent of the lung cancer deaths result from smoking and about 35 percent from air pollution. Hammond (*29*) estimated that about 31 percent of lung cancer deaths are due to air pollution. It is recognized that these estimates may not be very precise, but they do afford some idea of the relative importance of these two factors. Recently, Hueper (*30*) and Kotin (*31*) have defended their views that air pollution is the *major etiologic factor* in

lung cancer and that cigarette smoking plays a minor role, if any. Cigarette smokers have higher lung cancer death rates than nonsmokers in urban areas, where presumably both of these groups have had similar exposure to general air pollution. A definite need exists for determining the chemical nature of these pollutants and estimating more precisely the role of air pollution, particularly in relation to the effect of cigarette smoking.

Several studies indicate that occupational exposure to chromate ore (*32*), radioactive dust, and other agents (*30*) increases the risk of lung cancer. However, specific occupational exposures have been demonstrated to be responsible for only a small percentage of lung cancer deaths.

It is also possible that additional factors increase host susceptibility to these environmental factors. There is suggestive evidence that hormonal factors may have some influence (*33*). The possible existence of endogenous factors that influence susceptibility to exogenous agents should be further investigated, since such information may have some bearing on control efforts.

E) In addition to the five recent demonstrations of carcinogenic activity in tobacco smoke (*34–38*), Roffo (*39*) and Woglom (*40*) had previously reported the production of cancers from tobacco tar. Evidence for a cocarcinogenic effect of tobacco smoke condensate has been obtained by Gellhorn (*41*).

Several workers have now reported the presence of 3,4-benzopyrene in tobacco smoke (*42–46*). This has been demonstrated to be present in the neutral fraction of tobacco smoke condensate at concentrations of about 2 micrograms per 100 cigarettes. According to Wynder (*47*), the concentration is so low that the biological activity observed in his most purified fractions cannot be the result solely of 3,4-benzopyrene. Other carcinogenic polycyclic hydrocarbons are being sought. In addition to 3,4-benzopyrene, Bonnet and Neukomm (*43*) found other polycyclic hydrocarbons, including 3,4,9,10-dibenzopyrene at an estimated concentration of 1 microgram per 100 cigarettes.

Recently Lacassagne, Buu-Hoi, and others (*48*) produced sarcomas in mice by three subcutaneous injections totaling 1.8 milligrams of this compound per animal. The quantitative aspects of this problem obviously should be investigated.

F) In the normal human lung, particulate matter, upon inhalation, may penetrate diffusely throughout and into the alveoli. This is evident from many observations, both clinical and experimental. O. H. Robertson (*49*), in an exhaustive investigation and review of this subject, presents evidence to indicate that such factors as particle size and concentration and the depth of ventilation, as well as time of exposure, are important determinants of the amount of particulate matter that will enter the lung. It is estimated that the range of particulate size in cigarette tobacco smoke is between 0.3 and 1.0 microns. Particles of this size, upon inhalation, may readily be distributed diffusely throughout the lung.

Increased depth of ventilation, such as is seen in inhalation during smoking, favors the entrance of greater amounts of particulate matter into the lungs. Particles that penetrate the upper air passages come in contact with the mucus-covered surface of the bronchi, where they tend to adhere and to remain in contact with bronchial mucosa for varying periods of time, depending on the size and nature of the particles.

An irritant such as smoke may bring about alterations in the ciliary activity of the bronchial mucosa. It is this ciliary activity that is the main mechanism available for the removal of particulate matter from the lung (*50*). Slight temporary alteration in this ciliary activity will allow for the retention of particulate matter. Furthermore, any alteration in the quantity or quality of mucus in the tracheobronchial tree will also interfere with the removal of particulate matter. Particles may become concentrated in outdrifting mucus and remain in contact with bronchial mucosa for significant periods of time. Hilding (*51*) demonstrated the possible role of paralyzed cilia or deciliated areas in the accumulation of cigarette tar by exposing recently removed calf lungs to cigarette smoke.

G) After smoking, according to the degree of keratinization, some chronic cigarette smokers who were tested were found by Mellors (*52*) to have fat-soluble fluorescent substances in scrapings of the buccal mucosa. Such substances are not observed, to any appreciable degree, 12 hours after smoking.

H) It is well established that changes may be observed in epithelial surfaces that precede established forms of invasive carcinoma. These alterations consist of atypical hyperplasia, metaplasia, and carcinoma *in situ*. Although there may be disagreement in the terminology in these early morphologic changes, their presence and significance are generally accepted. It has been demonstrated by Black and Ackerman (*53*) that epidermoid carcinoma *in situ* is an important stage in the histogenesis of lung cancer. If smoking is related causally to the development of epidermoid carcinoma of the lung, then one would expect to find a greater incidence of these early morphologic changes in the bronchial tree in smokers than in nonsmokers. A study investigating this hypothesis was carried out by Auerbach and associates (*54*).

A total of 28,638 slides was made from the tracheobronchial tree of 150 autopsied individuals in whom a cigarette-smoking history had been obtained. Such changes as basal cell hyperplasia, stratification, squamous metaplasia, and carcinoma *in situ* were found, both quantitatively and qualitatively, to a significantly greater degree in smokers than in nonsmokers. The findings were accentuated in autopsied cases of bronchogenic carcinoma; all such patients had been smokers. Carcinoma *in situ* was found in 1 percent of the slides of those who did not smoke regularly whereas it was found in 6 percent of the slides in those individuals who smoked more than one pack of cigarettes a day. Determination of the incidence of the various stages of these lesions, as related to sex, age, and exact anatomic distribution, awaits the investigation of larger numbers of cases. The alterations recorded by Auerbach were similar in almost all details to those that are found to precede and develop into epidermoid carcinoma of the uterine cervix.

Chang (*55*) and Chang and Cowdry (*56*) studied whole amounts of bronchial epithelium obtained at autopsy from smokers and nonsmokers. They found metaplasia and thickening of the epithelium more common among the smokers than among the nonsmokers. These results are in good agreement with those of Auerbach. In addition, they observed that the cilia were shorter and that Goblet cells were more numerous in the lungs of smokers than in those of nonsmokers.

I) It is possible that an innocuous cigarette could be developed without prior identification of the active agents, and efforts along this line should parallel the work on characterization of the active materials. However, if empiric reduction is achieved, it would still be urgent to define the chemical nature of the agents and their mode of action.

Reduction in tumor activity might be sought by the removal or inactivation of carcinogenic, cocarcinogenic (promoting) factors or the precursors of either. Possibilities that suggest themselves include selection of tobacco strain, extraction of tobacco leaves, alteration of the burning temperature of the cigarette, and, possibly, selective removal of the active material from tobacco smoke. In this connection, it should be noted that the filters that are presently in use do not appear to be selective in their action; rather, they reduce tumor activity only to the extent that they remove whole smoke (*47*). In the case of most commercial cigarette filters, efficiency is not high, and accordingly the

amount of smoke that reaches the lungs is not reduced to any major degree.

An incidental but urgent requirement for the identification studies is improved assay procedures, since the work is at present hampered by the necessity for relying on slow and relatively insensitive methods.

J) The most desirable method of obtaining information concerning the effect of cessation of smoking would be by an experiment with human beings. A description of one of several designs follows. A group of smokers, who would volunteer to be included in the study, would be randomly allocated to an experimental and a control group. The control group would continue to smoke, whereas the experimental group would be asked to give up smoking. These groups would be followed for a number of years to determine the risk of dying, in general, and the risk for specific causes of death. Even though all individuals in the experimental group had not ceased smoking, comparisons of mortality rates in the two groups would be made. Obviously, success of the experiment would depend on the proportion of the experimental group who had stopped smoking; if it is 50 percent or more, meaningful results could be expected.

Consideration of sample sizes required for this experiment indicated that very large samples would be necessary to obtain results with respect to lung cancer because of the relatively low death rate from this cause. However, the estimated sample sizes for studying the effect of cessation of smoking on total mortality, particularly on death from cardiovascular disease, appeared to be within practical limits; at least, they were such that further exploration of the feasibility of such an experiment appears warranted. Prior to conducting a full-scale experiment, a pilot study should be undertaken. Such a study is important, not only from a biological viewpoint but also from a public health administrative viewpoint, in that it would be a means of evaluating the feasibility of certain control efforts.

It should be recognized, of course, that such an experiment would fail to show a difference between experimental and control groups if the damage to the organ system had been irreversibly established at the time smoking was stopped.

Further information on the effect of cessation can be obtained from the prospective studies of Hammond, Doll and Hill, and from the Veterans' Study that is now being conducted by the National Institutes of Health, It is recommended that collection of the necessary data continue to be made with respect to this aspect of these studies.

K) A large prospective study of the effect of smoking on lung cancer and other causes of death among approximately 220,000 veterans of World War I is now in progress, at the National Institutes of Health, under the direction of Harold F. Dorn. This study offers an excellent opportunity to explore, by additional questionnaires and interviews, some of the possible differences that may exist between smokers and nonsmokers. In addition, this study could also be expanded to include cardiovascular evaluation, perhaps even to the extent of including physical examinations and laboratory determinations on subsamples of the smoker and nonsmoker groups.

The study group has been in contact with Dorn and has suggested that additional questionnaires and clinical and laboratory determinations might be valuable. It is hoped that these suggestions will be developed into research actions with the help of the National Heart Institute and the U.S. Veterans Administration.

There is no evidence at present to indicate that the occurrence of cancer of the lung among cigarette smokers is limited to an undefined subgroup of susceptible individuals. Nevertheless, certain characteristics may well be correlated with greater or less susceptibility to lung cancer or heart disease. Research on host factors that may be associated with, or modify, certain disease states is of great importance. This is particularly true of chronic diseases in which the etiologic situations are often multiple and in which the host response may play a paramount role.

L) Pearl (*57*), Hammond and Horn (*19*), and Doll and Hill (*20*) have all shown an increase in mortality associated with smoking. Pearl found the mortality rate for all causes among cigarette smokers to be just twice that of nonsmokers among men from 60 to 65 years of age. In the same age group, Hammond and Horn reported a ratio of 1.9. Doll and Hill found that the mortality rate increased progressively with the amount smoked, so that heavy smokers for all age groups over 35 had a mortality rate 42 percent higher than nonsmokers.

For coronary artery diseases, Gertler and White (*58*) studied smoking habits, results of which showed a significantly higher number of smokers among the heart patients than among controls. English, Willius, and Berkson (*59*), in 1940, found a greater incidence of coronary disease in male smokers than among nonsmokers, particularly at ages under 50. Hammond and Horn (*19*) found that the death rates from coronary artery disease for men who smoked a pack or more of cigarettes a day were more than twice as high as the rates for men who had never smoked; this is true for age groups from 50 to 65. The findings of Doll and Hill (*20*) on death from coronary thrombosis "agree broadly with those of Hammond and Horn," but the increase is less marked.

M) Evidence that points to the effect of nicotine on the coronary circulation was obtained by Bargeron and associates (*60*), who found that cigarette smoking increases the coronary blood flow in individuals who do not have heart disease. That nicotine may cause a decrease in coronary blood flow if the coronary vessels are atherosclerotic has been suggested by ballistocardiographic studies. Davis and associates (*61*) have confirmed the reports of others that show definite ballistocardiographic abnormalities in patients with coronary heart disease; these alterations were not present in individuals with normal hearts.

Experimentally, Travell (*62*), at Cornell University, has demonstrated that nicotine causes a diminution in coronary blood flow in perfused hearts of rabbits that had previously been made atherosclerotic through dietary measures.

It is felt that one of the most pressing problems consists of direct investigation of the coronary circulation, during smoking, of patients with arteriosclerotic heart disease. The techniques for this investigation are being developed, but the present methods are not yet applicable.

N) In contrast to the studies of lung cancer, the number of studies concerned with the relationship of smoking to cardiovascular diseases have been relatively few. Most epidemiologic investigations of heart disease have been concerned with evaluating the etiologic role of diet, physical activity, and blood lipides. A definite need exists for both retrospective and prospective studies on smoking and heart disease. Several independent studies should be conducted in various parts of the country. Because of the possible influence of diet, physical exercise, and blood lipides, they should be taken into account to determine possible interrelationships of these factors with smoking. In addition, it is possible that studies of heart disease that are already in progress could be expanded to obtain further information concerning the effects of smoking. The study group considered that the Veterans' Study now being conducted by the National Institutes of Health offers an excellent opportunity for expansion to include the suggestions made here.

O) A few references to studies that relate smoking to some of these diseases should be noted. Lilienfeld, Levin, and Moore (*63*) demonstrated a statistical association between smoking and cancer of the urinary bladder and felt that it was highly suggestive of a cause-and-effect relationship. Friedell and Rosenthal (*64*) and Moore and associates

(*65*) have discussed the evidence for carcinogenic activity of unburned tobacco in producing oral cancers. Wynder (*66*) has reported some evidence that alcohol consumption increases a smoker's susceptibility to laryngeal cancer. The evidence regarding the etiologic role of smoking in gastrointestinal disease is highly controversial (*67, 68*).

Case and Lea (*69*) found an association between chronic bronchitis and lung cancer in World War I pensioners. Unfortunately, smoking histories were not available. However, Joules (*70*), Palmer (*71*), Oswald and Medvei (*72*), and Abbott and associates (*73*) found that chronic bronchitis was closely associated with heavy smoking (see *74*). Lowe (*75*) found that heavy smokers were significantly more common among tuberculosis patients than among control patients.

P) For references to the voluminous literature on this condition, see Allen, Barker, and Hines (*76*).

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H. N. Russell, Astronomer

The death of Henry Norris Russell on 18 February marks the passing of one of the most brilliant minds that has flourished in the modern scientific world. A scientist of truly remarkable breadth, he was for many years the leading theoretical astronomer in this country and a pioneer in the use of atomic physics for the analysis of stars.

Russell's astronomical career began, as it ended, at Princeton University, where he spent 62 of his 79 years. He entered Princeton with the class of 1897 and was graduated with the highest scholastic record of his generation. During the quarter of a century when Latin honors were awarded to high-standing seniors, he was the only Princeton undergraduate whose record was so outstanding that he was graduated *insigni cum laude*. His Ph.D. degree was obtained at Princeton 3 years later, under C. A. ("Twinkle") Young, his famous predecessor at the Princeton Observatory. After 2 years in Cambridge, England, he returned to Princeton University, where he rose rapidly up the academic ladder and became professor of astronomy in 1911, at the age of 33. The following year, he became director of the Princeton University Observatory, succeeding Young.

During his early years as an astronomer, Russell engaged in a number of programs, largely in such classical topics as stellar parallaxes, photographic positions of the moon, and celestial mechanics. In 1912 he turned to the analysis of stellar spectra, a subject in which he remained active throughout his career. The famous diagram of stellar luminosity against surface temperature, originated