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RESPONSE TO HEW REPORT,  
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RESPONSE TO HEW REPORT TO CONGRESS ON SMOKING AND  
HEALTH AND SURGEON GENERAL'S REPORT ON THE HEALTH  
CONSEQUENCES OF SMOKING--1967

I. Generally.

A. The Secretary's Report.

Pursuant to the Federal Cigarette Labeling and Advertising Act of 1965, Secretary Gardner has submitted a report to Congress concerning "current information on the health consequences of smoking" and "recommendations for legislation". The Secretary reports that the "principal thrust" of more than 2,000 recent research studies completed and reported in "the biomedical literature" has been to "strengthen the conclusions reached in 1964 and to determine more precisely the extent of death and disability attributable to cigarette smoking."\*

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\*Compare the words "attributable to" with the more careful wording in mortality and morbidity reports showing deaths and disabilities statistically "associated" with cigarette smoking: (1) The Division of Vital Statistics, in listing deaths from diseases statistically associated with smoking, warned that it had "no information" as to the proportion "actually caused" by smoking (HEW Appropriations Hearings, 1968, Part 4, p. 79); and (2) The National Center for Health Statistics pamphlet on "Cigarette Smoking and Health Characteristics," which presents statistics on disability, observed that data showing a statistical association "cannot establish any existing relationship as a causal one" (p. 6) When asked (see page 78 of the same volume on the HEW Hearings) why he referred to "at least 125,000 premature deaths, and maybe as many as 300,000 deaths . . . due to cigarette smoking", Surgeon General Stewart responded, "Did I say 'due to'?" See Appendix A and the discussion at pages 10 and 18.

The Secretary further reports (1) that the present warning label on cigarette packages "is inadequate"; (2) that the label has not been a significant deterrent to cigarette smoking ("as amply shown in the recent report of the Federal Trade Commission") and "does not have any impact on the many children and young people who are daily exposed to cigarette advertising"; and (3) that "the accumulated evidence strongly suggests that the lower the 'tar' and nicotine content of cigarette smoke, the lower the harmful effect" and that information concerning content "of the smoke of each brand of cigarettes should be put before the smoker and the potential smoker" so the consumer would "thus be able to make an informed choice of product".

The Secretary, based on the considerations stated, recommends (1) that the warning label on each package of cigarettes be "strengthened to state more specifically and positively that cigarette smoking is a hazard to health"; (2) that the warning should be required in advertisements as well as on cigarette packages; and (3) that both the label and advertising should be required to contain information on the "tar" and nicotine levels "in the smoke of the cigarette" and the identity and quantity of such other substances or agents in the smoke as may subsequently be found by the

appropriate Federal agency to contribute to the health hazards of smoking.

The Secretary attached a "Surgeon General's summary report", said to contain "detailed information on the health consequences of smoking", and referred to technical information, not attached, which "will be available as an addendum to the Surgeon General's Report".

This response will demonstrate that "the gaps in knowledge identified in 1964"\* in Smoking and Health still exist, particularly with respect to "the mechanism by which ingredients in cigarette smoke induce harmful effects on the human body"\* if, in fact, they do.

Until a "mechanism" has been identified, it is premature to assign a causative role to cigarette smoking with respect to any disease and meaningless to speak in terms of "how much illness and mortality would be averted by cessation of smoking".\* It is equally meaningless to modify the warning label imposed by Congress in 1965 unless some scientific breakthrough has implicated cigarette

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\*Secretary Gardner's statement, page 1.

smoking by producing evidence far more persuasive than that presented in the Surgeon General's 1967 report. In this respect it is certainly significant that the Secretary's statement, in dealing with the additional research efforts since 1964 refers in detail only to "epidemiological information"--as to which the Surgeon General's Advisory Committee had this to say: "Statistical methods cannot establish proof of a causal relationship in an association" (Smoking and Health, p.20).

The Secretary's recommendation that a warning be placed on cigarette advertising refers to "the recent report of the Federal Trade Commission". Since no data or other material supporting such a recommendation is incorporated in the HEW report, it will not be dealt with further in this response.

The Secretary advances no reason why or how "tar", which presented "a puzzling anomaly" (Smoking and Health, p. 33) in 1964, had suddenly become an indicator that would enable a smoker to make "an informed choice". Equally mysterious is the conclusion that the lower the nicotine content of cigarette smoke, "the lower the harmful effect". If the "principal thrust" of recent studies has been to "strengthen the conclusions reached in 1964", then one

of the conclusions "strengthened" is the following:

"(T)he chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very low and probably does not represent an important health hazard." (Smoking and Health, p. 32)

The "tar" and nicotine recommendation is discussed hereafter commencing at page 11.

B. The Surgeon General's Report--1967.

The 1967 report discusses generally current information on the health consequences of smoking and then presents "the major findings of research studies published in the past three to four years" under the following six headings:

1. Smoking and Overall Mortality.
2. Smoking and Overall Morbidity.
3. Smoking and Cardiovascular Diseases.
4. Smoking and Chronic Bronchopulmonary Diseases (Non-Neoplastic).
5. Smoking and Cancer.
6. Other Conditions and Research Areas.

The introductory portion of the Surgeon General's 1967 report refers to earlier deaths and excess disability which "would not have occurred if those affected had never smoked" and attributes practically all of the earlier deaths from lung cancer, a substantial portion of the earlier deaths from chronic bronchopulmonary diseases and a portion of the earlier deaths of cardiovascular origin to cigarette smoking. The report observed that the conclusion that cigarette smokers have higher death rates than their

nonsmoking counterparts has "changed the emphasis of the present problem away from the question 'Does cigarette smoking cause disease?'" to more precise questions dealing with the degree of association, the portion of early mortality and excess disability caused by smoking, the portion that could be averted by the cessation or reduction of cigarette smoking and (in fourth and last place on the Surgeon General's list) "What are the biomechanisms whereby these effects take place and what are the critical factors in these mechanisms?"

The "changed emphasis" away from the question of whether cigarette smoking causes disease and the placing of determination of biomechanisms in last place is proof that what many scientists who appeared before Congress in 1965 feared would happen has happened. An official position that cigarette smoking causes disease has been taken and the primary mission of much "research" is to show additional statistical "associations" between cigarette smoking and certain diseases rather than to discover the basic biomechanisms actually responsible for such diseases. In this regard, a recent publication listing "ongoing research" in the cigarette-health field reveals that a substantial part of the basic research

being done today is tobacco industry financed and administered either by the American Medical Association or the Council for Tobacco Research (through its independent Scientific Advisory Board); and that a substantial amount of Government supported "research" (over 1/3 of the total number of projects listed) consists of "behavioral" studies, educational programs and anti-smoking propaganda. A review of the footnotes to the 1967 Surgeon General's summary report discloses no reference to any research demonstrating a "mechanism" by which smoking is proved to cause any human disease. The references cited consist of the 1964 Surgeon General's Report, an unpublished smoking and health bibliography, two reports on mouse painting, fifteen statistical surveys and a report on cigarette smoking "patterns".

The "gaps" in the case against cigarettes which were pointed out after the 1964 Surgeon General's report still exist. Nothing contained in the 1967 summary report has eliminated or lessened them. Some of the material contained in the report, and considerable material which was not incorporated therein, supports

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\*Smoking itself cannot be the cause of any disease since non-smokers develop all of the diseases statistically associated with smoking.

"highlights" such as the following rather than those selected by the Surgeon General:

Several recent studies show no association between cardiovascular disease and cigarette smoking. The "consistent association" referred to in the Surgeon General's report in 1964 is no longer "consistent". Furthermore the recent literature contains strong evidence that cardiovascular disease is multifactorial in origin and that constitutional factors play a significant role in its cause.

The epidemiological data from which the association between lung cancer and cigarette smoking has been derived has been thrown into question by recent large scale studies showing no association.

Scientists have failed to discover any ingredient in cigarette smoke responsible for disease in man and no mechanism by which any human disease is caused by cigarette smoking has been demonstrated.

These and other observations are discussed in more detail in the following sections.

## II. Specific Areas

### A. Smoking and Overall Mortality.

"The primary addition to knowledge in the areas of smoking and overall mortality comes from the four major population studies", says the 1967 report. The "addition", for the most part, is simply a repetition of similar material included in the 1964 report.

Without specifying how much, the 1967 report states (p. 20) that "much of the excess" mortality would not have occurred "if it had not been for cigarette smoking". The report does not say, however, what the method of identification was nor how many deaths would properly be included. It does concede, with respect to the "remainder" that some of the excess deaths "would have occurred anyhow". Appendix A reviews some of the more inflammatory statements made about "excess deaths" and demonstrates a six hundred percent overstatement even if the 1964 Surgeon General's findings of causation (cancer of the lung and larynx, and bronchitis only) were accepted.

### 1. Measures of Exposure

For some reason the Surgeon General has included the section on "measures of exposure" in the section on mortality. This section discusses, for the most part, a paper written by Dr. Daniel Horn and others (12)\* which attempted to define current smoking patterns. The measures surveyed included average number of cigarettes smoked per day, the "tar" rating of the brand smoked, the portion of the cigarette smoked, and questions (which would clearly mean different things to different people\*\*) on both depth and frequency of inhalation. The report observes, at page 21, that "there are many individuals with high exposure on one measure but low exposure on another." Although Dr. Horn concluded in his paper that

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\*These and similar numbers in parentheses refer to the bibliography of cited references in the Surgeon General's 1967 report.

\*\*"In this study inhalation was looked at in terms of two basic dimensions, depth and frequency. They were ascertained by the following two questions:

1. 'When you now smoke cigarettes, how deeply do you usually draw in the smoke? Would you say: As deeply into the chest as possible, only partly into the chest, as far back as the throat, well back into the mouth, or just puff and don't really draw it in at all?'
2. 'Do you usually: Inhale almost every puff of each cigarette, inhale a few puffs of each cigarette, inhale a few puffs of some cigarettes, or do you not inhale at all?'

smokers who smoke only a few cigarettes may consume more of these cigarettes than persons who smoke more and that no "toleration" levels have been established for human health purposes, the 1967 report concludes (without citing any evidence whatsoever) that the "existence of a dose-response relationship between exposure to cigarette smoke and the risks most clearly associated with cigarette smoking is now generally accepted". This conclusion is also in conflict with the data indicating that inhalation may be immaterial or even negatively associated with "risk". See Smoking and Health, 188, and (7) in the 1967 report ("Bronchial Cancer and Tobacco", R. Doll).

The 1967 report next cites some work reported by Wynder and Hoffman in October, 1963. The Surgeon General states:

"Wynder and Hoffman (20) have shown in laboratory experiments with animals that the tumorigenicity of cigarette smoke can be reduced by alteration in the cigarette which reduces the 'tar' and nicotine content. They use the term 'indicator' for 'tar' and nicotine content (the two measures tend to be used jointly since when one is high the other tends to be high unless the nicotine has been removed in processing), or other measures which reflect this type of relationship lacking the identification of specific agents which are responsible for the effect."

"The purpose of laboratory studies" involving tobacco smoke condensate, said Wynder and Hoffman, "was not to establish cancer causation for man", but to determine if such condensate is carcinogenic to animal tissue and, if so, which constituents are primarily responsible for its "tumorigenic activity".

Wynder added copper nitrate and nickel acetate to standard tobacco and reported that such tobacco "yielded a condensate which produced significantly less tumorigenic activity than standard tobacco smoke condensate." He conceded that the "additives are not practical" but that the studies "add to our understanding of the formation of these components" (apparently benzo(a)pyrene and phenols).

The article discusses the varying content of benzo(a)pyrene and phenols in different type of tobacco and seems to imply that these are constituents "which at least in part may account for the tumorigenic activity" in animal tissue. (In this regard, a more recent report negates any significant effect of benzo(a)pyrene--see Section E, "Smoking and Cancer".)

The authors reaffirm in their summary that if the "results are applied to the human setting, caution must be used" and do not suggest, as the Surgeon General claims at page 22 that.

"tumorigenicity of cigarette smoke" can be reduced by reducing the "tar" and nicotine content. As a matter of fact, quantitative reduction was not even discussed and the authors did not link nicotine to carcinogenic activity, consider it an "indicator" or even comment on it.

A 1965 study by Bock, Moore and Clark (2) was cited to "show a similar variation in carcinogenic activity of tobacco 'tar' obtained from different types of cigarettes." It is not noted in the Surgeon General's report that Bock, et al., found that removal of the nicotine made no difference whatsoever with respect to tumorigenicity, learned that the mice developed a number of "spontaneous" pulmonary adenomas unrelated to the treatment and concluded that the same amount of "tar" from English cigarettes was much more "potent" than from American cigarettes. The 1967 report states, "The preponderance of scientific evidence strongly suggests that the "tar" and nicotine content of cigarette smoke is a meaningful factor in the measurement of dosage." This is an amazing statement if the articles cited are supposed to support it. The Horn study was simply a survey of smoking habits. The Wynder and Bock articles reported on mouse painting experiments. These experiments, in which

the back of the mouse is shaved and then periodically subjected to applications of artificially derived condensate of cigarette smoke, may be described as employing the wrong material in the wrong form and the wrong concentration upon the wrong tissue of the wrong animal. It has been said that the only way a man could get the same concentration over the area of the lung would be to smoke a hundred thousand cigarettes a day.

## 2. Cessation of Smoking

The heading "Smoking and Overall Mortality" also contains a subhead, "Cessation of Smoking." This is called "an extreme example of the reduction of dosage".

With respect to the "overall reduction" reported among British physicians it is extremely interesting to note that the British physicians had a much more favorable lung cancer death rate even when they smoked about the same amount as the general population, and that the overall decline cannot be attributed to any improvement of risk among former smokers ("... the actual results suggest that the risk for acquiring the disease remains almost the same as it was when smoking was discontinued . . ."). The decline

may be explained by some of the studies which report less lung cancer among the well-to-do and to the probability that diagnosis among British physicians has been much better than among the population generally (which could account for some of the continuing "increase" in the non-physician population) In any event, it would be most interesting to see additional data with respect to the age brackets covered by the survey, the percentage of non-response, etc. particularly in view of the limited number of confirmed lung cancer cases reported (277) and the anomalies in Doll's articles showing a high association of lung cancer with pipe and cigar smokers and higher rates among cigarette smokers who do not inhale.

The 1967 report concedes that data showing a reduction in mortality has been somewhat obscured by the fact that ill health is a frequent cause of giving up smoking "so that death rates and disability rates for ex-smokers as a group tend to be high for an initial period of time following cessation." (Compare this with the Doll article on British doctors which reports a greater improvement in death rates from lung cancer during the initial period studied.) As a matter of fact, death rates for ex-smokers in some instances are higher than for people who continue to smoke (Smoking

and Health, p. 93). On the other hand, some ex-smokers have been found to have less heart disease than persons who had never smoked. This was attributed by Dr. Daniel Horn to the probability that they were sufficiently concerned with their own health "to maintain proper dietary habits and adequate exercise, and thereby have a lower death rate." (Cigarette Labeling Hearings, House of Representatives, 1965)

B. Smoking and Overall Morbidity.

This section is based almost entirely on the National Health Survey, "Cigarette Smoking and Health Characteristics". Significantly this report specifically concedes that the statistical associations found cannot prove any causal relationship between cigarette smoking and any chronic condition (p. 6). It should also be observed that with the exception of chronic bronchitis (which may or may not have been confused by persons interviewed with a simple cough) none of the conditions mentioned have been found to be causally related in any way with cigarette smoking. This survey is reviewed in connection with some of the disease entities discussed hereafter and in some detail in Appendix B.

## C. Smoking and Cardiovascular Disease

### 1. Introduction

In 1964, the Advisory Committee to the Surgeon General of the Public Health Service concluded:

"Male cigarette smokers have a higher death rate from coronary artery disease than nonsmoking males, but it is not clear that the association has causal significance."  
(P. 327)

The Committee also found that the association between cigarette smoking and other cardiovascular disorders\* "is less well established" (P. 327).

Significantly, the Committee did not assert that smoking causes coronary artery disease.\*\* Furthermore, the Committee acknowledged that "other facts such as high blood pressure, high serum cholesterol and excessive obesity" were associated with "an unusually high death rate from coronary disease." (P. 327)

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\*"Other cardiovascular disorders" include miscellaneous circulatory diseases including other heart diseases, hypertensive heart disease, and general arteriosclerosis.

\*\*"Coronary Artery Disease " is sometimes called "Coronary Heart Disease" or "coronary disease."

Moreover, the Committee conceded that "the basic cause or causes of coronary heart disease are obscure."

In spite of the additional evidence that he alleges has accumulated in the intervening years, the Surgeon General did not arrive at any different conclusions with regard to the etiology of cardiovascular disease than the Advisory Committee did in 1964. In his 1967 Report, the Surgeon General did not assert that cigarette smoking is a cause of any cardiovascular disease. (Pp. 41-42)

## 2. Summary

The "highlights" of the cardiovascular disease section are, by and large, overstated and assailable. Certainly they are not borne out by the studies cited nor by the data outside the 1967 report. Presumably they are based on the nine cited articles and several articles to which no reference is made in the limited bibliography at the end of the report. The report, after stating that 2,000 additional articles on smoking and health had been published since 1964, omits numerous articles which do not support its conclusions.

Perhaps the most significant article to appear on

coronary heart disease since 1964 is the article by Lundman (14). In addition, the work of Cederlof (4, 5 and 6) on angina pectoris\* is highly significant. Yet, although both studies are cited in another section of the report, neither is either discussed or mentioned by the Surgeon General in connection with this subject.

Contrary to the "highlights" in cardiovascular section, the following are more appropriate conclusions based upon the material published regarding cardiovascular disease since the publication of Surgeon General's report in January 1964:

1. The association between cigarette smoking and coronary heart disease that was found by the Surgeon General's Advisory Committee in prospective and retrospective epidemiological studies is less clear today after more such studies have failed to find the alleged association.

2. Additional information has been published indicating that the cause or causes of coronary heart disease and other cardiovascular diseases are multifactorial.

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\*Sudden, intense and recurring short pains in the chest

3. As the evidence of a multifactorial etiology in coronary heart disease has developed, new methods of analyses using sophisticated computer technology have raised questions about the essentially univariate prospective mortality studies conducted in the years prior to the publication of the Surgeon General's report.

4. Recent studies have tended to confirm that constitutional factors enter into the etiology of coronary heart disease. Publications have cited stress as a possible factor in coronary heart disease and "way of life" is being studied as another factor.

5. Evidence showing any mechanism by which cigarette smoking causes coronary heart disease has not been forthcoming.

3. The Status According to the Surgeon General

The section on smoking and cardiovascular disease (pp. 37-42) includes nine citations, six of which are to the four mortality surveys already discussed in the previous section. A seventh citation is to a longitudinal study of San Francisco longshoremen, and the last two are to pamphlets in the Vital and Health Statistics Series (17, 18).

a. Prospective Mortality Studies

In the four major prospective studies about which data has been published since the issuance of Smoking and Health, there are inconsistencies which raise puzzling problems for the epidemiologist. All four of these studies were reported in some detail in Smoking and Health and therefore the recent reports on them are, for the most part, describing "old" rather than "new" data.

For instance, the Doll and Hill study found an association for men between cigarette smoking and only that portion of cardiovascular disease denominated "coronary disease without hypertension." By contrast, they found no relationship among women between cigarette smoking and cardiovascular disease. In fact, the death rate for women for continuing smokers was less than that for nonsmokers which, in turn, was less than that for former smokers. Thus, according to these figures, the risk of dying from coronary disease for females was greater for the nonsmoker than for the cigarette smoker, and, once a woman commences cigarette smoking, her risk of dying of the disease is even greater if she ceases than it is if she continues. This would seem to contradict a theory that, among women, coronary

disease is caused by cigarette smoking. Furthermore, the nonsmoking woman appears to have a three times higher risk of dying from "coronary disease without hypertension" than the woman who smokes one to fourteen cigarettes per day.

In the Doll and Hill study, the effect of inhalation was studied. According to the Surgeon General's 1964 Report, "at each level of consumption the [mortality] ratio increases with the amount of inhalation reported by the smokers." (P. 324) Nonetheless, in the Doll and Hill study, the death rate for "coronary disease without hypertension" for continuing smokers who inhale was only slightly different from the death rate for continuing smokers who do not inhale.<sup>3</sup> Thus, according to this information, it made little difference whether the continuing cigarette smoker did or did not inhale.

In the Hammond study, the mortality ratio from cerebrovascular lesions for men 75 to 84 years of age for cigarettes only was less than that for nonsmokers.<sup>4</sup> If such ratios are to be believed, once a person attains the age of 75, he should consider taking up cigarette smoking in order to increase his chances of not suffering death from cerebrovascular lesion.

b. Longshoremen Study

In addition to the four major mortality surveys, the Surgeon General referred in his 1967 Report to the study of San Francisco longshoremen (3). In this ten year follow-up of 3,994 longshoremen, the authors of this study found that for age 35 to 44, the death rate of the nonsmoker was three times that of the smoker.<sup>5</sup> At older ages, however, the death rates of the nonsmokers were lower than those of the smokers.

The authors of the longshoremen study admitted that no known mechanism existed to explain the statistical association between smoking and coronary heart disease.<sup>6</sup> The authors concede that:

"We do not know the etiology of many of the chronic diseases, such as coronary heart disease."

In a later study,<sup>7</sup> the authors reported on their longitudinal study of blood pressure among the longshoremen. They stated that their data supports the concept that hypertension and blood pressure are the result of multifactorial genetic traits. They acknowledged that their blood pressure data casts some doubt on the simple statistical association between coronary heart disease and cigarette smoking.

c. Morbidity Study

The Surgeon General, in his section on cardiovascular disease in the 1967 Report, fails to cite the pamphlet by the National Center for Health Statistics, entitled "Cigarette Smoking and Health Characteristics, United States, July 1964-June 1965" (16), even though he describes it in some detail in the previous section on morbidity. Nonetheless, he states without reference:

"Prospective morbidity studies confirm the relationship between cigarette smoking and coronary heart disease."

Bypassing the methodological problems with this study, which is reviewed in some detail in Appendix B, the statement of the Surgeon General cannot stand if it is based even in part on the statistics from this National Health Survey as printed in this pamphlet. This national morbidity survey, the first of its kind, does not confirm the relationship between cigarette smoking and heart conditions.\* For many smokers of under 11 cigarettes per day have a prevalence ratio lower than that of nonsmokers and smokers of from 11 to 20 cigarettes have

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\*"Heart Conditions" excludes rheumatic heart disease and includes arteriosclerotic heart disease including coronary disease.

a prevalence ratio almost comparable to that of nonsmokers.<sup>8</sup>

Furthermore, male former smokers have a prevalence ratio higher than male present smokers. In the subcategory of "arteriosclerotic heart diseases, including coronary diseases," male former smokers again have a higher prevalence ratio than male present smokers.

For females,<sup>9</sup> present smokers have a lower prevalence rate than nonsmokers for heart conditions. For arteriosclerotic heart disease, present smokers have a lower morbidity ratio than nonsmokers.

The findings of this morbidity survey do not confirm the assertion that cigarette smoking is associated with higher morbidity from heart disease in the United States. In fact, it seems to indicate that smoking may be affirmatively good for health insofar as health is affected by heart conditions and arteriosclerotic heart disease. This is especially true at amounts under one pack of cigarettes per day. Although these morbidity findings are not to be confused with mortality findings, nonetheless if cigarette smoking is a cause of cardiovascular disease, it should not result that nonsmokers have a

higher morbidity rate for heart conditions and arteriosclerotic heart disease than smokers. Furthermore, if the assertion that former smokers have lower death rates made in the prospective mortality surveys is true, it seems strange that former smokers should have higher morbidity rates than either nonsmokers or present cigarette smokers.

The Surgeon General's 1967 Report goes on to state that:

"Other types of evidence have also been presented to confirm the epidemiologic evidence."

Here the Surgeon General refers to "autopsy studies" and to "clinical and experimental studies", but does not indicate by reference or footnote which studies he is describing.

On the contrary, in a study of 989 autopsies of men performed at the New York Veterans Administration Hospital, no significant relationship was found between cigarette smoking and damage of the heart.

d. Mechanisms

The Surgeon General then proceeds to hypothesize two mechanisms "whereby smoking might increase the mortality from coronary heart disease." Again, neither instance showed the Surgeon General's reference. The first mechanism cited by

the Surgeon General is described as follows:

"Human and experimental studies indicate that the nicotine absorbed from smoking may cause an increase in the myocardial tissue demand for oxygen yet at the same time the carbon monoxide absorbed from smoking may cause a decrease in the supply of oxygen of the blood that is available to meet the increased myocardial tissue demand."

Volumes have been written on the possible effects of nicotine and smoking on various of the hundreds of physiological parameters involved in the cardiovascular system. Most of this material is described in the 1964 Report of the Surgeon General's Advisory Committee.<sup>11</sup> For the most part it is highly technical and inconclusive. Little evidence is available to demonstrate that the amount of nicotine absorbed from smoking is sufficient to cause a meaningful myocardial tissue demand for oxygen.

<sup>12</sup>  
A number of papers have reported an increase in carboxyhemoglobin\* levels or carbon monoxide content in the blood of smokers. These papers, however, do not support the contention that cigarette smoking causes coronary heart

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\*"Carboxyhemoglobin" is a compound formed from hemoglobin on exposure to carbon monoxide. Hemoglobin is the oxygen-carrying agent in the blood.

disease. No meaningful evidence is available regarding whether or not a significant amount of carbon monoxide is absorbed in the blood from smoking. The known concentration of carbon monoxide in cigarette smoke (4.2% Smoking and Health, p. 60), while above the permissible concentration for room air, has never been shown to accumulate sufficiently to produce carboxyhemoglobin levels which would be dangerous to health. Furthermore, no evidence exists that any decrease in the supply of oxygen, caused by the higher carboxyhemoglobin levels, is significant in itself or in causing some effect on the heart. The pathological significance of these increases in carboxyhemoglobin is open to question, and, most importantly, no relationship to coronary heart disease has ever been demonstrated.\*

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\*This first "mechanism" requires establishment of the following series of subsidiary points, several of which (particularly 3, 6, 8 and 9) are mere assumptions:

1. Nicotine is absorbed in the blood of the cigarette smoker when he is smoking.
2. Nicotine, when absorbed in the blood, causes increased myocardial tissue demand for oxygen.
3. The quantity of nicotine so absorbed from smoking is sufficient to cause a myocardial tissue demand for oxygen which is of a meaningful or significant amount.

4. Carbon monoxide is absorbed in the blood of the cigarette smoker when he is smoking.

5. The carbon monoxide so absorbed in the blood decreases the supply of oxygen in the blood.

6. The amount of carbon monoxide absorbed in the blood causes a meaningful or significant decrease in the supply of oxygen.

7. The combination of increased myocardial tissue demand for oxygen together with decreased supply of oxygen in the blood causes some effect on the coronary arteries of the heart.

8. This effect on the coronary arteries of the heart is significant.

9. This effect on the heart, in fact, causes what is known as "coronary heart disease."

The other proposed mechanism is described as follows:

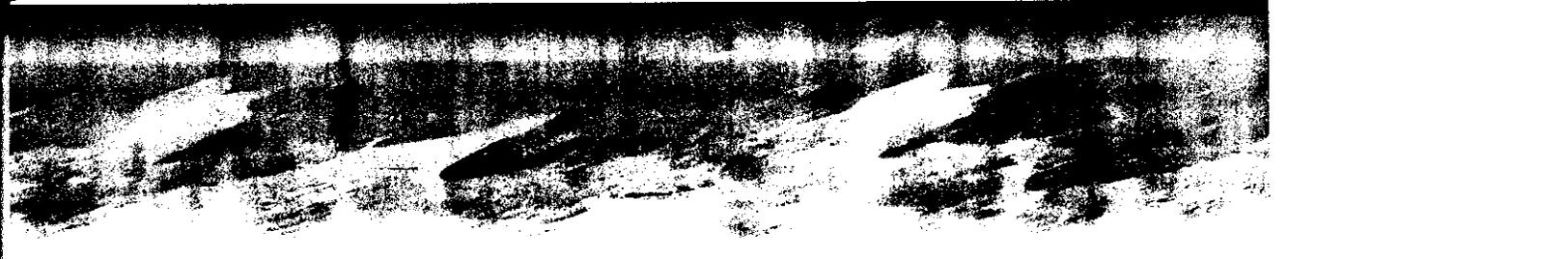
"Smoking apparently can accelerate thrombus formation of human blood, suggesting another possible mechanism whereby smoking might increase the mortality from coronary heart disease, especially those acute coronary events certified as 'coronary thrombosis.'"

The Surgeon General implies that the acceleration of thrombus formation is a known fact. A recent in vitro \* experiment <sup>13</sup> has indicated that blood taken out of the arms of smokers seems to coagulate faster than blood taken out of the arms of nonsmokers. If the problems of cardiovascular disease could be solved in laboratory glassware, excluding body defense mechanisms and other bodily functions, the etiology of cardiovascular disease would probably have been solved long ago. Such is not the case. Furthermore, the Surgeon General's Advisory Committee reported:

"The clotting time of the blood can be decreased 50 percent or more in experimental animals by stimulation of the sympathetic nervous system or by administration of epinephrine, but attempts to demonstrate that cigarette smoking alters the clotting properties of the blood in man have been unsuccessful." (P. 319)

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\*Observable within a test tube



Recent in vitro studies of smoking effect on blood clotting time are contradictory. Some indicate a decrease in blood clotting time associated with smoking, which is new data in the light of the statement by the Surgeon General's Advisory Committee. Other studies have indicated no significant change. Because these studies are in vitro, it can be doubted whether in vitro clotting time has any direct relation to the underlying processes of cardiovascular disease or of the cardiovascular system. Certainly no such relationship has ever been demonstrated. Finally, blood clotting does not necessarily cause coronary disease, and, in fact, a recent report indicates that it may not.

e. Cerebrovascular Disease

According to the Surgeon General's 1967 Report, "an increasing amount of evidence has been accumulated in the past few years relating to the development of clinical cerebrovascular disease to cigarette smoking." He cites no reference for this proposition.

By contrast, other studies (including the prospective mortality study by Doll and Hill which the Surgeon General cited in other connections) have found no relationship between cigarette smoking and cerebrovascular lesions.

#### 4. The Current Status

##### a. Prospective Studies

As stated before, the Surgeon General's Advisory Committee found an association between higher death rate from coronary artery disease and cigarette smoking, but did not find that this association was one of cause and effect. The Committee did assert that the association had been shown "with remarkable consistency" and that there had been "little dissenting evidence." (P. 322)

In his 1967 Report, the Surgeon General claimed that additional evidence had confirmed that cigarette smokers have increased death rates from coronary heart disease. However, since the publication of its report, there have been a number of reports which have raised serious questions about the association that the Surgeon General's Advisory Committee found. A number of papers have described various findings from prospective studies of coronary heart disease. Previous data from some of these studies were reported in Smoking and Health (p.322ff); some of the studies present new data not so reported.

Of major importance are the reports on the major



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epidemiological study being conducted in a total community in Tecumseh, Michigan, covering 8,641 persons<sup>18</sup>. This study commenced in 1957 but was not cited or reported in Smoking and Health. No association was found between cigarette smoking and cardiovascular disease. Actually there was a tendency for nonsmokers to show higher prevalence rates. The authors commented that "Smoking might be a less important contributor to risk than some of the other factors." Obesity and high blood pressure were associated with coronary heart disease incidence; blood sugar levels were also cited.

The prospective study of more than 1,000 male medical students at Johns-Hopkins<sup>19</sup> presents new data on the characteristics of cigarette smokers and nonsmokers. The study disclosed significant physical and psychological differences between the two groups. This data provides evidence to support the view that there may be a constitutional predisposition to both coronary heart disease and cigarette smoking, and that smoking is rather a reflection of the coronary prone type of individual than a cause. Evidence supporting the constitutional hypothesis is discussed in more detail below.



Another new study not reported in Smoking and Health, the Health Insurance Plan of Greater New York study,<sup>20</sup> deals with myocardial infarction and angina pectoris. In one of its reports, it reported an association for men and women smokers with myocardial infarction, as did Smoking and Health, but for men only with angina pectoris, which is somewhat at odds with Smoking and Health (p. 325). This latter finding is contradicted by the more extensive Framingham and Albany studies.<sup>21</sup> The HIP study also reported that lack of physical activity was related to risk of myocardial infarction. The authors raised the question of whether there are not "always important reservations about inferences from epidemiological studies." They also said:

"Conclusions about the meaning of association are necessarily highly qualified."

Among a group of 814 men, aged 40 to 59 years, in New York City's Anti-Coronary Club,<sup>22</sup> a prophylactic diet sharply reduced heart disease incidence over a five year period compared to non-dieters, although there had been no change in the smoking habits of either group.

A physiological study of men aged 65 to 92 years at the National Institute of Mental Health<sup>23</sup> (in a report published in 1963 but not cited in the Surgeon General's report) found no more signs of cardiovascular disease among the life-long cigarette smokers than among nonsmokers in the group.

Even in papers dealing with the findings of the Framingham study, which were reported in Smoking and Health and are repetitive of findings reported to the Surgeon General's Advisory Committee (Smoking and Health, p. 330), the association is not clear. A 1966 report on Framingham gives the 12-year experience of this study.<sup>24</sup> This describes the coronary-prone individual as follows: Male sex, older age, higher serum cholesterol and blood pressure, genetic factors including familial lipid disorders and hereditary diabetes, gout, and a family history of coronary heart disease, cigarette smoking, left ventricular hypertrophy, and myocardial infarction. The Framingham data, while citing smoking as one of many "risk factors," indicated "the risk was not related to the duration of the smoking habit." While the risk was related to daily consumption of cigarettes, the apparent overall absence of a dose-response relationship is striking.

A report of the combined Framingham-Albany data<sup>25</sup> on cigarette smoking is similar to the findings reported in Smoking and Health (p. 323). The authors speculate at length on the statistical association between cigarette smoking and coronary heart disease, without presenting other "risk factors" found in their data. They state:

"The association between heavy cigarette smoking and increased morbidity and mortality from coronary heart disease was unexplained."

This combined data shows no relationship between cigarette smoking and angina pectoris or chest pains however correlated. Yet the Surgeon General's Advisory Committee claimed that angina pectoris is related to myocardial infarction and sudden death. (p. 325)

b. Retrospective Studies

In addition, retrospective epidemiological data contradicts the statement of the Advisory Committee that there has been "little dissenting evidence". (P. 322) Several studies show no association between cigarette smoking and coronary heart disease. Furthermore, these studies suggest, as do the prospective studies, a multifactorial origin of heart disease.

In a Czechoslovakian study of 3,002 industrial and

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agricultural workers, it was reported that obesity plays a role which "eradicates" the differences between smokers and nonsmokers.

27  
In a study of myocardial infarction, the authors found no differences in smoking habits between patients and controls and also no differences in survival between smokers and nonsmokers at a five-year follow-up.

28  
A study among 50 male subjects who died of acute coronary insufficiency, aged 21 to 39, compared with 110 living subjects found slightly more smokers among the patients, but 50 percent more of the controls than of the patients were smokers of more than ten cigarettes per day. The authors of the study suggested many other factors which might be involved: familial factors, "mental" (as opposed to "physical") occupations, "athletic types," improper diet and obesity.

In a study of 181 people who died of coronary heart

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disease compared with 181 living matched pairs, the findings at the last periodic examination indicated that, in those who died, chest pain, hypertension, dyspnea\* and edema\*\* were found to be diagnostic aids. The authors said that "heavy cigarette smoking was not found to be a statistically significant group characteristic."

If the Surgeon General's Advisory Committee was correct in stating that there was no "dissenting evidence" (p. 322) against the association between higher death rate from coronary artery disease and cigarette smoking, certainly that is not the case today as is demonstrated by the selection of reports of studies described above. These certainly do not confirm the statistical association between coronary artery disease and cigarette smoking, and, in fact, question such an association.

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\* labored breathing

\*\* swelling

c. Multifactorial Disease

One of the threads connecting the studies described above is the idea of a multifactorial disease. In fact, the Surgeon General's Advisory Committee acknowledged that other factors were involved in the disease. The report stated:

"In general, it is apparent that multiple personal and environmental factors can markedly affect the incidence of coronary disease." (P. 322)

With such a multifactorial disease, the only way to study its etiology is to examine in depth the disease itself. Examination of the disease in connection with one of the hypothesized factors, in a vacuum, as has been done in most studies cited in Smoking and Health and by the Surgeon General in his 1967 Report, loses perspective. To properly assess the relative contributions, if any, of the various factors, the epidemiologist or medical statistician must take a multifactorial approach.

d. Multivariate Analysis in General

Methods of multivariate analysis represent an effort to understand the relationships between a number of variables which usually are related to one another in a complicated but largely unknown way. The traditional analytic method of the

epidemiologist has been the multiple cross-classification, but, as will be shown, this method quickly becomes impractical. In fact, until recently a sophisticated multifactorial approach toward many factors has been, if not impossible, at least impractical. Until the relatively recent advent of computer technology, applications of multivariate analyses have largely been limited to the case of two or, at most, three variables. Modern computer technology, however, now makes it possible to study interrelationships among much larger sets of variables. Bell, Rose and others in the Normative Aging Study in Boston, Massachusetts are collecting prospective and retrospective data with the intent of studying a broad spectrum of variables, including medical and dental evaluation, body build and function, biochemistry, perception and behavior.

The problem with multiple cross-classification as a method of multivariate analysis is the large number of persons who must be studied. Thus, if ten variables are under consideration and each variable is to be studied at three levels (for example, nonsmoker, smoker of under 11 cigarettes per day, and smoker of 11 or more cigarettes per day), there would be more

than 59,000 cells in the multiple cross-classification. Even with only ten cases for the denominator of the rate for each cell, a cohort of approximately 600,000 persons would be required. Study populations of this size are not often available. Consequently, one is led to seek more powerful forms of analysis than inspection of the results of a multiple cross-classification. Thus, the epidemiologist must turn to multiple regression analyses, correlation analyses, discriminant analyses, principal components (factor) analyses, or canonical correlation analyses. Such methods, however, have rarely been tried. They are not involved in any of the seven prospective mortality studies described in detail in Smoking and Health. Furthermore, they are not involved in the prospective or retrospective studies of coronary heart disease described in the report of the Surgeon General's Advisory Committee. Because of this, the results of these mortality studies are questionable, and such results cannot be fully accepted until their data have been reanalyzed using multivariate analyses.

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f. Multivariate Analyses and the Prospective Mortality Studies

Although very few epidemiological studies have used methods of multivariate analysis, three surveys published since 1964 have described such analyses.<sup>31</sup> These surveys were not the major mortality surveys, and consequently the associations developed by the mortality studies are still gross associations and no net association between cigarette smoking and disease are available. What changes in the mortality studies might result if net data on association were available is difficult to predict.<sup>32</sup> In a study taking a multivariate approach (and designed to determine whether or not cigarette smoking and coronary heart disease may both be associated with a third factor which is actually causative) the analysis has demonstrated that cigarette smoking as a "predictor" may be removed completely from consideration if sufficient other factors are considered at the same time.

In another study,<sup>33</sup> after correction by limited multivariate analysis, cigarette smoking appeared to bear no statistical relationship to coronary heart disease among women.

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In an article, reporting on portions of his data, Hammond stated that healthy males getting no exercise had a total excess mortality (not confined to cardiovascular disease) approximately 1.76 times that of similar subjects getting heavy exercise and 1.44 times of those getting only slight exercise. This would seem to indicate that exercise is a complicating factor in total excess mortality. Similar factors might be involved in cardiovascular disease. Nonetheless, in the article cited in the Surgeon General's bibliography to his 1967 Report, no factors other than cigarette smoking are considered. What changes might take place in Hammond's data if other factors were analyzed cannot be predicted.

f. Statistics Do Not Prove Cause

Nonetheless, it must be added that even with first-class multivariate analyses of data from prospective studies, statistical methods used by epidemiologists can only indicate associations but cannot establish causation. As the Surgeon General's Advisory Committee stated:

"Statistical methods cannot establish proof of a causal relationship in an association." (P. 20)

g. Twin Studies

Two of the most recent studies add a new dimension to the epidemiology of heart disease. Considering this, it is strange that the Surgeon General discussed these studies only in connection with respiratory disease in his 1967 Report, but failed to mention or cite them in the cardiovascular disease section. One of these studies is by Cederlof and the other is by Lundman. In the Cederlof study some association between smoking and angina pectoris or chest pains was found, but not among twin pairs with differing smoking habits. The authors concluded that this "speaks against a causal interpretation and favors a theory of constitutional factors playing an important part in the development of angina pectoris." (P. 736) Also angina pectoris is more common among urban smokers than among rural smokers, but not significantly so among twins.

"This speaks against a specific urban factor and in favor of an assumption that urban and rural population groups differ in regard to factors that determine the individual's choice of living habits relevant to disease."<sup>37</sup>

Lundman, in his study of Swedish twins, concluded that:

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1. Cigarette smoking is probably not associated with coronary heart disease, whether of the overt or the silent form as diagnosed by means of the post exercise electrocardiography.

2. Cigarette smoking most probably does not result in persistent hypertension. During abstinence from smoking blood pressure is lower in smokers than in nonsmokers.

3. Cigarette smoking seems not to produce any elevation of serum cholesterol or triglyceride levels. On the contrary, there is some evidence that the levels are lower for smokers than for nonsmokers.

4. There is reliable evidence of a significant genetic component in coronary disease and related parameters.<sup>38</sup>

Lundman concluded:

"It would seem that the excess morbidity and mortality from coronary heart disease reported in the large prospective studies can be due to constitutional differences between smokers and nonsmokers."<sup>39</sup>

h. Emotional Stress

As stated, cardiovascular disease appears to be a multifactorial disease. Stress, familial background, individual

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personality traits, occupation, urban residence, obesity, diet, heredity and and lack of exercise have all been subjects of research and possible involvement.

Emotional stress has been regarded by Russek as being of far more importance in the etiology of coronary disease than smoking, heredity, diet, obesity or exercise. In his survey of 10,000 physicians, dentists and lawyers (published in 1962 but not cited in Smoking and Health)<sup>40</sup> he found a striking tendency for coronary disease prevalence rates to increase with advance in stress rank of occupation. In a subsequent 1964 analysis of this material,<sup>41</sup> he suggested that smoking may simply be an indicator of stress rank and also that in his study, ex-smokers had a lower coronary disease prevalence rate than those who had never smoked. He concluded that "by itself" cigarette smoking may be "without etiologic significance in coronary atherosclerosis."

In the continuing survey of 3,524 subjects,<sup>42</sup> a two year follow-up found that the most important single significant factor in heart disease prognosis was a behavior pattern exhibiting hard driving, aggressive ambition and competitiveness.

A comparison between 679 Moscow clerks in jobs involving a marked degree of emotional tension with 565 industrial workers found heart disease (including infarction) more frequent

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among clerks although there were no significant differences  
in smoking habits or histories between the two groups. <sup>43</sup>

3. Personality Patterns

Rosenman and Friedman, in a comprehensive study  
over a five-year period of 3,524 men, aged 39 to 59, who are  
employees of 11 California corporations, <sup>44</sup> concluded that be-  
havior and personality patterns can often identify in advance  
the man who is likely to suffer a heart attack before age 50.  
This pattern is that of the hard-driving male with excessive  
ambition and competitiveness. The study found statistically  
significant relationships between coronary heart disease and  
cigarette smoking, as well as with three other factors. The  
authors said, "It is questionable whether these small differences  
are of true clinical relevance." <sup>45</sup> They concluded that:

"Above all, the present results clearly  
indicate that the presence or absence of a  
particular overt behavior pattern carries a  
profoundly important prognostic (predictive)  
relevance. To our knowledge, this factor has  
not been studied previously in any systema-  
tized fashion in any large scale epidemiological  
study." <sup>46</sup>

j. Predictors

One of the most important concepts to consider in regard to coronary heart disease is the difference between using statistics to show causation or etiology and using those same statistics in an attempt to predict those people who seem to predispose towards certain diseases in later life. In the one instance, a jump is made from statistical association to cause and effect, excluding other possible causes. In the other instance, the type of person who is likely to have coronary disease is indicated by a predictor. Prediction of disease and cause of disease are two different, separate things. It may be that cigarette smoking identifies people of a different constitutional and psychological makeup than those who don't smoke. Or, in other words, the kinds of people who smoke may be more susceptible to some diseases than the kinds of people who do not.

k. The Constitutional Hypothesis

The constitutional theory is one which links heredity with disease. It is argued that a person's predisposition to cigarette smoking and his predisposition to disease are linked

by a person's heredity. Thus, the twin studies are relevant to constitution.

The Surgeon General's Advisory Committee conceded that:

"If it could be shown that cigarette smokers and nonsmokers had significant constitutional differences apart from any differences that might be caused by smoking itself, than a possibility would exist that some predisposition of smokers to a particular disease might also be of constitutional origin and not caused by smoking."  
(P. 326)

The superficial treatment of the constitutional hypothesis in Smoking and Health is disappointing. It is even more disappointing that the Surgeon General in his 1967 Report does not even consider constitution in relation to cardiovascular disease.

Since 1964 a number of studies have developed information which amplifies the constitutional differences between smokers and nonsmokers. Lundman's study, <sup>47</sup> already discussed above, found a constitutional difference between smokers and nonsmokers and specifically an apparent genetic difference. He found strong evidence that smoking is not causally related to

coronary heart disease, but that both smoking and coronary heart disease are related to constitutional and genetic factors.

In a study of 900 same-sex monozygotic and dizygotic\* twin pairs from the Danish Twin Registry, Raaschou-Nielsen's findings suggest that the tendency to smoke, as well as the type and amount of smoking have a genetically based component.<sup>48</sup>

A striking example of constitutional factors is the male-female mortality differences wherein male nonsmokers have much higher mortality rates from coronary heart disease than female nonsmokers of the same age. This striking mortality ratio presents quite different odds to the average man and average woman at any level of smoking as to the association of smoking with shortening of life. The balance among androgens and estrogens among normal males and normal females differs substantially. Androgen/estrogen ratios may provide other new approaches to explore, and other hormone balance analyses might be undertaken.

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\*Monozygotic twins are derived from one cell or zygote.  
Dizygotic twins are derived from two separate cells or zygotes.

Light, moderate and heavy smokers seem to have different constitutional-personality characteristics among themselves as well as to have characteristics different from nonsmokers.

Morphology is also considered relevant to constitution.<sup>49</sup> Russek<sup>50</sup> believes that emotional stress is involved. Rose is studying the possibility that a pattern of life or a way of life is involved in disease.<sup>51</sup> The distinct patterns among various ethnic and national groups that have been found in cancer may also be found in cardiovascular disease.<sup>52</sup> These latter may or may not be involved with constitution which is based in heredity. They may show a very fine dividing line between "host" factors and environmental factors. It may be, for instance, that a person's constitution affects his pattern of life and his history of diseases, including chronic diseases.

##### 5. Conclusion

In conclusion, the statements of the 1967 Surgeon General's report are oversimplified and misleading. Coronary heart disease and cardiovascular disease are more complicated and sophisticated diseases than the simplistic presentation by

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the Surgeon General. The association claimed by the Advisory Committee to the Surgeon General in 1964 is much less clear today than it was when that conclusion was made. Coronary heart disease and cardiovascular disease is a multifactorial disease in which no particular factor has been pointed out as the most important. Much research needs to be done in all areas of the disease, and any suggestion at this point that a single factor has been indicated as a cause or the cause is misleading to both physicians and to the general public.<sup>53</sup> Reported associations between cigarette smoking and the disease are nothing more than that: statistical associations. A third factor, either constitutional, stress or way of life, may account fully for such findings.

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D. Smoking and Chronic Bronchopulmonary Diseases  
(Non-Neoplastic)

Since the 1964 Surgeon General's Report, the literature on chronic bronchitis and pulmonary emphysema has increased enormously. The cause of emphysema remains unknown and the very definition of "chronic bronchitis" remains in doubt. A multitude of factors has been associated with these various conditions described by the term "bronchopulmonary disease."

1. Unjustified broadening of 1964 conclusion

The Surgeon General's Advisory Committee concluded in 1964 that, although a relationship exists between pulmonary emphysema and cigarette smoking, "it has not been established that the relationship is causal." (Smoking and Health, p. 38) The results of current work do not change this conclusion. The author of one recent study has said:

"Despite statistical patterns compatible with a causal role, possible mechanisms and sites of action of tobacco smoke in the development of emphysema remain speculative."

Whereas the 1964 Surgeon General's Report concluded that cigarette smoking was the most important cause of chronic

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bronchitis, the 1967 report states:

"Cigarette smoking is the most important of the causes of chronic bronchopulmonary diseases in the United States."

No evidence is offered in justification for broadening the conclusion of the 1964 report to include cigarette smoking as a causal agent in chronic bronchopulmonary diseases in general. The results of research into the relationship between cigarette smoking and bronchitis and emphysema, two of the more important bronchopulmonary diseases, furnish no basis for any such conclusion.

If the term "chronic bronchopulmonary diseases" includes bronchial asthma, certainly there is no justification for such a broad conclusion. No statistical association has been demonstrated between cigarette smoking and bronchial asthma. The 1964 Surgeon General's Report agreed that smoking bears no relation to the incidence or severity of asthma.

## 2. Difficulties of Diagnosis

The difficulties in interpreting any epidemiological data relating to chronic bronchitis and emphysema are noted in the 1964 Surgeon General's Report, although no mention is made

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of these problems in the present report. The 1964 report stated (Page 278):

"The diagnosis of chronic bronchitis is based essentially on descriptions of clinical manifestations and is achieved by exclusion. Recollection and interpretation on the part of the subject are necessary. There is no simple sensitive pulmonary function test that will indicate which person has chronic bronchitis.

A clinical diagnosis of emphysema, based on the clinical syndrome and certain changes in pulmonary function is even less exact. The clinical features usually encountered in emphysema tend to be very similar to those found in chronic bronchitis. The clinical detection of emphysema is therefore not a simple matter, especially in the presence of chronic bronchitis."

It is further stated in the 1964 Report (Page 279):

"Emphysema may exist without any clinical manifestations and its clinical and functional alterations are not unique but occur in other pathologic conditions."

### 3. Four Prospective Mortality Studies

The 1967 Surgeon General's Report refers to the evidence from four major prospective studies indicating that cigarette smokers have a marked increase in the risk of dying from chronic bronchitis and pulmonary emphysema. These results, in fact, furnish the primary basis for the sweeping conclusions

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in the present report. It is strange that in relying on such results, the Surgeon General does not even mention the fact that outstanding researchers in the field of chronic bronchitis and emphysema have questioned the reliability and validity of such mortality statistics.

4. Reliability of Mortality Statistics Questioned

Dr. George W. Wright, in summarizing the proceedings of the seventh annual conference in Aspen, Colorado in 1964 on "Research in Emphysema and Chronic Bronchitis" referred to these difficulties as follows:

"I am disturbed by the fact that...vital statistics [were] obtained years ago, and are still being obtained in a manner that cannot possibly lead to accurate or useful information relative to the problems in hand. Death certificates as they were originally developed, have very little relevance for our problem....more often it is based on what the physician thinks is the most likely cause of death....there are a number of studies in the literature comparing the disease listed on the death certificate to the conditions found at autopsy. It is astonishing how poorly these two correlate, particularly in regard to respiratory diseases in the U. S."

The Surgeon General prudently refrains from adopting the extreme statement of the National Center for Chronic Disease

Control of the Public Health Service which stated in 1967:

"Cigarette smoking has caused deaths from chronic bronchitis and emphysema to increase 400% in the past ten years, and 900% in the past 20 years."

If an increase in this magnitude had actually occurred, it could certainly not be ascribed to cigarette smoking. No such increase in cigarette consumption has occurred over this period of time, nor in the past, and if that view were adopted the increase would obviously have to be attributed to other factors.

#### 5. Autopsy Studies

While the 1967 report concedes that problems of nomenclature and diagnosis make satisfactory differentiation of chronic bronchitis from pulmonary emphysema difficult when considering the epidemiologic data, it asserts that nevertheless autopsy studies support the relationship between smoking and mortality. The 1964 Surgeon General's Report took a different view of the significance of autopsy studies. The Report states that pathological changes in the lung "cannot be related with certainty to emphysema or other recognized diseases at the present time." (P. 301)

#### 6. Morbidity Studies

The present Surgeon General's Report notes that recent information from morbidity studies indicates that smoking is

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associated with symptoms of chronic bronchopulmonary disease. These morbidity studies are actually questionnaire surveys in which the subjects are asked about various symptoms thought to be indicative of the presence of chronic respiratory disease. Dr. George Wright sharply questioned the validity of such studies in his summary of the 1964 Aspen, Colorado conference as follows:

"While the questionnaire seems able to categorize populations as to prevalence of coughers, spitters, and breathless persons, I am not aware of data demonstrating the validity of the questionnaire method for recognizing and quantitating the severity of anatomical emphysema or bronchitis....the considerable number of persons shown at autopsy to have more than a minor portion of the lung involved by emphysema, but who, according to themselves or close relatives, did not experience unusual cough, expectoration, or even breathlessness during life speak eloquently for the need for restraint when interpreting epidemiologic data obtained by questionnaire as being applicable to the study of the cause of emphysema or bronchitis."

There is great variability in the results of these questionnaire surveys as they relate to certain respiratory symptoms. For example, the symptom of "breathlessness" has been studied in relation to cigarette smoking in a number of surveys. In a random sample of an agricultural community in Great Britain it was found that the prevalence of breathlessness among all men

and all women interviewed was greater in the nonsmoker than in the smoker. In a survey of a total community, female cigarette smokers had a higher prevalence of breathlessness than nonsmokers below the age of 40, but above this age the nonsmokers had a higher prevalence.

#### 7. Heredity and Constitutional Factors

The present report takes note of the findings that certain individuals have increased susceptibility to respiratory disease but concludes that cigarette smoking is of greater importance than hereditary and constitutional factors. This conclusion ignores the increasing body of work in recent years which indicates that hereditary and constitutional factors may be of far greater importance than has been suspected. One study in the Netherlands finds that in a large series of cases hereditary and constitutional susceptibility are the most important features distinguishing victims of chronic nonspecific lung diseases from people without these diseases. Other recent studies have disclosed that ethnic differences in populations are closely related to differences in the prevalence of chronic respiratory diseases.

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#### 8. Occupational Exposures and Air Pollution

While acknowledging that occupational exposures and air pollution may also cause respiratory disease, the report contends that cigarette smoking is of much greater importance. In various studies of the comparative prevalence of respiratory conditions in different geographical areas of the United States and Great Britain as well as other countries, differences in prevalence have been found which cannot be explained by differences in smoking habits.

#### 9. Experimental Evidence

The Report states that bronchial changes have been produced in experimental animals exposed to cigarette smoke. As stated earlier, many qualified scientists insist that these changes cannot be related with certainty to any human respiratory diseases and that the role and mechanism of action of cigarette smoke in relation to these changes is still highly uncertain.

The Surgeon General's Report mentions indirect evidence suggesting that smoking has a direct toxic effect upon the alveolar tissue of human lung. It is certainly true that there is no direct evidence that cigarette smoke has such an effect, and any

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conclusions based on such "indirect evidence" are unwarranted.

In relation to animal experiments referred to above, many observers have pointed out that the methods used to expose experimental animals to cigarette smoke are highly unnatural, result in exposures which have no relation to the quality or quantity of human cigarette smoke exposure, and that the interpretation of the pathology noted in the lungs of these animals is open to serious question.

10. Summary

In summary, the evidence reviewed in the present Surgeon General's Report is, in general, of the same nature of the evidence summarized in the 1964 Surgeon General's Report. No new evidence has been reported that warrants any broadening of the conclusions of the 1964 Report. Furthermore, the questions which existed in 1964 concerning the reliability and validity of mortality data and morbidity data have been highlighted by informed commentators and point to the necessity for restraint in drawing conclusions from this data.

Air pollution, occupational exposures, hereditary and constitutional factors have all been suggested in recent literature

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as important etiological or predisposing conditions in relation to chronic broncopulmonary diseases. The potential importance of each of these factors has not been fully investigated, but the presence of such findings argues strongly for continued research and against premature conclusions.

Review of recent literature indicates that satisfactory definitions of the clinical and anatomic manifestations of chronic bronchitis and pulmonary emphysema are still lacking. The term chronic bronchitis is still used to denote a variety of respiratory conditions, none of which appear to be clearly or solely associated with cigarette smoking. Recent findings also indicate that the degree of correlation between a clinical diagnosis of pulmonary emphysema and the appearance of emphysema at autopsy is very poor. It has also been pointed out that the results of pulmonary function tests are not reliable indicators of the presence of specific respiratory disease.

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E. Smoking and Cancer

Highlights of Current Information

1. The rate of increase in lung cancer mortality appears to be slowing progressively in the United States, Great Britain and Canada.

2. Examination of older medical records has revealed that lung cancer mortality was substantially understated in the early decades of this century. Recent studies have shown that deaths from lung cancer may have been substantially overstated in recent years. These facts have led observers to suggest that the actual historical rise in lung cancer in the United States has been no greater than would be expected as the result of the increased longevity of an enlarging population.

3. Even if there has been an actual rise in lung cancer deaths over the years of the magnitude reflected in the U. S. vital statistics, a number of explanations have been advanced which could account for this, apart from any association with cigarette smoking. Recent data has lent additional credence to some of these explanations, and none of the explanations has been contradicted by

scientific evidence.

4. Some recent case studies and population surveys have shown no association between cigarette consumption and lung cancer incidence or mortality. One of the significant population surveys is based on the total lung cancer mortality in Israel.

5. Analyses of vital statistics with respect to cancer in the United States have disclosed the following facts, inconsistent with the smoking theory of lung cancer causation:

a. Nearly all of the increase in lung cancer mortality is accounted for by deaths of persons born before 1901.

b. The age of maximum deaths from lung cancer has been increasing. Lung cancer deaths are no longer rising for men below age sixty. Since each succeeding generation born during this century is said to have begun smoking earlier and to have smoked more, according to the proponents of the smoking theory, the trends should have been in the opposite direction.

c. Vital statistics continue to show a wide divergence between male and female lung cancer deaths. Although it has been hypothesized that female lung cancer death rates would begin to approach those of males since the smoking patterns of the two sexes have become more similar in the past three or four decades, the mortality trends have been in the opposite direction.

d. A regional pattern for cancer deaths in the United States over the past twenty-five years has recently been described. This shows that deaths from all forms of cancer are highest in regions with the greatest population density.

e. International comparisons of death rates from lung cancer show no correlation with cigarette consumption. For example, the death rate in Austria with a low per capita consumption of cigarettes is considerably higher than in Canada with a relatively high level of cigarette consumption. Furthermore, a study of the cancer mortality figures for twenty-four

countries reveals that there is no correlation between the death rate for lung cancer and the death rates for most of the other sites of cancer which have been said to be statistically associated with cigarette smoking.

6. Questions have been raised concerning the significance of the findings of some prospective studies which show more favorable general mortality rates and lung cancer mortality rates for former smokers as compared to present smokers and for nonsmokers as compared to light smokers. A study of the general health characteristics of persons in relation to their smoking habits has shown that former smokers fare less well in terms of general health than present smokers and that many smokers may be as healthy as nonsmokers.

7. No significant work has been reported since the 1964 Surgeon General's Report on the identification of suspected carcinogens in cigarette smoke. On the contrary, recent work has indicated that the chemical compound long believed to be primarily responsible for the tumor producing effect of tobacco "tar" in animal skin painting experiments probably does not account for this result.

8. Attempts to produce lung cancer in animals with cigarette smoke and smoke condensate have continued to show negative results in studies reported since 1963. No experimental verification of the cigarette-lung cancer hypothesis exists.

9. Additional epidemiological evidence on lung cancer in women has become available. These studies fail to show any significant association between cigarette smoking and lung cancer in women.

10. Epidemiological studies published since the 1964 Surgeon General's report find strong associations between lung cancer mortality and incidence and history of prior lung diseases, occupation, socioeconomic status, lung cancer history in relatives and urban residence.

11. The conclusion in the 1964 Surgeon General's report that cigarette smoking is a significant factor in laryngeal cancer in the male is undermined by recently published vital statistics demonstrating that there has been no increase in mortality from this cause.

12. Reported statistical associations of cigarette smoking

with bladder cancer are not shown to represent a causal relationship. Published vital statistics show there has been no change in the death rate from this form of cancer in the period 1950-64.

13. As to cancer of the esophagus, the latest mortality data indicates that the ethnic and sex distribution of the deaths is contrary to the patterns of cigarette consumption in the United States. The death rates are higher in the non-white than in the white population and higher for females than for males.

## 1. Lung Cancer

### A. Mortality--General Background

The Surgeon General in his 1967 Report (p. 48) states that the deaths from lung cancer in the United States are continuing to rise rapidly.

Many questions have been raised as to the reality of the reported increase in lung cancer deaths. The recent literature has failed to clarify any of these questions.

The absolute number of lung cancer deaths should, of course, be expected to increase as the life span of the population increases and a greater number of people reach the ages at which lung cancer occurs. However, since the age-standardized death rate from lung cancer appears to be increasing, it is appropriate to point out that explanations have been offered for this phenomenon apart from the cigarette smoking theory of lung cancer causation.

There is suggestive evidence that the reported rise in deaths from lung cancer through the years has been considerably exaggerated. This rise in the number of deaths can be correlated with the progressively increasing ability of doctors to diagnose the disease, and to distinguish it from other respiratory diseases, during the present century. <sup>54</sup> The rise can also be correlated with

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a general increase in awareness of the disease among the medical profession stimulated in part by the efforts of public and voluntary health agencies.<sup>55</sup>

Many papers have questioned the accuracy of the reported increase in lung cancer due to discrepancies between the record on death certificates and the true cause of death.<sup>56</sup> For example, there is evidence that in past years when tuberculosis was a widely prevalent disease, a substantial number of lung cancer deaths may have been certified as due to tuberculosis.<sup>57</sup> There is also evidence from which it can be shown that the degree of overstatement of tuberculosis and corresponding heavy understatement of other pulmonary diseases, including especially lung cancer, was sufficiently great so that the actual increase in lung cancer mortality is roughly what one might expect due to aging of the population.<sup>58</sup>

There is also evidence from which it can be deduced that the increasing awareness of the importance of lung cancer as a cause of death has resulted in a greater tendency to diagnosis it.<sup>59</sup> Once cigarette smoking by men began to be widely recognized as associated with lung cancer, there would be a greater tendency to diagnosis lung cancer, and often to secure autopsies, for male

heavy smokers, than for others. This would, of course, tend to distort upward the apparent association between cigarette smoking and lung cancer. One author<sup>60</sup> has pointed out the need for the epidemiologist to exercise care "to evaluate all purported sharp increases in cancer of sites under the glare of extraordinary popular attention, so that the true state of affairs will not be submerged by a popular and understandable stampede to find a correlation between what may in fact be accidental, simultaneous occurrences, and to take the next step, and attribute to this correlation the property of causation."

There is good evidence of the tendency to over diagnose lung cancer in a recent study<sup>61</sup> which involved a review of the diagnosis of cases where the cause of death had been certified as lung cancer. This study found that even in an outstanding medical center the gross overstatement of lung cancer in this series of cases was over eighteen percent and the net overstatement around eight percent. If the error was of this order of magnitude at an outstanding center, it was probably much larger in most others.

Another factor contributing to the overstatement of lung cancer as a cause of death has been pointed out in a recent paper.<sup>62</sup>

The authors pointed out that autopsy diagnoses of cases clinically diagnosed as bronchogenic carcinoma have often revealed the pulmonary lesion to be secondary to carcinoma of various other sites. They suggest that there is even greater opportunity for inaccuracy in cases certified without autopsy on the basis of clinical or histological examination of respiratory tissues. Since the lung is a very frequent site of metastatic cancer, there is great likelihood of this type of misdiagnosis. In a study of 4,012 Massachusetts cancer autopsies published after the 1964 Surgeon General's report, 1,052 (or 26%) were found to have metastasized to the lungs. In a 1964 study of 104 cases of carcinoma of the pancreas, pulmonary metastases occurred in forty percent of the cases.

The rise in the lung cancer death rate has been accompanied by a sharp decrease in the number of deaths due to tuberculosis. Some authors believe that these facts may be related. One investigator (Lees) advanced the following theory:

"Due to improvement in the therapy of respiratory diseases, especially of tuberculosis, the type of persons who forty-five years ago might have died from, say, TB at age thirty, were instead healed if they had this disease only twenty-five years ago and survived now to more advanced ages when, due to their lungs being sensitized by the earlier

illness, they are exposed to an increased risk of dying from lung cancer." <sup>66</sup>

Some authors have theorized that the increase in lung cancer deaths is the result of some fundamental biological phenomenon. According to one such theory (Pearl), "If the lethal form of any [disease of the respiratory system] is controlled, it will soon be replaced, in whole or in part, by an increase in the fatal form of some other respiratory disease." <sup>67</sup> Under this theory, the rise in lung cancer deaths could be related to the sharp decline in the death rate from pneumonia and tuberculosis.

Another author has noted from a study of many national population and mortality statistics, that the total age-adjusted incidence of male and female cancer of all types tends to remain evenly balanced, e.g., currently high male lung cancer offset by high female cervical cancer. Hence, cancer is related primarily to reduced organic resistance to any effective triggering mechanism rather than to specific causes. <sup>68</sup>

Another investigator regards the present increase in lung cancer deaths as part of a recurring cyclical pattern which has been noticed over the years in the history of cancer. <sup>69</sup> According

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to this theory deaths from certain types of cancer increase while deaths from other types decline during one period of time, and in a succeeding period of time the pattern is reversed. He finds that the curves describing the rise and fall of particular forms of cancer follow a wave shaped pattern over the course of time. In England and Wales, the cohort death rates for successive generations for lung cancer, leukemia, Hodgkin's disease, cancer of the bladder, kidney and pancreas are increasing while the rates of cancer of the intestines, rectum, stomach and prostate have been rising at some time within the last fifty years and are now falling.

In summary, there exists various findings and theories which tend to explain the apparent increase in the lung cancer death rates on grounds other than the presumed presence of some causative agent in the environment.

B. Vital Statistics Inconsistent With  
Cigarette Theory

Although the Surgeon General cites the reported increase of deaths from lung cancer in the United States as a point in support of cigarette causation of this disease, there is other data to be derived from vital statistics which tends to confound this theory.

United Kingdom statistics published in mid-1965<sup>70</sup> show that the rate of increase in lung cancer mortality appears to be slowing progressively in England and Wales, and should become relatively stable by about the mid-1970's. This finding is in accord with earlier studies showing a similar trend in both the United States and Canada.<sup>71</sup> These trends contrast sharply with the rates of increase in per capita cigarette consumption in all four countries.

The British and U. S. figures also indicate that almost all of the recent reported increase in lung cancer incidence is accounted for by persons born before 1901. This is corroborated by data coming from several cancer registries in the United States showing that the mean age at death from lung cancer has increased.

in the past two decades. Lung cancer death rates for males under age sixty in Great Britain have been stable since 1960. Since smoking is said to have been initiated earlier in each successive generation during this century, the cigarette smoking theory would seem to require that lung cancer occur at earlier ages in each succeeding generation. These statistics tend to show the opposite result.

Vital statistics continue to show that the overwhelming preponderance of lung cancer deaths occur in males. Although in the past thirty-five years an increasing percentage of the female population has adopted cigarette smoking, the ratio of male to female deaths from lung cancer during this period has increased four-fold.

A recently reported analysis of U. S. vital statistics on death rates from all forms of cancer--including respiratory cancer--showed that the regions with highest cancer mortality were those with the greatest population density.<sup>72</sup> Although, as to respiratory cancer, this pattern might be said to be consonant with the cigarette theory, this would not explain why the same pattern of regional distribution was found for cancer of the

genito-urinary system. The authors point out that "no other categories of disease have patterns remotely resembling" the cancer death rate pattern, except diseases of the circulatory system.

International comparisons of death rates from lung cancer continue to show wide variations unrelated to similar variations in per capita cigarette consumption.<sup>13</sup>

In one recent study, lung cancer death rates in twenty-four countries were compared with death rates in those countries from larynx cancer and with buccal cavity and pharynx cancer in an attempt to determine whether there was a correlation between high death rates from lung cancer and high death rates from cancer of the other sites.<sup>14</sup> Since larynx cancer, buccal cavity cancer and pharynx cancer have all been associated statistically with cigarette smoking and since each of these sites is exposed to cigarette smoke, according to the cigarette theory of causation it would be expected that in countries where the lung cancer death rates from cancer are high, cancer of these other sites would similarly be high. On the contrary, it was found that no correlation existed between the lung cancer death rate and the death rate

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from cancer of these other sites. This was true of the figures  
for the United States as well as for the other countries.

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C. Increase in Lung Cancer Mortality--Pathologic Data

It is impossible to determine from United States vital statistics what percentage of the deaths recorded as "lung cancer" represent primary lung cancer, i.e., cancer which originates in the lung. Approximately half of the total number of deaths which are said to represent "lung cancer" are actually reported in vital statistics as "unspecified as to whether primary or secondary." As noted earlier, recent studies have reported that in a substantial percentage of cases where lung cancer is stated as the cause of death, autopsy data reveals that the primary cancer is located in some other part of the body. Studies of this kind reflect doubt on the reliability of vital statistics as an indicator of lung cancer mortality.

Vital statistics do not report the number of deaths from each of the several histological types of lung cancer. According to some advocates of the cigarette smoking theory, smoking is associated with two specific histological types. Although the vital statistics give no answer to the question whether the reported rise in lung cancer mortality is found principally in the types of lung cancer associated with smoking, there is data to indicate that this

may not be the case. A study at one large hospital disclosed that a large percentage of the increasing number of lung cancer cases over a period of years at that institution consisted of a histological type of lung cancer which has not been found to be significantly associated with cigarette smoking. <sup>75</sup>

D. Current Information on the Cigarette  
Smoking--Lung Cancer Association

The Surgeon General's 1967 report asserts that additional epidemiological data confirm the conclusions of the 1964 report regarding lung cancer in men and substantiate that smoking is also significantly related to lung cancer in women. This conclusion is based, however, on a selective review of the literature. Actually, several significant studies reported in recent years have cast considerable doubt on the accuracy of the Surgeon General's conclusion.

(1) No Statistical Association Found

A study just published by the World Health Organization, which was not reviewed in the Surgeon General's 1967 report, is probably the most significant population survey published since 1964.<sup>76</sup> This report reviews the total cancer morbidity and mortality in Israel from 1949 through 1961. The lung cancer data was analyzed separately in order to explore the question of the association between cigarette smoking and lung cancer. It was found that lung cancer rates were inversely related to cigarette consumption in the two principal segments of the population. The "occidental" population which smoked less than the "oriental" population had much

higher death rates from lung cancer. The investigators went on to explore whether the higher rate of lung cancer among the lighter smoking segment could result from the fact that many of the cases of lung cancer in that segment of the population were of the type which is not found to be statistically associated with cigarette smoking. A careful pathological study revealed that this was not the case. This study stands as powerful evidence opposing the conclusion that the statistical association between cigarette smoking and lung cancer which has been noted in studies in the United States has causal significance.

Other studies on a smaller scale have also failed to confirm the statistical association between cigarette smoking and lung cancer. A German study of 1,229 cases of lung cancer, plus an analysis of more than 26,000 autopsy records reaching back to the year 1908, found "no significant relationship . . . between cigarette smoking and the risk of bronchial carcinoma."<sup>77</sup> Another study of 1,000 proven cases of lung cancer at Mercy Hospital, Pittsburgh, found that nearly half--474 cases--were nonsmokers.<sup>78</sup>

(2) No Relation in Case of Females

The Surgeon General's conclusion in the 1967 report that

smoking is also significantly related to lung cancer in women is clearly contradicted on the basis of studies reported since 1964.

A histological study of 163 cases of lung cancer in women conducted at Barnes Hospital, St. Louis, found that thirty-five percent of the cases of squamous cell or oat cell carcinoma were nonsmokers, and in cases of other kinds of lung cancer eighty-one percent were nonsmokers.<sup>79</sup>

An analysis of the smoking habits of all lung cancer mortality cases in Switzerland during 1951-1960 revealed no association between smoking and lung cancer among women.<sup>80</sup>

Similar surveys in Venice, Italy,<sup>81</sup> and Vienna, Austria,<sup>82</sup> as well as in other regions, demonstrate that the occurrence of lung cancer in women is not significantly correlated with cigarette smoking patterns.

A recent epidemiological study of lung cancer among females in the United States found positive associations between lung cancer and chronic respiratory conditions; marriage before the age of twenty; childbirth before the age of twenty; a history of previous hysterectomy; and a negative association with single

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females. The author concluded that cigarette smoking does not appear to be related to lung cancer among females in a large proportion of all malignancies of the lung. <sup>63</sup>

(3) Effect of Other Respiratory Illness,  
Including Tuberculosis

The Surgeon General's 1967 report completely omits mention of the studies published since 1964 which have suggested the importance of previous respiratory illness in patients who develop lung cancer. As the 1964 Surgeon General's report admits (page 195) this association with previous lung ailments was noticed as long ago as 1920. A detailed study in the Netherlands of 150 lung cancer patients compared with two sets of controls concluded that chronic nonspecific lung disease "is an almost obligatory condition" in the production of squamous cell lung cancer and that this relationship was independent of smoking. <sup>8A</sup> Another recent study of 190 patients with bronchial cancer (Huizinga) found signs of chronic nonspecific respiratory disease in 75 percent of the cases and characteristic signs of chronic bronchitis in forty percent. <sup>45</sup>

Recent work also indicates that the association between lung cancer and tuberculosis is much stronger than had previously

been suspected.

Retrospective analyses of death certificates on a national scale and analyses based on Philadelphia Tuberculosis Registry listings show that lung cancer is associated with pulmonary tuberculosis several times more strongly than data based on incidence of either alone would suggest.<sup>86</sup> An analysis of Philadelphia death certificates showed a marked excess of deaths for both diseases was associated with three low income occupations of a total of nine occupational categories. It was similarly associated with the lowest three median income districts of the city's ten health districts. The author of this study concluded that the aggregation of tuberculosis and lung cancer in similar strata of the society could be construed as an effect of a social predilection among those who have a certain inborn trait. He also stated that this association "alleviates the burden that has been placed on cigarette smoking as the sole factor of the historical rise in lung cancer."

The same author also analyzed pulmonary tuberculosis and lung cancer mortality rates over time in several countries.<sup>87</sup>

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He noted:

"It seems more than coincidence that lung cancer increase follows a decrease in tuberculosis . . . An explanation hereof would contain a mechanism by which fewer tuberculosis deaths create more lung cancer." 88

These observations have given rise to a theory that there may be a common constitutional susceptibility to tuberculosis and lung cancer. If this were true, it would represent a reasonable explanation for the increase in lung cancer deaths in the United States as being the result of the fact that the type of persons who years ago might have died from tuberculosis at an early age survive now to more advanced ages when they are exposed to an increased risk of dying from lung cancer.

(4) No "Dose-Response" Shown

The Surgeon General's 1967 report notes as one item of current information regarding lung cancer that

"Epidemiological evidence concerning cigarette smoking and lung cancer has confirmed positive relationships with increasing numbers of cigarettes smoked, with increasing duration, and with decreasing age of initiation of the habit."  
(Page 48)

The 1964 report stated,

"Herein lies the greatest coherence with the known facts of the disease." (Page 187)

The "coherence" of this relationship is highly questionable in light of investigative findings published both before and since the 1964 report.

Studies in England (Passey) reveal that the age at which lung cancer develops is determined by neither the amount smoked nor the age at which smoking began.<sup>89</sup> Smokers of various amounts of cigarettes and of differing patterns of inhalation tend to develop lung cancer--if they do at all--at about the same age, in the late sixties. In 1965, confirmation of these findings was reported by Pike and Doll, the latter being one of the chief architects of the cigarette theory of lung cancer.<sup>90</sup>

The "coherence" of this association is even further weakened by the findings in later British and U. S. statistics, previously mentioned, that almost all of the recent increase in lung cancer is accounted for by persons born before 1901. Studies of several populations have found an increase in the age of the

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maximum death rate from lung cancer, and a stabilization in death rates in the age groups below sixty. Since the generations now reaching the ages at which lung cancer tends to occur with highest frequency have, according to most data, smoked longer and smoked more than preceding generations, these findings would seem to undermine the asserted "positive relationships" between lung cancer and number of cigarettes smoked and duration of smoking.

A study of eight cities in England by Stokes, reported in 1966, found a diminishing relation between amount smoked and lung cancer incidence with advancing age and a disproportionate mortality among smokers at about age 40. These findings, he said, are "incomprehensible according to current ideas as to how smoking affects lung cancer incidence."<sup>91</sup>

If amount and duration of cigarette smoking were clearly related to lung cancer death rates, it should show a similar relationship in both men and women. However, available data shows that at identical smoking levels, the lung cancer mortality ratio for men is many times that for women. The Surgeon General does

point out that "the mortality rates for women who smoke, although significantly higher than for nonsmokers, are lower than for men who smoke." This statement is only partially true. The mortality rates for women smoking up to nine cigarettes per day are not significantly higher than for nonsmokers. In fact, in the lower age groups the mortality ratios of women smokers are less than one. Furthermore, data from the National Health Survey cited in the 1967 report show that present light smokers (less than 11 cigarettes per day) of both sexes reported significantly less chronic illness than nonsmokers. Present moderate smokers (11-20 cigarettes per day) reported no statistically significant increase in chronic conditions for males and only a small increase for females. If one combines the five primary measures reported by the National Health Survey for determining the health status of smokers as compared to nonsmokers, it appears that persons who on the basis of their present smoking habits are classified as light smokers are about just as healthy as nonsmokers. The elevated lung cancer mortality ratio reported for male light smokers appears, therefore, to be out of step with other recent evidence cited by the Surgeon General concerning the health status of light smokers.

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(5) Cessation of Smoking

The current Surgeon General report states that "the finding of reduced lung cancer rates in the population of British physicians over a period of time in which the proportion of cigarette smokers was dropping significantly . . . provides critical confirmation of the judgment that cigarette smoking is the major cause of lung cancer . . . ." This interpretation is open to serious question. In a paper published in 1966, the authors of the study of British physicians presented detailed data for smoking patterns of the physicians for the periods 1951-1956 and 1956-1961. The percentage of total male British physicians who were ex-cigarette smokers apparently continued through 1961 to remain a small percentage of the sample population. A reported reduction in the lung cancer death rate of the magnitude described simply cannot be explained by the cigarette theory; in this respect it should be noted that no explanation is offered for the fact that the lung cancer death rate for British physicians was substantially lower than for all men in England and Wales when the study began (and may have already

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been in decline) even though the percentage of smokers among the British physicians was then approximately the same as that of the general population.

It is also peculiar that the largest decline in the lung cancer death rates among British physicians occurred in the earliest time interval and a much lower drop occurred in the next time interval. yet discontinued smokers did not improve their rate of risk and could not have been instrumental in contributing to the reported decline.

The Surgeon General states (page 47) that

"Ex-cigarette smokers are shown to have a significant decrease in death rates compared with those who continue to smoke."

However, the Surgeon General fails to mention the most interesting data on ex-cigarette smokers which has appeared since the 1964 report. This is the data in the National Health Survey. According to the study, for most of the health characteristics measured the ex-smokers had a poorer history than either the present smokers or those who had never smoked cigarettes. Any discussion concerning the observed effects of cessation of smoking should take account of this data.

E. Current Information Concerning Suspected  
Carcinogenic Agents in Tobacco Smoke

The Surgeon General's 1967 report asserts,

"Additional information is available concerning the presence of known or suspected carcinogens in tobacco smoke." (Page 49)

However, it appears that this additional information, whatever it may be, fails to explain the statistical association between cigarette smoking and lung cancer since the report goes on to state:

"Research is needed to identify and separate the tumor-initiating and tumor-promoting agents in tobacco smoke and to elucidate their interactions in the pathogenesis of cancer."

This is essentially the same conclusion that was reached in the 1964 report.

The fact is that since the publication of the 1964 report no additional animal carcinogens of any significance have been reported in cigarette smoke. Numerous theories have been advanced and investigated since 1964 in efforts to explain the assumed carcinogenicity of cigarette smoke, but these remain wholly speculative and none has weathered scientific examination.

For many years suspicion centered on the presence in cigarette smoke of infinitesimal amounts of a compound called benzo(a)pyrene. Although the 1964 report pointed out that the amount of this compound present in cigarette smoke condensate was far too small to account for the experimental tumor production by the total smoke condensate, the notion persisted that the amount of benzo(a)pyrene in smoke tending to play an important part in the production of tumors on the skin of experimental animals. In a recent study, four French investigators reported no correlation between biological activity (including appearance of mouse skin cancer) and the benzo(a)pyrene content of cigarette smoke condensate. This result, they say, seems "conclusive enough so that the part benzo(a)pyrene is often supposed to play in experimental animal carcinogenesis by cigarette smoke is now to be seriously questioned."<sup>q2</sup>

In 1964, investigators reported finding a radioactive substance, polonium 210, in tobacco, and suggested that some of it might be transferred to the lungs of smokers.<sup>q3</sup> In a later study, these investigators proposed that this substance might be responsible for lung cancer in smokers.<sup>q4</sup> Other investigators, examining

the lungs of smokers, found that the amounts of polonium 210 in smokers' lungs were so small that carcinogenesis caused by inhalation of this substance with tobacco smoke is rather unlikely. <sup>95</sup>

A flurry of interest was created by the 1967 announcement that cigarette paper contains an estimated ten parts per million of selenium. <sup>96</sup> No evidence has yet been produced that any selenium is transferred to the lungs of smokers. Furthermore, the carcinogenicity of selenium is in dispute.

Other recent work has suggested that the presence in tobacco of fungi or aflatoxins may cause lung damage from smoking. <sup>97</sup> This suggestion remains unconfirmed.

The present report states,

"It has been reported that the 'tar' and nicotine content of cigarette smoke tends to reflect the tumorigenicity of this smoke, and that a reduction of the 'tar' and nicotine content is accompanied by a reduction in the tumorigenicity."

Interestingly, on the same day that the 1967 report was released, an announcement was made by Columbia University that it owned the rights to a filter said to be capable of removing from cigarette

smoke two-thirds of its tar and nicotine content. When asked for his comment on this development, the Surgeon General was quick to point out that even if all the tar and nicotine could be removed from cigarette smoke, "the gaseous content of the smoke also constitutes a significant danger." Equally interesting are statements made by Public Health Service officials in the Spring of 1967 when PHS was seeking research funds. Some of these are attached as Appendix C.

It is a strange finding indeed that the nicotine content of cigarette smoke tends to reflect the tumorigenicity of this smoke. It has never been seriously suggested that nicotine has any cancer causing properties. Furthermore, the 1964 Surgeon General's report stated:

"There is no acceptable evidence that prolonged exposure to nicotine creates either dangerous functional change of an objective nature or degenerative disease."

It was also stated that ". . . the chronic toxicity of nicotine in quantities absorbed from smoking and other methods of tobacco use is very low and probably does not represent an important health hazard."

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A search of the recent literature as well as the older literature will fail to disclose any finding that indicates that nicotine may be responsible for the production of cancer. It is difficult to believe that the Surgeon General would seriously suggest that the nicotine content of smoke is responsible for any tumorigenic effect. As a matter of fact the article by Bock et al. (footnote 2 to the 1967 Report) specifically rebuts this.

As to the significance of the "tar" content of cigarette smoke, none of the recent literature reveals that this conglomerate material has any biological activity beyond that which was identified in the 1964 report, namely, the ability to produce cancers on the skins of a susceptible strain of mice. It is generally acknowledged that this type of experiment does not establish that cigarette "tar" causes cancer in any human tissue.

It is interesting that one such mouse skin painting experiment produced a result in contradiction with the epidemiological data relating to smoking. <sup>98</sup> This study in 1963 was designed to test the relative effects of cigarette, cigar and pipe smoke condensate. It was found that the pipe smoke condensate was most active while cigarette and cigar smoke condensates had about the

same degree of biological activity. These results were in sharp contrast to the statistical findings reported in the 1964 report relating to cigarette, cigar and pipe smokers. It was found that death rate for pipe smokers were little, if at all, higher than for nonsmokers.

Since the 1964 report, additional studies have been published describing unsuccessful attempts to produce cancer in animal tissue with cigarette "tar".<sup>99</sup>

The suggestion in the footnote at the bottom of page 49 that the total particulate matter in cigarette smoke is related to biological activity is contradicted by the results of experimental work by Swiss investigators in which results have been observed from the inhalation of whole smoke by mice.<sup>100</sup> This work suggests that from a qualitative point of view, particulate material is not of great consequence. In addition, the dose-response relationship which is said to be found in studies involving the painting of "tar" on mouse skin could not be confirmed in the inhalation work.

The statement on page 49 to the effect that ". . . while

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additional data are available concerning experimental carcinogenesis, it is not yet certain that the typical characteristics of human squamous-cell lung cancer, with invasion and metastasis, have been experimentally produced by tobacco smoke in animals "unfairly characterizes the present state of the data from experimental studies. It is a plain fact that human type epidermoid carcinoma has not been experimentally produced with cigarette smoke. This should have been forthrightly stated in the Surgeon General's 1967 report. The current literature indicates that even the application of cigarette "tar" to the lung tissues of experimental animals has failed to produce lung cancer. Two recent studies report that "tar" application produced no cancers in grafts of embryonic lung tissue of rats. In short, the experimental work to date fails to demonstrate that cigarette smoke has the potential to produce cancer in lung tissue.

F. The 1967 Report Understates the Evidence That Exposures Other Than To Cigarette Smoke Appear to be Related to Lung Cancer

At page 50 of the 1967 report it is stated, "There is evidence that certain other exposures, for example, occupational exposures to asbestos and uranium ore may interact with the cigarette effect to produce an enhancement of the tumor-producing effect." The fact is that studies published since 1964 have found significant associations between high lung cancer incidence and certain occupational and other environmental exposures, entirely independently of smoking.

A large study of lung cancer cases in a major industrial area of West Germany found that lung cancer incidence was highest among outdoor workers, industrial workers and persons exposed to vehicular traffic. Among the five major groups studied, the heaviest cigarette smoking was found in the group with the lowest incidence of squamous cell cancer.<sup>107</sup>

Studies of working populations have revealed that lung cancer cases tend to be concentrated in particular occupational groups. The German study mentioned in the preceding paragraph was preceded by a study of workers in Berlin which found significant

differences in occupation between lung cancer and stomach cancer patients, with lung cancer being commonest among metal workers, mechanics, fitters, woodworkers and "commercial occupations."<sup>103</sup>

Studies published since the 1964 Surgeon General's Report tend to confirm the earlier observations that the high incidence of lung cancer in certain occupational groups is not related to smoking habits. One such study reported that fluorspar miners in Newfoundland had a lung cancer rate 20 times higher than the general population. The authors concluded that this was due to radioactive elements in the mines. Smoking did not account for this high lung cancer rate.<sup>104</sup> A study of insulation workers revealed a lung cancer rate 6.8 times higher than the general population. Smoking did not account for this difference.

A British study of mortality among gas workers<sup>105</sup> published in 1965 found lung cancer incidence 69% higher among workers exposed to products of coal coking than among workers with no such exposure, but no significant variations in smoking habits.

Since 1964, many writers have continued to call attention to the strong association between lung cancer and general atmospheric pollution. A major German analysis of 790 autopsies

and 439 clinical cases of lung cancer,<sup>106</sup> showed no association between smoking and bronchial cancer. The authors pointed to air pollution as an essential factor in the disease.

Professor Myddelton stated in a recent note in a medical journal that "the startling contrast between lung cancer deaths in London and the rural counties of Ireland is obviously unconnected with cigarette smoking."<sup>107</sup> He also noted the strong connection between lung cancer death rates and degree of urbanization pointing out that Canada, with the second highest cigarette consumption in the world, has the lowest lung cancer death rate, while Austria which has the second highest lung cancer mortality rate in the world has the lowest cigarette consumption.

A publication of the Mayo Clinic reviewed the subject of lung cancer in 1964 and pointed to air pollution as a suspected factor.<sup>108</sup> It was considered questionable that cigarette smoking alone could be responsible for the excess lung cancer in city dwellers. Another extended U. S. review concluded that that available evidence "strongly implicates the atmosphere as one dominant factor in the pathogenesis of lung cancer."<sup>109</sup>

The present Surgeon General's 1967 report also ignores recent data which confirms the association between high lung cancer death rates, tuberculosis and low socioeconomic level. Such findings were made in population studies in Philadelphia<sup>110</sup> and in Copenhagen.<sup>111</sup>

G. Generally

Other recent findings which are ignored in the present Surgeon General's report include those which indicate that susceptibility to lung cancer as well as the tendency to smoke cigarettes may be the result of common heredity factors<sup>112</sup> or personality and constitutional factors.<sup>113</sup>

The section in the 1967 report on lung cancer concludes with the statement, "There is also information to indicate that the occurrence of second primary lung cancers in smokers may be more frequent than previously indicated." This study ignores the information published in the journal Cancer in November 1965 in which, on the basis of a study of multiple primary tumors, Moore found that multiple primary tumors at sites exposed to cigarette smoke in men could not be ascribed to a common etiological factor.<sup>114</sup>

A discussion of constitutional factors appears also in the section on cardiovascular disease.

## 2. Oral Cancer

The discussion of the subject of oral cancer at Page 50 of the 1967 Surgeon General's Report does not present a fair review of the recent information on this subject.

While the report concedes that "there is some evidence implicating alcohol and/or dietary deficiencies in some of these sites" it omits to mention that in a study of the association of alcohol and tobacco with cancer of the pharynx published in 1965 it was found that the association between alcohol consumption and cancer was more than twice as strong as that between smoking and cancer.<sup>115</sup>

A great many of the recent papers relating to oral cancer show associations with chewing of non-tobacco materials such as betel nut, and habits that involves the chewing of tobacco along with other substances such as lime. Almost all of the data shows that nearly all cases of oral cancer occur in the lowest socioeconomic groups of the populations studied and the strength of the association with nutritional deficiencies appears to overshadow the association with tobacco.<sup>116</sup>

The 1964 Surgeon General's Report found neither

consistency, specificity nor coherence in the association of oral cancer with tobacco use. In a statement made before the Subcommittee of the House Committee on Appropriations in 1966, Dr. S. J. Kreshover, acting director of the National Institute of Dental Research said, "I don't know whether we today are very much closer to finding the specific causes of oral cancer." This is the only proper conclusion to be drawn from the information presently available.

### 3. Laryngeal Cancer

The 1967 report states:

"The conclusion of the Surgeon General's 1964 report that cigarette smoking is a significant factor in the causation of laryngeal cancer in the male is supported by additional epidemiological evidence."

The evidence actually indicates that there appears to be no connection whatever between cigarette smoking and laryngeal cancer in the male. In a report issued in October 1966 by the National Center for Health Statistics ("Mortality from Diseases Associated with Smoking: United States, 1950-64"), it was noted that the age-adjusted death rate for laryngeal cancer in the male population remained relatively stable during the period 1950-64-

2.0 deaths per 100,000 for 1950 and 2.1 deaths for 1964.

After relying heavily on the vital statistics concerning lung cancer in order to support the assertion of a causal connection between smoking and that disease, the Surgeon General's 1967 Report completely ignores the vital statistics relating to laryngeal cancer. If cigarette smoking were a significant factor in the causation of laryngeal cancer, a large increase in mortality or frequency of the disease corresponding to the increase in cigarette consumption should have occurred.

Another piece of information which is not explained in the current report tends to contradict the theory that smoking is relating to this form of cancer. The 1964 Report noted that the ratio of males to females with cancer of the larynx was approximately 6 to 1 thirty years ago when comparatively few women smoked. Now, when many more women smoke, the ratio has widened to 10 to 1. This is the opposite of what should have occurred if smoking were a significant causal factor.

#### 4. Urinary Bladder Cancer

The present Surgeon General's Report states as to bladder cancer that the presently available data are insufficient to infer that the relationship is causal. This conclusion is

correct. No new substantive evidence of a relationship between smoking and cancer of the urinary bladder has appeared since the publication of the 1964 Surgeon General's report.

The chief pathologist of the National Cancer Institute has criticized the notion that smoking may be causally related to bladder cancer.<sup>117</sup> Further, the publication by the National Center for Health Statistics in 1966 "Mortality from Diseases Associated with Smoking" states:

"There was no change in the death rate from cancer of the bladder and other urinary organs during 1950-64."

##### 5. Esophageal Cancer

The present Surgeon General's report takes note of certain new findings in relation to cancer of the esophagus, but does not suggest a change in the conclusion of the 1964 report that the data are not adequate to decide whether the relationship is causal. Certainly the study referred to in the present report does not afford a sufficient basis for inferring a causal relationship between cigarette smoking and cancer of the esophagus.

The autopsy study cited is by Dr. Auerbach and reported

the observation of changes in esophageal tissues from both smokers and nonsmokers who died from causes other than esophageal cancer. It should be pointed out that, as in the case of his studies on the tracheobronchial tree, this was an autopsy study on men whose histories, apart from smoking habits, were unknown. Other factors which have been suggested as being associated with cancer of the esophagus, such as alcohol, hot foods, nutritional deficiencies, were not investigated. Without investigation of such other suspected factors, the findings of the cited study cannot be accepted as significant.

The frequency of the changes found in the esophageal tissues appears to be entirely unrelated to the frequency of occurrence of esophageal cancer, which is relatively low. The 1964 Surgeon General's report noted (page 217) that "few of the studies revealed increasing gradients of risk with amount smoked."

The epidemiological data relating to cancer of the esophagus in the United States also does not accord with the theory that cigarette smoking is causally related to this condition. This is the only cause of death among all of the diseases statistically associated with cigarette smoking for which the level of mortality is higher in the non-white than in the white population.

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["Mortality From Diseases Associated With Smoking!" United States, 1950-64, Page 16] Furthermore, the relative increase from 1950 to 1964 in mortality from this cause was slightly higher in the female population than in the male population. Neither of these facts is in accord with the patterns of cigarette consumption in the United States.

Based on the data presently available, it would appear that any statistical association shown between cigarette smoking and mortality from cancer of the esophagus cannot be considered to indicate a causal relationship.

### III. Conclusion

The Secretary, in his report to Congress on smoking and health, made the following recommendations:

- "1. The warning statement required by the Federal Cigarette Labeling and Advertising Act to be placed on each package of cigarettes should be strengthened to state more specifically and positively that cigarette smoking is a hazard to health.
- "2. This warning should be required in advertisements as well as on cigarette packages.
- "3. The cigarette package label and advertising should be required to contain information on the "tar" and nicotine levels in the smoke of the cigarette, and the identity and quantity of such other substances or agents in the smoke as may subsequently be found by the appropriate Federal agency to contribute to the health hazards of smoking."

These recommendations are not supported either by information contained in the three-page statement by the Secretary nor by the "summary report" of the Surgeon General attached thereto.

#### "Tar" and Nicotine

The Secretary's statement that accumulated evidence strongly suggests that "tar" and nicotine content of cigarette smoke can

help a consumer make "an informed choice of product" goes far beyond any evidence cited. The data in the "summary report" fails completely to support any relationship between nicotine and "health consequences" and demonstrates that publicizing the "tar" content of cigarettes is probably meaningless and perhaps misleading.

The two articles cited by the Surgeon General to demonstrate carcinogenic activity of cigarette smoke condensate both dealt with animal experiments and both found that the carcinogenic activity of "tar" was not necessarily related to the amount of "tar" used. In one case, an additive was reported to have reduced carcinogenic activity, and in the other the type of tobacco involved was found to be a factor. In one article nicotine was not found to have any significance, and in the other it was found to be completely unrelated to tumorigenic activity. To cite these articles as supporting the proposition that a quantitative reduction of "tar" and nicotine content would be meaningful in terms of human experience is most misleading - neither stand for that proposition nor even for the proposition that such a reduction would be significant so far as the animals were concerned.

One of the most striking aspects of the 1967 report is the complete absence of any scientific evidence identifying a

constituent in cigarette smoke as responsible for any of the diseases with which smoking is said to be statistically associated. There is not even evidence explaining the reported carcinogenicity of tobacco smoke condensate when applied to the shaved backs of mice. Such bioassay results remain "a puzzling anomaly"\* and continue to present "a gigantic problem for exploration,"\* as they did in 1964. Furthermore, the 1967 report specifically concedes the continuing failure to produce bronchiogenic carcinoma in animals by exposing them to whole cigarette smoke.

The fact remains, as stated by the Surgeon General on April 3, 1967, in testimony before a subcommittee holding hearings concerning HEW appropriations for 1968 that there is "no specific agent in cigarette smoke that can be specifically pointed to as the cause of lung cancer" (Part 4, page 108), much less as the cause of any other disease. The Surgeon General had earlier stated that even though he believed there was a cause and effect relationship between cigarette smoking and lung cancer, "this does not mean that we know what it is in the cigarette smoke - the specific etiological agent in the smoke - that causes the cancer." (Part 4, page 61).

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\*Smoking and Health, 58-59.

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In view of the foregoing it is difficult to understand how information as to "tar", nicotine or any other ingredient can be deemed helpful to a consumer.

Advertising

The Secretary's recommendation with respect to placing a warning on cigarette advertising refers only to the recent report of the Federal Trade Commission. It is somewhat surprising that no independent material to support HEW's second recommendation was included as a part of its report.

A "Strengthened" Warning

The Secretary's first recommendation is not supported by the 1967 summary report of the Surgeon General. As a matter of fact, if the "current information on the health consequences of smoking" is viewed objectively, the cumulative evidence said to link cigarette smoking with certain diseases is weaker in 1967 than it was in 1965 when the present law was enacted.

Even within the confines of the Surgeon General's own summary report, for example, one finds four cited references which tend to exonerate the cigarette as a cause of cardiovascular disease

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and demonstrate the importance of constitutional factors. Strangely, they are not cited for any cardiovascular disease findings but for a far less significant reason. Since these studies have been generally approved by the Public Health Service (as demonstrated by their being included in the twenty "cited references" to the summary report) this one-sided use of such material is most disappointing.

The Surgeon General's discussion of lung cancer omitted reference to recent large scale studies that demonstrate no statistical association between such disease and cigarette smoking. If the report is suppose to be a review of scientific data, rather than an adversary's brief, such studies should certainly have been brought to the attention of Congress as significant "current information on the health consequences of smoking." Articles indicating that a constitutional factor can explain not only the reported increase in lung cancer mortality but also the sex ratio were also completely ignored. (Some extremely significant work in this regard has been done in the Netherlands and indicates a strong relationship between chronic nonspecific lung diseases and lung cancer, "which is independent of smoking.")

With respect to chronic bronchopulmonary diseases, some

conclusions with respect to such diseases were advanced during recent HEW Appropriation Hearings that better describe the true situation than does the 1967 summary report. Public Health Service officials referred to the fact that bronchitis has been going down in recent years as a cause of death,<sup>118</sup> that the "mechanisms" of chronic respiratory disease are "poorly understood"<sup>119</sup> and that scientists "know very little at this point in time about the disease emphysema".<sup>120</sup>

It is not surprising that the present report does not, for the most part, extend the conclusions of the Surgeon General's Advisory Committee Report of 1964 with respect to causality. Even after three and one-half years of intensive effort, the "evidence" presented remains speculative and inconclusive. If anything, recent data tends to support the "possible" explanation advanced in "Cigarette Smoking and Health Characteristics", a publication of the U. S. Department of Health, Education and Welfare. This recent "morbidity" (illness) study states candidly that reported statistical associations between cigarette smoking and certain diseases or conditions may be the result of "some third factor, possibly psychologic or biologic (that) is causing both the condition and the smoking habit."

Finally, neither the Secretary nor the Surgeon General ever suggested any answer to a question that the Advisory Committee in 1964 thought relevant:

"An attempted evaluation of smoking on mental health becomes more realistic if one is willing to confront the question, ridiculous as it may seem, what would satisfy the psychological needs of 70,000,000 Americans who smoked in 1963 if they were suddenly deprived of tobacco." (Smoking and Health, p. 355)

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