

**CRUDE MALE DEATH RATE FOR LUNG CANCER
IN 1950 AND PER CAPITA CONSUMPTION OF
CIGARETTES IN 1930 IN VARIOUS COUNTRIES.**

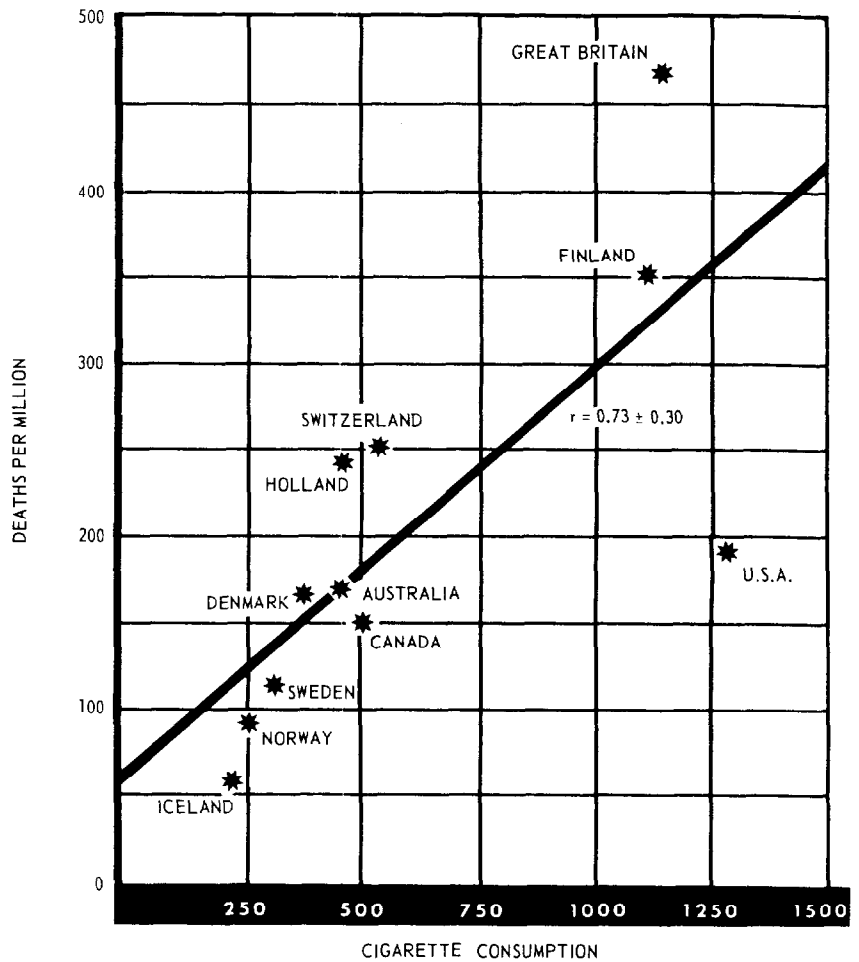


FIGURE 9.

Source: Doll, R (76)

represented (Great Britain, Finland, Switzerland, Holland, the United States, Australia, Denmark, Canada, Sweden, Norway, and Iceland), it seemed reasonable to compare the annual per capita consumption of each country with the crude, male lung cancer death rates.

It will be noted in Figure 9 that the data from the United States show a relatively low death rate in relation to cigarette consumption. Doll suggested two explanations: the influence of a higher proportion of young

people in the U.S. population and the method of smoking, with the U.S. smokers consuming less of each cigarette than the British smokers. Since Doll's explanations of the discrepancy, additional information has become available. Studies on length of cigarette butts discarded have shown American discards to be significantly longer than British discards; 30.9 mm (156) and 18.7 mm (85) respectively. Also, there is a significantly greater percentage of smokers in Great Britain than in the United States in the age groups in which lung cancer occurs at high rates (52.6 percent in 60+ year age group and 29.2 percent in 65+ year age group respectively).

Strictly comparable data do not exist on inhalation practices for the two countries. Such information would aid in explaining this discrepancy as well as a similar disparity between Holland and Great Britain. In Holland (156) the length of the cigarette butts was almost the same as in Great Britain (19.7 mm), but the crude male lung cancer death rate in Holland was significantly lower than in Great Britain. This correlates well, as shown in Figure 9, with the annual per capita consumption of cigarettes in Holland which has been much lower than in Great Britain.

It should be mentioned that differences in intensity of air pollution and industrial exposures in these countries have not been taken into account. However, for reasons given below, these latter factors do not account for the magnitude of the difference in incidence of lung cancer nearly as well as the amount of each cigarette smoked and the degree of inhalation. Finally, the varying composition of the tobacco in the several countries was not considered in these studies.

An elaboration of the disparities between male and female lung cancer mortality rates and their correlation with differences in smoking patterns is also in order, for the sex disparity has also been posed as contradictory to the smoking-lung cancer hypothesis. Although the opponents of the hypothesis, pointing to the sex disparity (116, 229), have minimized the differences in smoking habits, the fact remains that the magnitudes of the differences are quite large. In a representative cross-sectional survey of smoking habits coupled with the Current Population Survey of the Bureau of the Census in 1955, Haenszel, et al. (151) found the following disparities between male and female smoking patterns:

1. Whereas only 22.9 percent of males had *never* smoked, 67.5 percent of females had not.
2. Males showed relatively little variation among the component age groups in percentage not smoking, whereas females after age 25-34 showed a consistently increasing percentage of non-smokers in successively higher age groups (Figure 10).
3. Sixty-five percent of males smoked cigarettes as compared with 32 percent of females.
4. Cohort analyses revealed the adoption of cigarette smoking late in life for both males and females among cohorts born before 1890; but male cohorts born after 1900 successively began to smoke earlier in life. Large-scale adoption of cigarette smoking by women did not occur until the decades of the 1920's and 1930's.

**PERCENTAGE OF PERSONS WHO HAVE NEVER SMOKEI
BY SEX AND AGE, UNITED STATES, 1955**

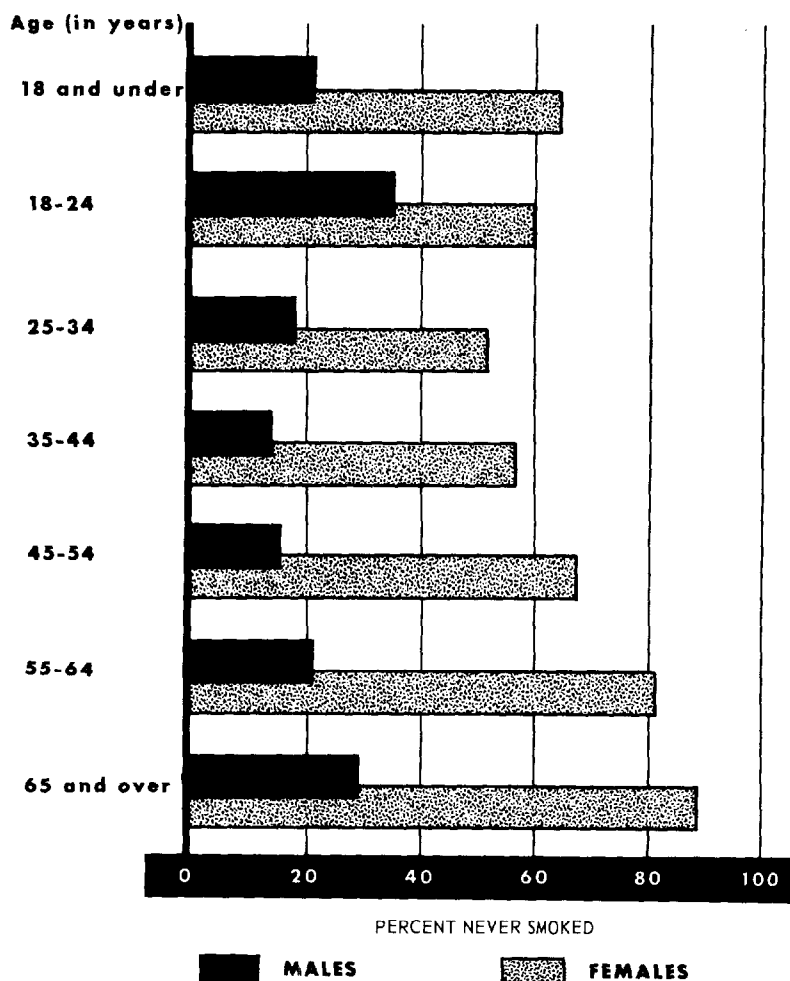


FIGURE 10.

Source: Haenszel, W. M. et al. (151)

5. The median age at which males started smoking has remained fairly stable for the several age cohorts: from 19.3 years for ages 65 and over to 17.9 years for age 25-34; the median age that females started smoking has dropped dramatically from 39.9 years for the age group 65 and over to 20.0 years for age 25-34.
6. Males in all age groups smoked considerably more cigarettes per day than did females. In ages 55 and over, 6.9 percent of the

males smoked more than a pack a day, compared with only 0.6 percent of the females. Although urban-rural and geographic regional differences were noted, significant disparities between male and female smoking were maintained throughout. Thus it can readily be deduced that these findings are consistent not only with the sex disparity in lung cancer mortality but also with the slower but nevertheless continuing rise in female lung cancer mortality.

British studies (344) also revealed that females, especially before World War II, consumed much less tobacco than did males. A correction for the marked disparity in smoking habits of males and females reduced the observed 5-fold excess of male lung cancer deaths to a 1.4-fold excess as of 1953 (149). Supporting this finding are the data from two retrospective studies (147, 152) in which the age-adjusted lung cancer death rates in 1958-59 among male and female non-smokers were 12.5 and 9.4 respectively for a ratio of 1.33 (145). This residual ratio implies that there may be other factors operating to produce a portion of the sex differential in mortality.

DIRECT MEASURE OF THE ASSOCIATION

For a direct measure of the association between lung cancer and smoking it is, of course, essential that both variables or attributes be measured in the same populations. The 29 retrospective studies, described earlier, consider smoking (usually kind, amount, and duration) and non-smoking among cases of lung cancer and individuals without lung cancer. The seven prospective studies consider the occurrence or lack of occurrence of lung cancer among smokers and non-smokers.

ESTABLISHMENT OF ASSOCIATION.—A number of investigators, though accepting the existence of an association, have questioned its significance in terms of a causal hypothesis (58, 102, 114, 115, 116, 117, 141, 178, 218, 219, 287, 288, 298, 299). Some of these doubts have been on the basis of a possible genetic underlay which might determine both smoking and lung cancer (114, 115, 116, 117). Some have followed contradictory observations in the dissenter's own work (58, 102, 141), incorrectly assessed evidence of lung cancer mortality trends, or the belief that the causal hypothesis requires cigarette smoking to be the sole cause of lung cancer (178, 287, 288). Others believe that the lung cancer rise is spurious and can be attributed either to improvements in diagnosis and reporting (218, 219, 287, 288, 298, 299) or to the aging of the population. In the latter explanation they ignore the fact that aging of the population does not affect age-specific mortality rates which, for lung cancer, are also rising with the passage of time. Still others express doubt on the basis of the lack of a concomitant rise in cancers of the oral cavity (178, 298) or of the skin of the fingers (178). Finally, some doubts have been based on supposed incongruencies between the cigarette-smoking hypothesis and urban-rural as well as sex differences in lung cancer mortality (116, 178, 229). There are a few investigators who maintain that the association may be spurious or that it has not been proved (22, 23, 24, 228, 229, 230).

A number of these objections have been assessed in earlier discussions in this section; others will be evaluated below. These latter criticisms have revolved about defects inherent in the retrospective or the prospective

methods of approach, biases of selection in either method, biases of non-response, the validity of the results in the early phases of a prospective study, and the misclassification of both variables: smoking habits and lung cancer.

It should be noted that the Current Population Survey of 1955 yielded results highly consistent with data on tobacco production and taxation (151); that classification errors in terms of amount of smoking were relatively minor in a reliability study by Finkner (113); and that, in at least three prospective studies, in which subjects were requestioned on smoking habits at intervals of at least two years, the replies were closely reproducible (87, 88, 157, 159, 162, 163), particularly if no illness had intervened (159).

With regard to the retrospective studies, it has also been suggested that knowledge of the illness might have introduced bias in relation to histories of smoking habits (158, 229). In at least one retrospective study, both patient and interviewer were unaware of the diagnosis of lung cancer, the smoking histories having been obtained before the diagnosis was made (207). Furthermore, patients initially believed to have lung cancer who, after interview, were found not to have the disease, reported smoking histories similar to the control groups and not the lung cancer groups (84). Finally, this bias cannot have influenced the findings of several studies in which a significantly greater proportion of cigarette smokers and heavy cigarette smokers were associated with epidermoid cancers than with adenocarcinoma (86, 150, 163, 313, 375). The reliability of response to smoking history would thus appear to be markedly above the critical level for the firm establishment of an association by the retrospective method. In prospective studies, this factor is less of a problem.

In retrospective studies the investigator can confine himself to cases with accurate diagnoses. In the prospective approach, accuracy of diagnosis may not always be attainable, but all cases must be included. In assessing the results of the prospective studies it must be kept in mind that all deaths from any cause were involved in the calculations, with the cigarette smoker rates higher than those for non-smokers and with a gradient by amount of smoking demonstrated in all of the studies. Evidence that the specific estimates of risk for lung cancer among smokers actually might have been underestimated has been presented by Hammond and Horn (162, 163), who found higher relative risk ratios among smokers for confirmed cases than for those with less well-established diagnoses. Most of the prospective studies yield relative risks of lung cancer by various smoking categories which approximate those found in the Doll and Hill physician study (83) where, obviously, diagnostic evidence would be more readily available than in the general population. It would thus appear that in the data from retrospective and prospective studies, diagnostic accuracy was not a critical factor in the establishment of an association between smoking and lung cancer.

The question of *selection bias* is, of course, a more complicated problem. Several criticisms have been leveled at both the retrospective and prospective methods. Although in retrospective studies the selection of a control group may pose a more serious problem, even the selection of the case material may interject difficulties. It has been claimed by Berkson (24) that the selection of hospitalized cases may lead to bias if smokers with lung cancer

were more often hospitalized than non-smokers with the disease. However, nearly all lung cancer cases are hospitalized, a point which, he concedes, would thus minimize this bias. Furthermore, several retrospective studies have surveyed all the cases in the area regardless of hospitalization (238, 335), or all deaths regardless of cause or hospitalization (379).

Another criticism of patient selection in retrospective studies deals with the danger that, in studies highly cross-sectional in time, if smokers live longer than non-smokers, there would obviously be more smokers in the disease group, and thus a spurious association of disease with smoking would result (254). There is no evidence for this basic assumption. Furthermore, it is inapplicable because almost all the retrospective studies were actually based on newly diagnosed cases collected serially over an interval of time long enough to remove this bias.

Control groups pose a problem in retrospective studies. In 27 of the 29 retrospective studies (exceptions are references 147 and 152) the controls were subjects without lung cancer, such as patients with other cancers, with diseases other than cancer, or so-called normals selected from the population. Analysis of the prospective studies proved that the biases interjected by the selection of sick controls in the retrospective studies actually operated to produce an underestimation of the association, for it has been shown that a number of other diseases are also associated with smoking. Furthermore, several studies have, in addition to controls with other diseases, selected a second set of random controls from the general population (82, 150, 222), only to find that the association utilizing sick controls, significant though it proved to be, was intermediate to the association utilizing random population controls.

The problem of selection bias in prospective studies is much more subtle, since there may be self-selection on the basis of illness existing at the time the study begins. This is essentially a problem of non-response which has been handled in detail in Chapter 8. The character of this non-response presents at least two nuances: a combination of self-selection and operator selection, as in the volunteer studies of Hammond and Horn (162) and Hammond (157) and the response to questionnaires in a total population study such as Dorn's (88).

Suffice it to say at this point that, regardless of whether there is over-representation of sick smokers or well non-smokers or both in a prospective study, with the passage of time more deaths of sick persons would occur (without regard to the independent variable of smoking). Thus the death rates of smokers would tend to approach the death rate of non-smokers, removing the original selection bias and providing greater confidence in the residual association of the death rate with smoking if it persisted. In two of the studies (157, 162, 163) exclusion of ill persons on entry did take place. Further, in the studies that provide this comparison, the high lung cancer mortality ratio of cigarette smokers was maintained with the passage of time. In the Dorn study the mortality ratio was 9.9 after three years experience and 12.0 after six years experience; the Hammond study gave 9.0 after 10.5 months (157) and 9.6 after 22 months, while Doll and Hill (84) showed that the gradient of increase in lung cancer death rate with increasing amount smoked appeared consistently in each of the first four years of their study.

This also weakens the criticism by Mainland and Herrera (230) of the use of non-professional volunteer workers for subject selection.

Thus it would appear that an association between cigarette smoking and lung cancer does indeed exist.

CAUSAL SIGNIFICANCE OF THE ASSOCIATION.—As already stated, statistical methods cannot establish proof of a causal relationship in an association. The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability. To judge or evaluate the causal significance of the association between cigarette smoking and lung cancer a number of criteria must be utilized, no one of which by itself is pathognomonic or a *sine qua non* for judgment. These criteria include:

- (a) The consistency of the association
- (b) The strength of the association
- (c) The specificity of the association
- (d) The temporal relationship of the association
- (e) The coherence of the association.

THE CONSISTENCY OF THE ASSOCIATION.—This criterion implies that diverse methods of approach in the study of an association will provide similar conclusions. It is noteworthy that all 29 retrospective studies found an association between cigarette smoking and lung cancer. The very nature of the criticisms leveled against these retrospective studies indicates a diversity of characteristics of approach and, for that matter, marked differences in shortcomings which have been discussed in detail above. It is indeed remarkable that no reasonably well designed retrospective study has found results to the contrary. Seven prospective studies have also revealed highly significant associations. Where relative risks could be calculated on the basis of some reasonable assumptions in some of the retrospective studies, a consistency not only among them (38, 82, 147, 152, 222, 283, 301, 313, 381) but also with the prospective studies could be demonstrated. Such a situation would prevail if the association were either causal, or spurious on the basis of an unknown source of bias. It is difficult to conceive of a universally acting bias in all the diverse approaches unless it be a constitutional genetic characteristic or one acquired early in life, which will be discussed later in the section, Constitutional Hypothesis.

Two studies of tobacco workers (58, 141) have been cited as inconsistent with the 29 retrospective and particularly the 7 prospective studies cited in detail in the early portions of this section. Both these studies can be dismissed because of major defects in methodology and concept. The heavier smoking among the tobacco workers in these studies was considered, but no comparison of observed-to-expected rates was made on the basis of smoking classes within this population. Furthermore their conclusions are based on expectancies in the general population without regard to the fact that persons with acute, chronic, or disabling illness are initially excluded from employment and that those developing permanent illness are lost to employee rolls.

THE STRENGTH OF THE ASSOCIATION.—The most direct measure of the strength of the association between smoking and lung cancer is the ratio of lung cancer rates for smokers to the rates for non-smokers, provided these two rates have been adjusted for the age characteristics of each group. Another way of expressing this is the ratio of the number of observed cases

in the smoker group to the expected number calculated by applying the non-smoker rate to the population of smokers. This provides us with a measure of relative risk which can yield a judgment on the *size of the effect* of a factor on a disease and which, even in the presence of another agent without causal effect, but correlated with the causal agent, will not be obscured by the presence of the non-causal agent. Cornfield et al. (62) have not only provided us with a detailed analysis of the applications of both absolute and relative measures of risk, but have also demonstrated the usefulness of the relative risk measure in judging causal and non-causal effects with mathematical proof of their statements.

An absolute measure of difference in prevalence of a disease between populations with or without the agent (e.g., cigarette smoke), where the agent may be causal in its effect on several diseases, can provide us with the means of appraising the public health significance of the disease, i.e. the size of the problem, in relation to other diseases. It is less effective for appraising the non-causal nature of agents having apparent effects, the importance of one agent with respect to other agents, or the effects of refinement of disease classification. This, Cornfield and his co-authors (62) have demonstrated.

In essence, then, a relative risk ratio measuring the strength of an association provides for an evaluation of whether this factor is important in the production of a disease. In the data of the nine retrospective studies for which relative risks of lung cancer among smokers and non-smokers were calculated, the ratios were not only high in all of the studies but showed a remarkable similarity in magnitude. More important, in the seven prospective studies which inherently can reveal direct estimates of risks among smokers and non-smokers, the relative risk ratios for lung cancer were uniformly high and, again, remarkably close in magnitude. Furthermore, the retrospective and prospective studies yielded quite similar ratios.

Important to the strength as well as to the coherence of the association is the dose-effect phenomenon. In every prospective study that provided this information, the dose-effect was apparent, with the relative risk ratio increasing as the amount of tobacco (84) or of cigarettes (25, 88, 96, 97, 163) smoked per day increased (Table 5). Even the retrospective studies for which relative risks were calculated by amount smoked (38, 147, 152, 222) showed similar increases in risks with amount smoked (Table 4).

It may be estimated from the data in the prospective studies that, in comparison with non-smokers, average smokers of cigarettes have a 9- to 10-fold risk of developing lung cancer, and heavy smokers, at least a 20-fold risk. Thus it would appear that the strength of the association between cigarette smoking and lung cancer must be judged to be high.

THE SPECIFICITY OF THE ASSOCIATION.—This concept cannot be entirely dissociated from the concept inherent in the strength of the association. It implies the precision with which one component of an associated pair can be utilized to predict the occurrence of the other, i.e., how frequently the presence of one variable (e.g., lung cancer) will predict, in the same individual, the presence of another (e.g., cigarette smoking).

In a discussion of the specificity of the relationship between any factor possibly causal in character and a disease it may produce, it must be rec-

ognized that rarely, if ever, in our biologic universe, does the presence of an agent invariably predict the occurrence of a disease. Second, but not less important, is our growing recognition that a given disease may have multiple causes. The ideal state in which smoking or smoking of cigarettes and every case of lung cancer was correlated one-to-one would pose much less difficulty in a judgment of causality, but the existence of lung cancer in non-smokers does indeed complicate matters somewhat. It is evident that the greater the number of causal agents producing a given disease the less strong and the less specific will be the association between any one of them and the total load of the disease. But this could not be posed as a contradiction to a causal hypothesis for any one of them even though the predictive value of any one of them might be small. For example, the pathologist who examines a lung at autopsy and finds tubercle formation and caseation necrosis would almost invariably be able to predict the coexistence of tubercle bacilli. Experience has shown that the lesions are highly specific for *Mycobacterium tuberculosis*. On the other hand, a clinician may encounter a combination of signs and symptoms including stiff neck, stiff back, fever, nausea, vomiting, and lymphocytes in the spinal fluid. Experience has revealed that any one of a number of organisms may be associated with this syndrome: polio virus, ECHO viruses, Coxsackie viruses and *Leptospirae*, to name but a few. The predictability of the coexistence of polio virus per se is rather low. In other words, the syndrome as noted is not very specific for polio virus. This may well be the condition which prevails in coronary heart disease where the mortality ratio is between 1.6 and 1.8 or a 60 to 80 percent excess among smokers of cigarettes. If this ratio is applicable to the entire population from which the sample data are derived, another way of expressing this relationship is that, of the total load of coronary heart disease mortality among males only 61 to 64 percent is associated with cigarette smoking. The large residual among non-cigarette smokers implies either other causes in addition to smoking or, as a somewhat greater possibility, factors actually causally related to coronary heart disease and frequently, but not invariably, associated with smoking.

However, in lung cancer, we are dealing with relative risk ratios averaging 9.0 to 10.0 for cigarette smokers compared to non-smokers. This is an excess of 900 to 1,000 percent among smokers of cigarettes. Similarly, this means that of the total load of lung cancer in males about 90 percent is associated with cigarette smoking. In order to account for risk ratios of this magnitude as due to an association of smoking history with still another causative factor X (hormonal, constitutional, or other), a necessary condition would be that factor X be present at least nine times more frequently among smokers than non-smokers. No such factors with such high relative prevalence among smokers have yet been demonstrated.

Another aspect of specificity requires some insight. Several critics of the causal hypothesis have questioned the significance of the association on the grounds that the existence of an association with such a wide variety of diseases, as elicited in the prospective studies, detracts from specificity for any one of them (22, 7). In a sense, this viewpoint is an exaggeration, for not all the specific disease mortality ratios in excess of 1.0 are large

enough to warrant secure judgments of the strength of the association and of causal significance. A detailed discussion of this latter point has been presented in Chapter 8. The number of diseases in which the ratios remain significantly high, after consideration of the non-response bias, is not so great as to cast serious doubt on the causal hypothesis. Even if we were dealing with a single pure substance in the environment, the production of a number of disease entities does not contradict the hypothesis. It is well known that a single substance may have several modes of action on the several organ systems and that neither inhalation nor ingestion implies action restricted to the respiratory or digestive tracts, respectively. In tobacco we encounter a complex of substances whose additive and synergistic characteristics before and after combustion remain inadequately explored. It would not be surprising to find that the diverse substances in tobacco smoke could produce more than a single disease.

Actually, the finding that an excess risk for smokers does not occur for every one of the causes of death reinforces the specificity of the excess risk for those causes where the excess is significant.

Thus, it is reasonable to conclude that the association between cigarette smoking and lung cancer has a high degree of specificity.

TEMPORAL RELATIONSHIP OF ASSOCIATED VARIABLES.—In chronic diseases, insidious onset and ignorance of precise induction periods automatically present problems on which came first—the suspected agent or the disease. In any evaluation of the significance of an association, exposure to an agent presumed to be causal must precede, temporally, the onset of a disease which it is purported to produce. The early exposure to tobacco smoke and late manifestation of lung cancer among smokers, seem, at least superficially, to fulfill this condition. This does not, however, preclude the possibility that such patients who, many years after the initiation of smoking are diagnosed as having lung cancer, may have had the primitive cellular changes or anlage (as postulated by Cohnheim) before the advent of their smoking. However, no evidence has thus far been brought forth to indicate that the initiation of the carcinomatous process in a smoker who developed lung cancer antedated the onset of smoking.

COHERENCE OF THE ASSOCIATION.—A final criterion for the appraisal of causal significance of an association is its coherence with known facts in the natural history and biology of the disease. In the lung cancer-cigarette smoking relationship the following should be noted:

(1.) **Rise in Lung Cancer Mortality.**—The increases in per capita consumption of cigarettes (76, 138, 211, 239, 255) and the age-cohort patterns of smoking among males and females (151) are highly compatible with a real increase in lung cancer mortality.

(2.) **Sex Differential in Mortality.**—The current sex differences in tobacco use (151, 160), the pronounced differences in age-cohort patterns between males and females, particularly in the older age groups—over 55 (151) and over 50 (160)—and the more recent adoption of cigarette smoking by women (151, 344) are all compatible with the high male-to-female ratio of lung cancer mortality and also with the lower ratios of 30 years ago (130). Haenzel and Shimkin (149) developed a statistical model for determining whether the results of the retrospective and prospective studies

“were compatible with the information on distribution of lung cancer and thus valid for generalization to larger populations.” Applying their model of scheduled relative risks to data on cigarette consumption by age and sex derived from the Current Population Survey of 1955, their predicted male/female ratio came quite close to the observed ratio in the general population.

(3.) Urban-Rural Differences in Lung Cancer Mortality.—A number of sources in this country (90, 136, 148, 175, 238, 252) and overseas (82, 199, 335) have firmly established the existence of an urban excess in lung cancer mortality. Because of the possible implication of an air pollution effect, this urban lung cancer mortality excess has been cited as either being incompatible with the smoking-lung cancer hypothesis (178, 229) or minimizing its significance (69, 70, 71, 101, 190). The data of the studies of a number of authors have clearly shown, however, that although adjustment for smoking history does not equalize the urban-rural lung cancer mortality ratio (149), control on the urban-rural residence factor nevertheless leaves a large mortality risk difference between smokers and non-smokers. Haenszel has demonstrated this fact in his two population sample studies on males and females (147, 152). Mills and Porter (238) demonstrated a much greater effect of smoking on lung cancer mortality than the urban-rural factor. Stocks (335) also demonstrated that though smoking is not the sole factor, as manifested by a rural-urban gradient among non-smokers, it represented a much more preponderant factor in accounting for the lung cancer mortality than did presumed air pollution or at least urbanization. He noted that his regression lines on amount smoked were parallel for the different areas in England and North Wales and that the urban-rural mortality ratios declined from 2.3 among non-smokers and 2.5 among light cigarette smokers to unity among heavy smokers. The first prospective study of Hammond and Horn (162) also showed higher lung cancer mortality rates irrespective of residence. In Dean's second study in South Africa (70), in which he corrected the critical defect in his first study of not studying the smoking habits of the test populations, he continued to emphasize urbanization or air pollution as the major factor in lung cancer. A perusal of his data, however, shows that by controlling on smoking, the lung cancer mortality rates are doubled by the factor of country of origin; whereas, with country of origin controlled, the lung cancer risk increases from 3 to 20 times as the amount of cigarette smoking increases. After smoking patterns are controlled, the residuals in the urban over rural excess imply other factors, although the smoking factor preponderates in the urban-rural differences in lung cancer mortality in all of these studies. Thus the urban excess of lung cancer mortality is not incompatible with the smoking-lung cancer hypothesis.

(4.) Socio-Economic Differentials in Lung Cancer Mortality.—Distinct socio-economic differentials have been demonstrated convincingly in the epidemiology of lung cancer. Cohart (57) found a 40-percent excess of lung cancer incidence among the lowest economic class (both sexes) in the New Haven population, and the morbidity survey by Dorn and Cutler (90) demonstrated a distinct gradient by income class among white males, with the highest rates among the lowest income groups. In Denmark, Clemmesen and Nielsen, utilizing data derived from the Danish Cancer Registry, also

found a much higher incidence of lung cancer among males in the lower rental groups (55). In relation to the contribution which smoking makes to this differential, there is evidence that cigarette smoking may be inversely related to socio-economic status. The components of socio-economic status are, at best, difficult to define, compartmentalize, and measure. Direct inquiries of family income are rare and, when made, are subject to considerable error. Studies based on rental values, as in the Danish studies, express more adequately socio-economic status.

Another high correlate of income is educational achievement, which has been considered by Hammond in his current prospective study (161) in relation to smoking habits. Among males, the highest proportion of cigarette smokers (past or present) and the highest proportion of those smoking 20 or more cigarettes per day (past or present) were found in the group classified as "some high school education (but not high school graduates)," whereas the lowest proportion was found among college graduates. The highest proportion of ex-cigarette smokers (as of 1961-62) was among college graduates. Although the relation of smoking and educational level in women is more complicated, the group which had been to college also had the highest proportion of ex-smokers. Finally, college graduates had the next to the lowest proportion of heavy cigarette smokers. None of the female gradients was as sharp as those for the men.

Occupation has also been utilized as a measure of socio-economic status, but this measure obviously has severe limitations. No definitive study has been reported in which lung cancer has been correlated with occupation and smoking class; the current Hammond (157) and Dorn (88) prospective studies may ultimately yield definitive findings in this regard. However, some indirect evidence of a partial correlation between the observed higher lung cancer death rates in lower socio-economic groups may be found in Table 26 of the Survey of Tobacco Smoking Patterns in the United States (151). Keeping in mind that type of occupation is not a critical index of income, it will nevertheless be noted that the professional and farmer and farm manager groups had higher proportions of non-smokers among them than did the laborers and craftsmen. This finding is in the proper direction for compatibility with the socio-economic differential in lung cancer mortality but the disparity does not appear to be sufficient to provide a satisfying correction. In fact, in this U.S. study, analyses by amount of cigarettes smoked tended to obscure the ordering by social class. In Great Britain, however, the inverse relationship of socio-economic class to heavy cigarette smoking remained apparent (174). In the U.S. study, classification by industry showed the highest proportions of non-smokers to be in the professional and agricultural groups and the lowest among industries. Thus, though the measures are admittedly crude, they are compatible with the socio-economic differential in lung cancer mortality.

(5.) The Dose-Response Relationship.—If cigarette smoking is an important factor in lung cancer, then the risk should be related to the amount smoked, amount inhaled, duration of smoking, age when started smoking, discontinuance of smoking, time since discontinuance, and amount smoked prior to discontinuance. Herein lies the greatest coherence with the known facts of the disease. In almost every study for which data were adequate

and which was directed to amount of smoking, duration of smoking and age when smoking was begun, the associations or calculated relative risks (direct or indirect) revealed gradients in the direction of supporting a true dose effect. Where discontinuance, time since discontinuance, and amount smoked prior to discontinuance were considered in either retrospective studies or, with more detail, in prospective studies, these all showed lower risks for ex-smokers, still lower risks as the length of time since discontinuance increased, and lower risks among ex-smokers if they had been light smokers. These findings have been described in detail in the section on Retrospective Studies.

Some contradictory information has been presented in regard to inhalation of tobacco smoke. This is the lack of association between inhalation and lung cancer as noted by Doll and Hill (82) alluded to earlier. These authors have begun collecting data (in their prospective study) on inhalation for the mortality experience since 1958. These data are not presently available (80). However, until the current ongoing prospective studies will have yielded information on this point in regard to lung cancer, four retrospective studies provide information on inhalation contrary to the Doll and Hill early negative findings (38, 211, 222, 313). In two of these (222, 313) inhalation and amount of smoking were considered and led to the provocative finding that with increase in daily amounts of cigarettes smoked the differences in risks between inhalers and noninhalers diminished. There is no immediate explanation for this apparent discrepancy.

Hammond has studied the smoking habits of the men and women in his current prospective study quite intensively (160). He has observed that the majority of men (92.9 percent) who smoke cigarettes inhale, and of these the majority inhale "moderately" to "deeply." Pipe or cigar smokers inhale rarely. Combination smokers (i.e., cigarettes in combination with pipes and/or cigars) inhale in proportions intermediate to these. These findings become compatible with the hypothesis that the degree of inhalation accounts for a gradient of lung cancer risks, high to low, for smokers of cigarettes only, combination smokers, and pipe or cigar smokers (Table 5). An explanation of the diminishing differences in risks between "inhalers" and "non-inhalers" with increase in amount smoked might be obtained if a more objective measure of inhalation were available.

(6.) Localization of Cancer in Relation to Type of Smoking.—Although historically a relationship between cancer and smoking was suspected by Holland (176) and Soemmerring (322) with reference to the lower lip, it was not until the systematic, controlled study of lung, lip, pharynx, esophagus, colon and rectum cancers in relation to types of smoking by Levin in 1950 that significantly distinctive associations between localization of the cancer and type of smoking were elicited (207). Levin noted that statistical significance was achieved for cigarette smoking and lung cancer and for pipe smoking and lip cancer and stated, "It is somewhat surprising that type of smoking is the associated factor, rather than the actual use of tobacco." Since then other studies have pointed up the relationship between type of smoking and localization of cancer. Sadowsky (301) in relative risk estimations of types of smoking and cancer site, also noted the highest significant values for cigarettes with lung, larynx and esophagus; for pipes with lip.

tongue and oral cavity; and for cigars with tongue and oral cavity. The complexities involved in a rational explanation for these phenomena are legion, especially since critics of the smoking-lung cancer hypothesis would point to no phenomenal rise of laryngeal cancer (only a slight rise for whites between 1930 and 1955) in the face of increased cigarette consumption. Although among cigarette smokers, the relative risk of mortality from lung cancer is presently greater than the relative risk for laryngeal cancer, the reverse seems to be true among cigar and pipe smokers (Chapter 8, Tables 19 and 24). Furthermore, the per capita rise in cigarette consumption has been accompanied by a concomitant decline in consumption of pipe and cigar tobacco, the smoke of which was not deeply inhaled. It is thus conceivable that the increase in cigarette consumption (and decline in cigar and pipe smoking) could affect an increase in lung cancer more significantly than in laryngeal cancer.

Finally, there is no reason to assume that the susceptibility of the larynx to cancer equals that of the bronchus. Thus, a reasonable explanation for the difference in localization and relative risk is apparent, especially when it is known that in certain industrial exposures in which the irritant is inhaled and lung cancer is associated with such inhalation (chromates), laryngeal and tracheal cancer is rare. It is, on the other hand, easier to visualize a mode of action for pipe and cigar tobacco in production of lip and tongue and other oral cavity cancers. Thus, none of these considerations detract from the coherence of the association between cigarette smoking and lung cancer.

HISTOPATHOLOGIC EVIDENCE

In earlier sections of this Chapter it has been noted that the application of tobacco extracts, smoke or condensates to the lung or tracheobronchial tree of experimental animals has failed to produce bronchogenic carcinoma, except possibly in dogs (289). In addition, no animal experiments have thus far been devised to duplicate precisely the act of smoking as it is practiced by man. However, that the lungs of experimental animals are susceptible to carcinogens, particularly polycyclic aromatic hydrocarbons isolated from tobacco smoke, has been demonstrated by a number of workers (5, 197, 302). Of immediate import to the smoking-lung cancer relationship is the observation that the histopathologic characteristics of the cancers thus produced are similar to those observed in man and are predominantly squamous in type. Furthermore, certain bronchial epithelial changes, sequentially observed prior to the malignant changes in animals exposed to these carcinogens are similar to those in the bronchial epithelium of human smokers (9). In this latter extensive and well-controlled study, these changes were rarely seen among non-smokers, but increased in frequency and intensity with the number of cigarettes smoked daily by individuals without lung cancer and were most frequent and intense in patients dying of lung cancer (Table 6 of this Chapter). Ex-cigarette smokers and pipe and cigar smokers yielded a higher frequency of such cellular changes than non-smokers but less than did current cigarette smokers. Thus, the histopathologic evidence derived from laboratory and clinical material support the cigarette smoking-lung cancer hypothesis.

CONSTITUTIONAL HYPOTHESIS

GENETIC CONSIDERATIONS.—Thus far in the evaluation, the Committee has considered whether the available data are consistent with the hypothesis that smoking causes cancer of the lung. The analysis must consider with equal attention the alternative hypothesis that both the smoking of cigarettes and cancer of the lung have a common cause which determines both that an individual shall become a smoker and also that he shall be predisposed to lung cancer. This has often been called the constitutional hypothesis. However, one should distinguish between the morphologic and physiologic characteristics of any individual due to a given environment and those characteristics (phenotype) that are due to an interaction of hereditary susceptibility and the environment.

The characteristics of individuals studied in relation to smoking have been numerous and varied. Some of them have been physical attributes such as physique or somatotype, height and weight and their ratios, masculinity, anthropometric variables, physiologic variables (heart rate, pulse pressure, blood pressure, cholesterol levels), and physical activity; others have been psychosocial (including personality) in character (Chapter 14). Cigarette smokers have been described as consuming more alcohol, drinking more black coffee, being more neurotic, engaging more often in athletics, and as being more likely to have at least one parent with hypertension or coronary disease (150, 214, 235). Many studies have been poorly designed and controlled, others have yielded contradictory findings, and still others, by admission of their authors, have included characteristics that could either have been acquired or have been produced by smoking. None of these constitutional attributes have been included in a prospective study of mortality from lung cancer fulfilling satisfactory epidemiological criteria, except for a breakdown by longevity of parents and grandparents in one study (159). The genetics of the characteristics themselves has not been determined, and adequate analysis of common genetic determinants in relation to the habit of smoking has not been attempted. No environmental determinants that would universally induce smoking and also produce the characteristics are evident (62) or have been proposed.

Fisher (118) has been foremost in calling attention to the possibility that cancer of the lung and the habit of smoking may be due to a common genotype. Selection of smokers then would automatically provide a population in which pulmonary cancer would appear on the basis of genetic susceptibility. Studies on the concordance of smoking in twins (122, 127, 281, 356) were used to support the hypothesis, since more monozygotic pairs have similar smoking habits than do dizygotic pairs. Although the data on the smoking habits of identical and fraternal twins raised apart are compatible with this hypothesis, the history of cancer in twins whose smoking habits are known has never been documented sufficiently to be useful in helping to resolve the question of whether the concept of the constitutional hypothesis is valid. Also information about the habits and medical history of other siblings, offspring, and parents is singularly scanty, and efforts to separate genetic factors from influences of the environment in such studies have been only rudimentary.

Although single genes may be involved in a few exceptional neoplastic and preneoplastic states such as retinoblastoma and precancerous colonic polyposis, genes for susceptibility to human cancer are usually multiple (48). Whether multiple genes for susceptibility may also be operating in the instance of cancer of the lung has not been established. The linkage (in a genetic sense) between multiple genes related to a habit (smoking) and a disease (lung cancer) in a heterogeneous population would require numerous coincidences with small probabilities. Also, in order to adhere to a consistent argument in explaining the reduced incidence of cancer of the lung in this group, it would be necessary to postulate another common genotype for those who smoke and subsequently terminate the habit. The argument becomes even more labored when multiple examples of identical genotypes for susceptibility to smoking and respective specific types of cancer are required by the hypothesis to explain the multiple types of cancer associated with smoking.

Since cancer of the lung occurs in both men and women who do not smoke, susceptibility genes acting alone or in combination with extrinsic or additional intrinsic factors can be effective without exposure to tobacco smoke. The occurrence of the disease, therefore, is not invariably linked to hypothetical genes responsible for the habit of smoking. Since susceptibility to cancer may be due to multiple genes with variable penetrance, and since the expression of these genes may change with environmental conditions, a minor portion of the cases of pulmonary cancer can be explained as the expression of genetic susceptibility in an environment excluding the habit of smoking.

Smoking then may add an extrinsic determinant which can increase the incidence of cancer of the lung beyond that which would otherwise prevail in the same population.

It should be emphasized that comparisons of lung cancer mortality in smokers, non-smokers and ex-smokers have been made on different populations. Thus, in considering the fact that the incidence of lung cancer appears to decrease when smoking is discontinued, it must be remembered that the population which can stop or does stop smoking may differ from that which continues. It is possible that the ability to terminate the habit may also be determined genetically.

In assessing the importance of a possible genetic influence in the etiology of lung cancer, it should be recalled that the great rise in lung cancer incidence in both men and women has occurred in recent decades. This points either to a change in the genic pool, or to the introduction of an agent into the environment, or a quantitative increase of an agent or agents capable of inducing this type of cancer. The genetic factors in man were evidently not strong enough to cause the development of many cases of lung cancer under environmental conditions which existed half a century ago. In terms of what is known about rates, pressures, and equilibria of human mutations the assumption that the genome of man could have changed gradually, simultaneously and identically in many countries during this century is almost inconceivable.

Smoking may be placed more properly in the role of an environmental determinant than as part of the phenotype of the pluripotential gene or genes, interacting with the environment and resulting in cancer of the lung.

Current evidence is compatible with the opinion that genetic factors play a minor role compared to the contribution of the smoking habit in the etiology of lung cancer today.

EPIDEMIOLOGICAL CONSIDERATIONS.—Although evidences for the constitutional hypothesis are, at present, either tenuous or actually lacking, the basic philosophical and logical prerequisites for this hypothesis are contradicted by a number of well-established observations (62):

(1.) Lung Cancer Mortality.—Lung cancer mortality has been increasing in the last 50 years and much more in males than females. This increase could be due to either an environmental change or a mutation. Since an unchanging constitutional makeup cannot of itself explain the increase, we must postulate either that there are genetic differences which make some individuals sensitive to a new environmental factor (not tobacco), or that differences in constitutional makeup are not genetic but the result of differential exposure to some new factor that predisposes to lung cancer and creates the desire to smoke, or that the mutation has produced an increased susceptibility and a desire to smoke. For the first two postulates a new environmental factor, other than tobacco, is required. Such a factor, it must be remembered, must be correlated with lung cancer as highly as are cigarettes and also highly correlated with cigarette consumption. None has yet been found. In order to account for the magnitude of the lung cancer mortality increase, the third postulate would require a mutation rate which far exceeds any observed.

(2.) Tobacco Tars.—Tobacco tars have been found to be carcinogenic for experimental animals. Although carcinogenicity of tobacco tars has not been demonstrated in man, the constitutional hypothesis would require that they are not, and that the association with lung cancer in man of substances found to be carcinogenic for experimental animals is a coincidence.

(3.) Pipe and Cigar Smoking.—Pipe and cigar smoking appears to have a higher correlation with laryngeal and oral cancer than with lung cancer. The constitutional hypothesis would require that there shall be two constitutional makeups, one predisposing to cigarette smoking but not to pipe and cigar smoking and also to cancer of the lung; the other predisposing to tobacco consumption in any form and to cancer of the larynx and oral cavity but not to cancer of the lung. The alternative within this hypothesis would require that the special constitutional makeup predisposes to cigarette smoking and lung cancer, but that tobacco smoke, whether from cigarettes, cigars or pipes, is carcinogenic for the larynx and oral cavity but not for the lung. These requirements are unrealistic.

(4.) Ex-cigarette Smokers.—Ex-cigarette smokers have a lower lung-cancer mortality and a gradient is noted by length of time smoking has been discontinued and by the amount previously smoked. This would require complicated genetic interrelationships if the constitutional hypothesis were to be satisfied. A simpler hypothesis, which involves a causal relationship be-

tween smoking and lung cancer, but recognizes differences, defined or ill defined, between smokers and non-smokers may be stated as follows: There are factors in the individual acquired early (or genetic) which predispose to cigarette smoking, and cigarette smoking by direct action of smoke on the bronchial epithelium is a major factor in producing lung cancer in susceptible individuals.

A detailed discussion of the significances of the data on psycho-social, constitutional, and physical characteristics of smokers and non-smokers is presented later in this report (Chapters 14 and 15). The role of the genetic factor in carcinogenesis has been discussed earlier in this Chapter.

OTHER ETIOLOGIC FACTORS AND CONFOUNDING VARIABLES

Throughout this evaluation, it has been recognized that a causal hypothesis for the cigarette smoking-lung cancer relationship does not exclude other factors. This is attested to by the fact that a small but not insignificant percentage of cases of lung cancer does occur among non-smokers. Some estimates in retrospective studies and most of the prospective studies indicate that approximately 10 percent of the lung cancer cases are in non-smokers. Doll (78) has provided a higher estimate of 20 percent. Furthermore, the inability to account for the higher lung-cancer incidence in the lower economic classes entirely by disparities in smoking habits, which do exist, does imply other causal factors.

Several other possible etiologic factors which have been explored merit discussion. These include occupational hazards, urbanization or industrialization and air pollution, and previous illness.

(1.) Occupational Hazards.—In an extensive review of the literature on lung cancer in chromium and nickel workers and in uranium miners, Seltser (318) found the evidence for an excess of lung cancer mortality among chromate workers highly consistent. However, because of the smallness of the numbers involved, caution must be exercised in any calculation of the magnitude of the risk. Furthermore no evidence has been presented either for or against an excess risk of lung cancer among workers exposed to other chromium products or chromium mining. The evidence for an excess risk among nickel processing workers in refineries was even more consistent than for chromate workers. The lung cancer risk was five times greater among nickel processing workers than in other occupational groups in the same area (the risk for nasal cancer was 150 times higher). Among uranium miners an excess risk is apparent (360), and is greater than in certain other miners of similar ores without the high radioactivity component (361). Although the induction of lung cancer by radio nuclides is probable in man, the evidence is not as firm as in animals.

In addition, Doll has found a significant excess of lung cancer deaths among coal gas workers (81) and asbestos workers (77). In another review article, Doll (79) has added arsenic and hematite as suspects to the list, with isopropyl oil, beryllium, copper, and printing ink as possible risks.

The evidence for the possible role of arsenic as a factor in the etiology of lung cancer has been summarized by Hueper (178), and Buechley (45) has

recently suggested that it merits epidemiological investigation. The chief points of evidence cited include 1) the universality of arsenic in many ores and in the atmospheres in and near smelters; 2) the widespread use of arsenic as an insecticide and the consequent exposure of workers in insecticide manufacture, agricultural workers, and those handling or consuming crops with arsenic residues; and 3) reports of a relatively high incidence of lung cancers in people living around smelters processing arsenic-containing ores, and also in vineyard workers exposed to large amounts of arsenical pesticides and consuming large amounts of arsenic-contaminated beverages.

It is noteworthy that for the nickel and chromate material the lung cancer mortality is referable to a high exposure period in the respective industries, a situation which probably does not prevail today. Of greater importance is the regrettable fact that in none of these occupational hazard studies were smoking histories obtained. Thus the contribution which smoking, as a contributory or etiologic factor, may have made to the lung cancer picture in these risk situations is unknown. However, the series of cases in non-smoking chromate workers is large enough to exclude the possibility that cancers of the lung in chromate workers develop only in those who smoke cigarettes. Nevertheless, it must be emphasized quite strongly that the population exposed to industrial carcinogens is relatively small and that these agents cannot account for the increasing lung cancer risk in the general population.

(2.) Urbanization, Industrialization, and Air Pollution.—The urban-rural differences in lung cancer mortality risk, though small and accounted for in part by differences in smoking habits (see section entitled Coherence of Association), nevertheless may have a residual which implies other etiologic factors in an urban environment. This has been the explanation offered in the studies by Stocks and Campbell (337) and Stocks (335) who noted a gradient among non-smokers, light cigarette smokers and pipe smokers by density of population but who found no gradient among heavy smokers. Less direct evidence was derived by Eastcott (101) and Dean (69, 71) who found higher lung cancer rates among migrants from Great Britain to New Zealand, South Africa and Australia, respectively. Their inferences were that these immigrants had had significant exposure to air pollution in England prior to coming to the Commonwealth countries. Unfortunately, these interpretations were untenable for there was no individual case-control information on tobacco consumption. A correction of method by Dean in a later study (70) did elicit smoking histories and revealed a marked influence of cigarette smoking but a significant though lesser factor of urbanization. Doll's study of non-smoking lung cancer cases (78) revealed no differences in risk among men and women and in residents of areas of different population density. His findings cannot be considered to be conclusive of a negative result, for density of population need not necessarily be highly correlated with pollution. In a more recent, as yet unpublished, paper by Stocks* a

*Stocks, P.: A Study of Tobacco Smoking, Air Pollution, Residential and Occupational Histories and Mortality from Cancer of the Lung in Two Cities. Inter-regional Symposium on Criteria for Air Quality and Methods of Measurement, W.H.O., Geneva, Switzerland, August 6-12, 1963.

mathematical model embodying amount of smoking, age, air pollution measurements by specific carcinogenic constituents, proportion of life spent in country and town, and lung cancer mortality was applied to the data derived from Belfast and Dublin. The lung cancer death rates were found to be compatible with an hypothesis that in Belfast about two-thirds of the deaths of men resulted from cigarette smoking and one-third from air pollution by smoke and, in Dublin, 75 percent from cigarette smoking and 25 percent from air pollution. These data are not offered as proof but represent the approaches necessary for future research in the area of proportional contributions to lung cancer mortality. Such applications may be useful in determining the role of air pollution in such disparate lung cancer mortality rates between, for example, the United States and Great Britain when adjustments in smoking habits still do not eliminate the difference completely.

Two studies (147, 152) have also indicated that migration of rural people into urban areas subjects them to lung cancer risks greater than for lifetime urban residents. This effect is noted among non-smokers as well. The least that can be said is that the intensity of urbanization or industrialization may have a residual influence on lung cancer mortality.

(3.) Previous Respiratory Infections.—Relatively few soundly designed studies have tested the effect of prior respiratory disease, particularly infections, on the development of lung cancer.

Winternitz (371) called attention in 1920 to proliferative changes in cases of post-influenzal pneumonia similar to those seen in invasive, malignant neoplasms of the lung but this report stimulated relatively few epidemiologic observations. In the retrospective study of the smoking-lung cancer relationship by Doll and Hill (82) inquiry into a history of previous respiratory infections led to finding a significant excess of antecedent chronic bronchitis and pneumonia among lung cancer patients even when smoking class was controlled. However, because a collateral comparison with another control group of patients, for whom a lung cancer diagnosis was subsequently found to be in error, failed to reveal a difference, Doll and Hill concluded that either "chronic bronchitis and pneumonia predispose to a whole group of respiratory disorders . . . or that patients with respiratory disorders recall previous chronic bronchitis and pneumonia more readily than do patients with diseases with other symptoms." However, almost simultaneously Beebe (20) investigated the relationship between mustard gas exposure, chronic bronchitis, pneumonia and influenza and lung cancer, and Case and Lea (53) between mustard gas exposure and/or chronic bronchitis and lung cancer. Smoking histories were controlled in these studies. Beebe found no evidence of an increased lung cancer risk with an antecedent history of influenzal pneumonia and primary pneumonia but there did appear a highly suggestive association between mustard gas exposure and lung cancer. No relationship between chronic bronchitis and lung cancer was noted. Case and Lea, however, interpreted their findings to mean a sequential relationship between mustard gas exposure, chronic bronchitis, and lung cancer. The lung cancer risk was doubled by pre-existing chronic bronchitis. Doll,

in a later review (76), however, indicated that since the smoking-lung cancer relationship is stronger than the chronic bronchitis-lung cancer relationship, chronic bronchitis is not a necessary intermediate pathogenetic process. The failure of the Beebè study to affirm the Case and Lea findings in regard to chronic bronchitis may lie in the problem of differences in British and American diagnoses of chronic bronchitis.

In an epidemiologic approach to other factors in lung cancer risks, Denoix et al. (72) studied 160 characteristics. Among other factors, much less strongly associated with lung cancer than smoking of cigarettes, they found a history of exposure to war gas and chronic bronchitis to predispose to lung cancer. The war gas component was strong enough to double the risk of lung cancer even with control on smoking class.

Thus, the observations on previous respiratory illness are too few in number to place any degree of assurance on a relationship, but the studies by Case and Lea and by Denoix et al. remain interesting.

(4.) Other Factors.—Numerous other factors, such as coffee drinking, alcohol consumption, nutritional status, and beer drinking, have been studied and some associations with lung cancer have been found, but none of them does more than double the risk (and sometimes these are noted to be associated with lung cancer via the smoking component) as compared to the 9- to 10-fold risk in average cigarette smokers and the 20+ fold risk in heavy smokers.

Conclusions

1. Cigarette smoking is causally related to lung cancer in men; the magnitude of the effect of cigarette smoking far outweighs all other factors. The data for women, though less extensive, point in the same direction.

2. The risk of developing lung cancer increases with duration of smoking and the number of cigarettes smoked per day, and is diminished by discontinuing smoking.

3. The risk of developing cancer of the lung for the combined group of pipe smokers, cigar smokers, and pipe and cigar smokers is greater than in non-smokers, but much less than for cigarette smokers. The data are insufficient to warrant a conclusion for each group individually.

ORAL CANCER

Epidemiological Evidence

The suspicion of an association between use of tobacco and oral cancer dates back to the early 18th Century when Holland (176) first noted cancer of the lip among users of tobacco. In 1795, Soemmering (322) made the same observation. In the present era, additional clinical observations have been recorded. The investigators noted the proportions of users of the

various forms of tobacco among the various cases of oral cancer and found clues to a relationship. These observations lacked controls. Notable among these reports are the review by Haase (142) emphasizing location of the cancer of the lip and mouth according to where the pipe was held; the analysis by Ahlbom (1) by specific type of tobacco use in relation to site; and the work of Potter and Tully (280) which indicated an increase in risk of oral cancer with increase in smoking. From the first two studies mentioned (1, 142), it is immediately apparent that any reasonably meaningful study of the relationship between tobacco and oral cancer must take into account not only the specific sites (lip, cheek, gingiva, tongue, oropharynx, etc.) but also the precise form of tobacco use (pipes, cigars, cigarettes, chewing tobacco, snuff, etc.).

Of additional interest is the specialized use of tobacco as a component of betel nut quids in certain areas of the world: several observations suggest an association with oral cancer (66, 67, 269, 319). In contrast, observations of populations using betel nut quids without tobacco (104, 234, 367) in certain other areas of the world show no association of betel nut with oral cavity cancer.

More formalized case-control or retrospective studies varying in specific approach, in suitability of controls and in sample size have appeared between 1920 and the present (26, 41, 103, 202, 207, 221, 237, 245, 272, 301, 306, 314, 326, 355, 369, 385, 387, 388, 398). These studies are described in Table 10 which includes general smoking data, for the most part, on combinations of specific sites of oral cancer. A number of these investigations either did not separate the several sites of the oral cavity because of the small number of cases for each site or, upon separation into such sites, found the smoking classes too numerous for testing of significance (26, 221, 237, 388). Since associations with form of tobacco use varied according to smoking classes and, wherever possible, to specific sites (Table 10A), in this summary table, a statistically significant positive association is designated by a plus sign, whereas the lack of such an association is designated by a minus sign. A plus-minus sign indicates that there was some evidence of an association which was not, however, statistically significant.

It will immediately be noted that in 10 of 17 studies all oral sites were combined in an attempt to elicit an association with forms of tobacco-use (26, 202, 221, 237, 245, 272, 306, 314, 326, 388). Although eight of these showed positive association, they were so scattered among the several forms of tobacco use that little can be derived from them. Furthermore, distinctly specific site associations may be masked by such combinations. In examining the data for specific site localizations and forms of tobacco use, several associations become clarified.

It would appear that pipe smoking is associated with lip cancer in all six studies in which this site and form of tobacco use was analyzed (41, 103, 207, 301, 378, 385).

In one additional study (237) an association with pipe and cigars com-

TABLE 10.—Outline of retrospective studies of tobacco use and cancer of the oral cavity

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Broders 1920	(41)	U.S.A.	M F	526 11	Series of clinic patients with epithelioma of the lip. 80.5% tobacco users 75.1% smokers 0.9% cigarettes 24.0% chew 59.0% pipes 38.5% cigars	500	Series of clinic patients without epithelioma of the lip. 78.6% tobacco users 75.2% smokers 44.4% cigarettes 13.4% chew 28.6% pipes 44.0% cigars	Apparently by interview in the clinic.
Lombard and Doering 1928.	(221)	U.S.A.	M-F	217	Clinic patients with cancer of various sites. Site breakdown and smoking data not clear.	217	Clinic patients without cancer, matched by sex and age. Smoking data not clear.	Personal interview by investigators in clinics.
Bigelow and Lombard, 1933.	(26)	U.S.A.	M-F	(?)	Clinic and hospital patients, apparently several hundred. 14.2% non-users 36.4% excessive users (Table 111).	(?)	Patients without cancer, in comparable numbers. 26.5% non-users 24.0% excessive users (Table 111).	Personal interview in hospitals and clinics.
Ebenius 1943	(103)	Sweden	M F	439 33	Clinic patients with cancer of the lip. 79.7% tobacco users, M 57.6% tobacco users, F (all pipes) 61.8% pipes, M 47.4% chew or use snuff, M 12.9% cigars and cigarettes, M		Not defined. 68.7% tobacco users, M 1 to 2% tobacco users, F 22.9% pipes, M 60.7% chew or use snuff, M 32.8% cigars and cigarettes, M	
Levin et al. 1950	(207)	U.S.A.	M	143	Cancer institute patients with cancer of the lip. 84.5% smokers 45.3% cigarettes 48.1% pipes 26.5% cigars	51	Cancer institute patients with non-cancer diseases of same site. 74.0% smokers 43.0% cigarettes 30.7% pipes 34.9% cigars	Routine clinic interview.
Mills and Porter 1950	(237)	U.S.A.	M	124	Deaths from cancer of oral cavity in Cincinnati and Detroit, 1940-45 and 1942-46, respectively. 35.5% cigarettes only 54.8% pipes, cigars, or combinations.	185	Sample of population of Columbus, Ohio, and in same proportion of color, sex, and age as in cases. 32.4% cigarettes only 29.7% pipes, cigars, or combinations.	From next of kin of deceased by mail questionnaire or by personal interview. Controls by house-to-house interview.

Moore et al. 1953	(245)	U.S.A.	M	112	Patients over 50 yrs. old since 1951 with cancer of oral cavity. 58.0% chew 42.0% pipes 38.4% cigars and cigarettes	38	Patients of same age groups with benign oral lesions or benign surgical conditions. 31.6% chew 47.4% pipes 52.6% cigars and cigarettes	Personal interview of controls; for cases, next-of-kin were visited or contacted by letter.
Sadowsky et al., 1953	(301)	U.S.A.	M	1,136	Hospital patients with oral and pharyngeal cancer, 1938-43. 42.3% cigarettes only 4.0% cigars only 17.8% pipes only 28.2% mixed	615	Patients with illness other than cancer. 53.3% cigarettes only 3.4% cigars only 7.0% pipes only 23.1% mixed	By trained lay interviewers.
Sanghvi et al., 1955	(306)	India	M F	657 81	Hospital patients with cancer of oral cavity and pharynx. 38.8% smoke and chew, M; 3.7% F 46.7% smoke only, M; 6.2% F 11.7% chew only, M; 64.2% F 2.7% neither, M; 25.9% F (Smoking is of bidis among both cases and controls.)	M 288 F 112	Hospital patients with diseases other than cancer. 24.0% smoke and chew, M; 0% F 50.0% smoke only, M; 6.3% F 8.7% chew only, M; 23.2% F 17.3% neither, M; 70.5% F	Personal history interview in hospital.
Ledermann 1955	(202)	France	M	240	Patients with cancer of oral cavity & pharynx. 4.6% non-smokers 23.4% >20 cigarettes per day	62	Patients with cancer of skin, bone, muscle. 17.2% non-smokers 18.6% >20 cigarettes per day	
Wynder et al., 1957	(378)	U.S.A.	M F	543 116	Patients with cancer of oral cavity 3% non-users, M; 47% F 20% cigars, M 11% pipes, M 8% mixed, M 17% chew, M 57% cigarettes, M; 53% F 29% >35 cigarettes per day, M 34% >16 cigarettes per day, F	M 207 F 232	Patients with cancer of other sites and benign diseases. 10% non-users, M; 70% F 13% cigars, M 6% pipes, M 8% mixed, M 8% chew, M 63% cigarettes, M; 30% F 17% >35 cigarettes per day, M 11% >16 cigarettes per day, F	Personal interviews in hospital or clinic.
Wilkins and Vogler 1957.	(369)	U.S.A.	M F	37 44	Clinic and hospital patients with cancer of gingiva. 32% chew or chew and smoke, M 20% smokers, M 52% use snuff, F 9% smokers, F		None.	Clinic and hospital histories.
Schwartz et al.	(314)	France	M	332	Hospital patients with cancer of oral cavity and pharynx. 16.4% non-smokers 62.7% cigarettes only 3.3% pipes only	608	Hospital patients with non-cancer illness and accident cases, matched by age. 23.4% non-smokers 58.2% cigarettes only 3.0% pipes only	Questioned about the same time by the same interviewer.

TABLE 10.—Outline of retrospective studies of tobacco use and cancer of the oral cavity—Continued

Investigator and year	Reference	Country	Sex	Cases		Controls		Collection of data
				Number	Method of selection	Number	Method of selection	
Wynder et al. 1957	(388)	Cuba	M F	178 34	Hospital clinic patients with cancer of oral cavity and pharynx. 4% non-smokers, M; 24% F 45% cigarettes predom., M; 62% F 33% cigars predom., M; 12% F	M 220 F 214	Patients in same clinics with non-malignant conditions, matched by sex and age. 16% non-smokers, M; 66% F 45% cigarettes predom., M; 27% F 22% cigars predom., M; 6% F	Personal questioning in clinic, all by 2 interviewers.
Wynder et al. 1957	(385)	Sweden	M F	115 140	Hospital patients with cancer of oral cavity and pharynx. 36.5% cigarettes, M 13.0% cigars, M 12.2% pipes, M 15.7% mixed, M	M 115 F 156	Patients in same hospital with cancer of sites other than oral, pharynx, larynx, lung, esophagus and breast. 36% cigarettes, M 9% cigars, M 16% pipes, M 13% mixed, M	Personal interview in hospital; and medical histories.
Peacock et al. 1960	(272)	U.S.A.	M F	25 20	Hospital patients with oral cancer 55.6% chewed or used snuff over 20 years.	M 74 F 72	Patients in same hospital without oral cancer and 117 male and 100 female randomly selected outpatients. 32.6% of first group, 43.3% of second group chewed or used snuff over 20 years.	Personal interviews.
Staszewski 1960	(327)	Poland	M	383	Male patients with oral cancer 5.7% non-smokers 72.8% "heavy" smoking index 72.3% cigarettes only 12.8% pipes and/or cigars	912	Male patients with other cancer and non-cancerous conditions. 17.3% non-smokers 49.0% "heavy" smoking index 60.5% cigarettes only 11.1% pipes and/or cigars	Personal interviews.
Vogler et al. 1962	(355)	U.S.A.	M F	188 92	Clinic patients with cancer of lip and oral cavity. 32.9% chewers, M ¹ 22.9% excessive chewers, M 72.0% snuff dippers, F 41.3% excessive snuff dippers, F 90% tobacco users, M + F	M 521 F 1,064	Patients of same clinic with other cancer or non-malignant conditions. 6.1% snuff dippers, F ² 56% tobacco users, M + F	Personal interviews in clinic.

¹ Estimate of prevalence of use.² Due to varying tabular treatment of the data, the percentages of tobacco users are not all based on the same numbers of cases.