An Evaluation And Review Of The Report On Smoking And Health By The Advisory Committee To The Surgeon General

Introduction

The Advisory Committee to the Surgeon General has concluded that evidence in existence now establishes beyond all reasonable doubt that smoking of cigarettes leads to definite effects on the health and mortality of smokers. Its report maintains that this conclusion is reached on scientific evidence and by scientific reasoning. Yet, other investigators have reviewed the same evidence in the past and have come up with different answers. It is obvious, therefore, that in evaluating this report we have to examine the process by which the committee reached its conclusions. However, to do so imposes a difficult problem. The committee's attitude toward and handling of evidence reflects a certain scientific disposition which has become prevalent in the last three decades in many public health problems. During that time a bewildering number of statements, unjustified by solid evidence in the views of many, have been made about some effects on health of air and water pollutants, foods, low dose diagnostic radiations, certain drugs, and a variety of other agents. While the judgment of the committee may be understood best in the content of current epidemiological practices, it would take us too far afield to review the status of epidemiology today. Also, the need here is not so much to understand why such a report could have been written but if the conclusions reached by the committee really are warranted.

In organizing my own views of the report I have chosen therefore to examine first the implicit and explicit attitudes toward scientific judgments

contained in the report. Only after having clarified its premises can we evaluate the way in which the committee organized the old evidence and used it to support various conclusions. However, all judgments in the report can not be accounted for completely by the basic scientific attitude of the committee. A number of technical shortcomings exist which tend to mislead as well as detract from the importance of some data. These technical shortcomings are discussed separately and integrated with the committee's own evaluation of its criteria and evidence.

Finally, the very shortcomings of the report point to a number of investigations which would, if properly executed, clarify the whole issue on smoking and health. The most important of these is outlined as an appendix to this review.

The Implicit Attitude Toward Scientific Conclusions

In the realm of public health the physician as well as the scientist is often asked to make decisions. It is necessary to keep in mind when such decisions are motivated by purposes of science and when they are motivated by public health necessities and aims.

The scientific decision process seeks to derive statements of fact about the existence of phenomena or associations for no other reasons than to unearth and state them. This does not mean that the scientist seeks to avoid contaminations with extraneous thoughts for any purist reasons. He has learned that correct statements of fact bestow upon him immense powers to manipulate and modify nature to his and man's benefit and satisfaction. He has learned also from history of science that to be effective the scientific decision game must be played to stringent and hard headed rules. Primary among these is that the decision process can not be influenced by extraneous motives. It does not matter whether these motives arise from the noblest, selfless aspirations or from the basest drive for self aggrandization. Any possible influences on scientific decisions that are not relevant to the problem itself are direct or implicit sources of bias. Included in such sources of biases are considerations of the social or political consequences of the scientific decision itself. The care with which unnecessary criteria are eliminated from the scientific process is reflected in the manner of presenting its conclusions.

1. The conclusion has a reasonably high probability of being correct.
2. Alternative conclusions either have a high probability of being incorrect or have a much lower probability of being correct than the preferred statement.
3. Sources of bias which are extraneous to the evidence itself have been eliminated from any influence on the decision process.

It is generally recognized that special care must be taken if decisions are based predominantly on evidence of statistical associations between agent and disease. For many purists such an association does not reach the status of a scientific fact until the disease itself can be called forth or prevented under controlled conditions. Correct conclusions as to cause and effect have been drawn purely from epidemiological coincidence in the past. These occasions have been more than counterbalanced by the many instances in which exclusive reliance on statistical association has proven to be misleading. Most of the well accepted epidemiological findings have been confirmed by experiments that tested the suggested associations under laboratory conditions.

In contrast to the purely scientific, the public health decision concerns itself with whether or not action should be taken. Such a decision may be about the safety of a particular product with the eventual intention of either permitting it on or withdrawing it from the market place. A decision on whether or not a patient has a certain disease falls within this realm. The emphasis on such decisions is clearly with respect to the medical activity which they call forth. Consequently criteria for decision are:

1. Whether or not an action is reasonably based on the evidence and
2. Whether or not harm would befall a person or a community if such actions were not taken.

It is quite clear, however, that such a decision need not be taken only on firmly established scientific facts. On the contrary, decisions may be taken in situations where scientific facts would call for entirely different conclusions. A common incidence of this type exists every time a physician has to choose between two or more possible diagnoses. Ordinarily he decides for that diagnosis which has the highest probability of being correct. However, if the consequences of not treating the patient for the disease indicated by the preferred diagnosis are trivial and if the consequences of not treating the patient for the less likely disease are severe, the physician may be guided by the consequences of his actions rather than by the largest probability of making the correct statement. He does so not because he is uncertain in any way of his preferred diagnosis but because consequences of not making the correct decision in this case would be to the great detriment of the patient. In a similar way the Public Health Service may decide to withdraw from consumption a given product because residue of a pesticide or herbicide are found on it. There may not exist any proof that the concentration of the chemical agent found on this product is in any way harmful to man. But if a presumption exists that it might perhaps lead to harmful effects, the Public Health Service can, does, and indeed should withdraw such a product from consumption if such action does not interfere with other public needs. It is the clear duty of the physician, whether he makes

a decision for a patient or for the community, to be guided by certain risks he might take in not instituting a course of action which will protect the patient or the community.

The distinction which we have drawn here is one which unfortunately was not apparent to the committee. The introduction to the report and indeed the publicity given it proceeds on the presumption that the committee has reached a decision in a scientific sense. However it is quite clear that basic criteria for decisions were based on the public health point of view. For instance, on page 32 we find the following statement:

> "It is established that male cigarette smokers have a higher death rate from coronary artery disease than non-smoking males. Although the causative role of cigarette smoking in deaths from coronary disease is not proven, the Committee considers it more prudent from the public health viewpoint to assume that the established association has causative meaning than to suspend judgment until no uncertainty remains."

The conclusions reached in the report can not be understood unless one realizes that the committee considered causality in terms of consequences of public health activities.

It is at the point of scientific versus public health attitude that interpreters of the data on smoking and health have failed to reach a common understanding and appreciation of their respective points of view. For the proponents of public action the demonstrated statistical association between smoking and increased incidence of mortality is sufficient to justify public concern and even legislative action. For the proponents of hard headed

scientific judgment, the statistical association does not represent adequate evidence on which to base conclusions. Therefore the public health orientation has led to the repetition of basically the same study demonstrating over and over again that certain statistical coincidences do indeed exist and the scientific orientation has kept on being disturbed by constantly recurring anomalies within the statistical evidence, by the lack of adequate methodology, and above all by the failure of laboratory experiments to produce positive evidence on the presumed effect of smoking.

Insofar as the report Smoking and Health purports to be a scientific evaluation of causality it must be judged on its scientific rather than its public health merits. The report maintains that this conclusion is reached on scientific evidence and by scientific reasoning without recourse to the fancied necessity to do something about an ill understood public health problem. If this is true then the logic and method used by the committee ought to stand up under rigorous critique. More so, it ought to establish a pattern for evaluation of epidemiological data that can serve as an example for the solution of similar problems in the future.

The Explicitly Stated Criteria for Proof of Causality

The major items on which the committee based its conclusions were:

1. An observed increase in the mortality rate due to lung cancer and certain other diseases over the last few decades and the association of this increase with an increased amount of smoking over the same time periods.

2. An excess incidence of mortality of cigarette smokers which appears during the comparison of groups of individuals called smokers and non-smokers.
3. An apparent dose response effect which is admittedly barely perceptible between no, light, and heavy smokers with respect to certain diseases.
4. Differences in types of cancer between cigarette, cigar, and pipe smokers.
5. Differences in cell types found in the lungs of smokers and non-smokers.

On the other hand, experimental proof of the association between smoking and mortality for these diseases or between smoking and shortening of the life period was completely negative.

Of these elements of proof the epidemiological findings serve as the major props. Therefore, the committee's judgment on the value of statistical association in epidemiological studies is crucially important. We find the following statement on page 20.

> "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 the attribute of agent and the disease, or effect upon health, a number of criteria must be utilized, no one of which is an all-sufficient basis 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."

Two key ingredients for scientific decisions have been omitted from this list of criteria. These are:

1. A reasonable demonstration that no other confounding factors could have accounted for the observed associations, and
2. The ability to demonstrate that the association does or does not exist under rigorous experimental conditions.

We should stress that these criteria are not matters of personal opinion. The ability of validating scientific assertions by both rejection of alternative hypotheses and experimental manipulation is firmly established in our scientific society and does not need any further arguments. One is really at loss what to make of these omissions. Insofar as the committee deems it worth while to discuss the meaning of causality at some length and refer to it repeatedly the omission is highly significant. One does not wish to malign the committee in any way, however, one is struck with the fact that existing experimental evidence appears to be negative. The conclusions of the report would have been weakened a good deal if results of laboratory investigations had been included with the criteria for establishing causality. It is true that examination of alternative hypothesis did take place, although only very cursorily and to some extent inadequately. Nevertheless the failure to include the critical evaluation of alternative hypothesis on the list of criteria is also a very definite shortcoming of the report.

The stated criteria are confusing in the extreme. (They are again discussed later in reference to the total evidence) They are not defined

until late in the report and then very inadequately. Also, these criteria do not appear in any authoritative scientific context nor are they commonly used. The impression is given that the criteria are discussed and validated in other places of the report. In fact, all through the report the reader is referred to other pages in which presumably he will be enlightened further. Often these references are misleading. Thus an impression of well established substance is created where none exists. This is immediately apparent when we read on (page 20):

> "These criteria were utilized in various sections of this report. The most extensive and illuminating account of their utilization is to be found in Chapter 9 in the section entitled "Evaluation of the Association between Smoking and Lung Cancer"."

When we turn to page 175 in Chapter 9 in which this section occurs we find that this section is introduced by two very scant paragraphs which read as follows:

> "It is not practical to attempt an experiment in man to test whether a causal relationship exists between smoking of tobacco and lung cancer. Such an experiment would imply the random selection of very young subjects living under environmental conditions as nearly identical as possible, and random selection of those who were to be smokers and those who were to be the non-smoker controls. Their smoking and other habits would need to be held constant for many years. Because of the relatively low incidence of lung cancer in the human population, both the test and the control groups would have to be very large."
>
> "As such an experiment in man is not feasible, the judging of causality must be made on other grounds. The epidemiologic method, when coupled with clinical and laboratory observations, can provide the basis from which judgments of causality may be derived."

This obviously is a belated apology for not having included an important scientific consideration. It is typical of this report that the critical reader is always referred to some other chapter or some other page to get a clarification of points which the committee considers very important. When the discussion of these criteria finally takes place it is unclear and muddled, as we shall see later.

Summarizing the criteria by which the committee proceeded we find the following:

1. The committee has stated certain criteria by which it will assign causal association in the recognition that statistical association is insufficient to establish causality.
2. The criteria listed by the committee are unclear and never are defined adequately.
3. Two important criteria, generally recognized as necessary to extend statistical association to scientific proof of causality are not mentioned at all. These are the possible consideration and rejection of alternative hypotheses and the actual demonstration by means of experiments that the association which is suggested by the statistics actually does exist.

Organization of the Available Evidence

Very little has to be said about the apparent association observed since the 1920's between the increase in cigarette smoking and the increase in deaths due to lung cancer and other diseases. It has been generally recognized that the increases of deaths due to degenerative causes has

been accompanied by decreases due to other diseases in the last few decades as well as by so many other environmental and social changes so that it would be impossible to ascribe this change in mortality pattern to any single factor. The committee makes a stronger case of this association than it should have.

Major emphasis is placed on the associations between smoking and disease as compared to the association between non-smoking and disease. Here a number of studies are considered which clearly indicate that among what populations were measured smokers seemed to have a higher incidence of disease than non-smokers. These studies have been amply criticized on a variety of occasions. The main points of criticisms have been:

1. That population on which these studies are based were highly selected and did not represent by any stretch of the imagination a representative sample of the population.
2. That the response and follow up rates in all the samples was very poor.
3. That certain anomalies exist in the death rates of these samples when compared to the death rate of the white male population in general which throws some doubt as to soundness and unbiasedness of the samples.

The committee does indeed consider these three objections. Some corrections and assumptions are made which are thought to adjust for various source of bias. Recognizing that one set of assumptions may be as good as any other set of assumptions little need to be said at this point. The fact that some of these assumptions would, if modified, lead to somewhat different conclusions are not stressed by the committee. However, the committee

certainly is free to make whatever assumptions it wishes to make and by and large these assumptions are defensible.

For what these observations are worth then (and there is some doubt whether these observations are worth it indeed) the evidence does indicate that in the groups studied smokers in general have a higher incidence of mortality from most diseases than do non-smokers.

The Fate of Alternative Hypotheses

While the committee did not list the evaluation of alternative hypotheses as one of its criteria of causality it did refer to it in the text. We find on page 190 under the heading of "Constitutional Hypotheses" the following paragraph:

> "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."

The committee does recognize the importance of alternative hypotheses even though it considers only one specific alternative. The gain in scientific acumen is, however, immediately wiped out by the next sentence:

> "This has often been called a constitutional hypothesis."

It is obviously untrue that the only alternative hypothesis that could explain the epidemiological findings is one referring to genetic causes.

The point here is not that we can't adduce other alternative hypotheses which are very reasonable and fall within this realm but that the committee has not considered them. This is extremely surprising. Two very outstanding and feasible hypotheses are immediately apparent. The first one is that some individuals live in a style of life which is inimical to good health and that smoking is one of the characteristics of this style of life. On the other hand, other individuals live a style of life which is generally considered healthy of which non-smoking is one of the ingredients. Thus the association one observes may not be between cigarette smoking and disease but it may be between a certain style of life and disease. While this hypothesis seems reasonable it is not mentioned by the committee. In fact, evidence presented in the report, if organized properly, could easily lead to the conclusion that cigarette smoking constitutes part of a behavioral syndrome which in itself appears to be associated with increase in death from certain causes. (These data are reviewed in the appended suggested experimental design) A second alternative hypothesis is not so much concerned with a common factor underlying smoking and non-smoking but seems to flow from the presented evidence rather easily. For what it is worth differences between cigarette smokers on one and pipe and cigar smokers on the other hand suggest, as an alternative hypothesis, that the association between smoking and disease is some byproduct of cigarette paper combustion. Although it is true that the contents of this combustion are not much different from tobacco smoke itself there still remains a hypotheses which strongly suggests itself and which should have been mentioned if the committee indeed concerned

itself with critical evaluation of evidence.

In summary then, although alternative hypotheses are considered by the committee the one alternative mentioned is very disappointing. The committee has not stressed itself to think of other alternate hypotheses which have to be rejected before the association between smoking and disease can be accepted.

Experimental Evidence

The discussion of experimentally induced carcinogenesis occupies slightly less than one page. In view of the importance of controlled experiments to the issue here at stake one would think that the committee would spend some more time on this topic. One has the feeling that the committee is belittling somewhat this particular part of its report. The discussion starts out with a statement that:

> "Few attempts have been made to produce bronchogenic carcinoma in experimental animals with tobacco extracts, smoke, or smoke condensates." (Page 165)

Yet nine relevant studies are mentioned. Considering the fact that there are only seven epidemiological studies of importance in the report, nine do not seem to be such few experiments. Also in the summary of this conclusion the committee fails to make any remark that might indicate that the failure to produce carcinogenesis by means of tobacco smoke is in any way important. It simply notes that:

> "Bronchogenic carcinoma has not been produced by the application of tobacco extracts, smoke, or condensates to the lung or the tracheobronchial tree of experimental animals with the possible exception of dogs." (Page 165)

At the same time it is pointed out that the lungs of mice, rats, hamsters, and primates had been found to be susceptible to the introduction of bronchogenic carcinoma by the administration of the polycyclic aromatic hydrocarbons, certain metals, radio-active substances, and oncogenic viruses (Page 167). The histopathologic characteristics of the tumors produced in such fashion are similar to those observed in man and are frequently of the squamous variety. Especially in view of the fact that tumors and cancers can be produced in a variety of animals by substances other than cigarette smoke and at the same time that these animals do not respond with carcinomas to cigarette smoke is extremely important and cannot be stressed enough.

Major Technical Shortcomings

There are a number of technical flaws which seriously impair the value of the committee's arguments.

Suitability of the study populations for inferences about the universe of smokers and non-smokers:

This suitability has been challenged before. A study based on a random sample of the population has not been made yet and would admittedly be an expensive undertaking. However, individuals gathered through volunteers of the American Cancer Society serve as a relatively poor sample. Volunteers of the American Cancer Society are probably not a disinterested group. In addition, the follow-up and response of all populations was much lower than usual. Finally, the death-rates of the various study populations

differ significantly from each other as well as from the death-rates of the general population of white males.

The committee bases its acceptance of these populations on a great number of assumptions. It had to be assumed that non-respondents have the same death rates as do respondents. There appears to be some evidence that this assumption cannot be made. The assumptions introduced by the committee to correct for non-response may be sound but, are not the only assumptions possible. Again, it is probably true that a sample selected at any time for follow-up excludes the very sick so that initially the sample may show a lower death-rate than the general population. However, there is no evidence given that this effect occurred or as to what may have been its magnitude. While the assumption is reasonable, it does not answer the problem completely. Nor is ther a satisfactory explanation for the large divergences between the death rates of different study populations. This is important because some of the deat-rates are quite low. Table 15, page 95, deserves closer study. California Occupational and California Legion groups have very low death rates. On the other hand, Canadian Veterans have considerably higher rates. Either of these rates are quite different from those of men in the Twenty-Five States study, and again, men in the Twenty-Five States study, although selected by the same methods as the study for men in Nine States, again show a considerable difference from the latter. Obviously there are large fluctuations within the population itself. There are many problems raised by the fact that populations acquired by different selection criteria tend to have a higher deat-rate than non-smokers. Whether or not these biases

actually would cause an artificial correlation between smoking and health may be unlikely but, nevertheless, is subject to discussion. In short, the suitability of accepting the study populations depend on one's willingness to go along with the many assumptions made. How strong the argument remains after all assumptions have been made is a matter of considerable opinion.

Comparison of effect due to smoking with that due to other variables:

The constant references made to the relative magnitude of the effect of smoking as compared to air pollution or to occupational hazards are not adequately documented. This is more than a minor annoyance. A distinct impression is given that exact enough evidence exists of the effects of smoking, air pollution, and other hazards so that quantitative comparisons are possible. Certainly the effects of community air pollution or morbidity and mortality are not known that well! Occupational hazards vary. Does the committee mean to imply that smoking is more hazardous than deep sea diving? The comparisons seem unnecessary and express a general lack of critical evaluation that one would think has no place in a report of importance as this one.

The use of Mortality Ratio to define and scale effects of smoking on health:

The comparisons of mortality incidents between smokers and non-smokers is based predominantly on the mortality ratio. The mortality ratio is obtained by dividing age specific death rate for a disease of smokers by the corresponding age specific death rate for the disease of non-smokers. The number thus obtained should be in the approximate region of unity if no

differences exists with respect to the age specific death rates. (One assumption which we shall glance over is the usefulness of the age specific death rate. I have in a previous article raised some doubts on the usefulness of this particular biometric index. However, age specific death rate is generally accepted as a legitimate expression of mortality.)

At page 102, Table 19, we find a group of diseases which were arranged according to mortality ratio. Cancer of the lung has the highest mortality ratio, bronchitis and emphysema the next highest, cancer of the larynx the next highest, and so on. From this ranking the conclusion is reached that the most important effect of smoking is on cancer of the lung, bronchitis, cancer of the larynx, etc. But does the mortality ratio really indicate what weights should be given to the association between smoking and various diseases?

There are altogether 15,653.9 expected deaths from all causes. Of these 15,653.9, 6430.7 would be expected to be due to coronary artery disease alone. It stands to reason that if non-smokers have roughly 45 per cent of all deaths due to coronary artery disease, smokers, even if all 26,223 deaths had been due to this cause, could not have had a mortality ratio higher than 4. There is a limitation here to the maximum size of the mortality ratio. Yet the mortality ratio increases to 1.7, an increase which actually represents a very large number of excess deaths.

On the other hand, the expected number of deaths due to cancer of the lung among smokers turns out to be 170.3. This represents roughly one per cent of the total number of expected deaths. Therefore a relatively

small increase in the number of lung cancer deaths among the smokers could possibly yield a large increase in the mortality ratio. The mortality ratio is therefore dependent on the actual proportion of death from a specific cause within a population. The question which now remains unresolved is if an increase in the percentage of deaths due to coronary artery disease observed in this population indicates a greater or a lesser effect of smoking than the deaths due to cancer of the lung, or bronchitis, or emphysema, or cancer of the larynx? Even if smoking had the effect ascribed to it, is this effect measured accurately by the mortality ratio so that we can say that the major effect is cancer of the lung and only a relatively small effect on coronary artery disease? This is by no means a minor point. In terms of the confounding hypotheses we had mentioned before it would be very suggestive if one would say that the major effect of smoking is on coronary artery disease since, as we shall mention again below, one of the properties of the difference between smokers and non-smokers is precisely in those medical criteria which are usually associated with coronary artery disease. It should be pointed out here that according to Berkson's as well as to my own published calculations the effect of lung cancer is actually minimal as compared to that of circulatory disease. This problem is given no discussion in the report except that the mortality ratio is installed as the correct statistic to use.

Patterns of mortality differences

Of all the shortcomings of the technical side of this report, the assumption that the effect of cigarette smoking is specific as to mortality is the most

serious. Whether we accept the mortality ratio or not it is obvious that smokers in the samples died at a faster rate than non-smokers from practically all diseases. There is only one disease, cancer of the intestine, for which smokers die at a lesser rate than non-smokers, and one disease, cancer of the rectum, for which the rates for both smokers and non-smokers are alike. The conclusion that has been drawn in the past from this data was that smokers differ from non-smokers in their total pattern of mortality. This has given rise to the serious question if one either has to ascribe an effect of smoking to all diseases or if one should look for some sampling bias that would account for the consistent increase. The conclusion that all excess mortality is caused by smoking has proven very unpopular in the past. It does seem unreasonable that one particular agent would cause all these damages. What the committee has done, however, has been to by-pass this particular problem. Instead effects of smoking were decided by a disease by disease comparison according to the criterion of statistical significance.

This is an extremely dangerous procedure. If no effect due to smoking would exist, there still would be some diseases for which the incidence of death for a particular cause is greater among smokers than it would be among non-smokers due to sampling error. If comparisons were made between a hundred mortality disease ratios and if a statistical significance of 5 per cent were to be used, it is obviously clear that approximately 5 out of 100 comparisons in any sampling would yield statistical significance in favor of the smokers and 5 out of 100 would yield statistical significance

in favor of the non-smokers. If one ignored the total distribution of all diseases, one could ascribe an effect to smoking even if such an effect were nonexistent. No investigator would proceed in this fashion. Observing that the number of increases and decreases in mortality ratios are approximately what he would expect to occur by chance his conclusion would have to be that smoking has no effect on disease. However, the same reasoning must be followed if a difference does appear to exist for a large number of disease mortality ratios. Let us assume that there does exist a difference in the mortality pattern between smokers and non-smokers. We would expect, therefore, that for some diseases this difference would be larger and for others it would be smaller and that this variation is one purely due to chance. Observing within the data that most of the diseases are different and few of them are alike one would be forced to the conclusion that the general pattern of mortality is different--not that only some of these diseases differ and others do not. To do any other way is to ignore some data and select others for one's purposes.

The committee seems to go out of its way to point out that it is actually clearing tobacco or smoking of causing some diseases but having to indict it in others. This apparent open mindedness is a trap in which the committee has fallen. There is simply no question, according to the presented data, that one must assume that smoking causes all increases in diseases or that an underlying sampling bias may exist.

In summary, a number of technical problems handled by the committee have resulted in two major flaws.

1. The assignment of the importance of the effect of smoking was done according to mortality ratios which are so influenced by differences in the actual number of occurrences of diseases that they do not lend themselves to this task.
2. The failure to recognize the existence of a total pattern of disease differences gives the impression of a specificity of smoking effects which is simply untrue.

To these groups of technical problems ought to be added one more. In discussing the various possible biases in connection with non-responding, the committee's reasoning becomes unclear. One gets the definite impression the committee is saying that with the large numbers of observations whatever biases exist should disappear. (Page 101). This is a rather peculiar misconception since a bias operating with a small population or a large population will still give a biased estimate.

The Committee Applies its Own Criteria

As was pointed out before, the committee stated but never defined five criteria which it used to find a causal connection between smoking and disease. Somewhat later in the text, (Part II, starting page 182) the committee begins to discuss in some detail the application of these criteria.

The Consistency of the Association

> "This criterion implies that the diverse methods of approach in the study of an association will provide similar conclusions." (Page 182)

The committee finds indeed that all 29 retrospective studies it considered

found an association between cigarette smoking and lung cancer. Nevertheless, the committee manages to make a number of peculiar statements:

> "The very nature of the criticisms levelled against these retrospective studies indicates a diversity of characteristics of approach and, for that matter, marked differences and shortcomings which have been discussed in detail above." (Page 182)

It is somewhat difficult to follow the argument at this point. Apparently the fact that the 29 studies were open for criticism now becomes a strong point proving doubly that an association had been established. At the same time the committee is unwilling to accept two studies on tobacco workers which had been cited as inconsistent with the other retrospective and prospective studies. Apparently here the committee is willing to criticize other studies and therefore exclude them from this collection. If criticism, and perhaps justifiable criticism, of studies contrary to findings of others is sufficient reason to eliminate those it certainly cannot be a source of strength if it is leveled against studies which agree with the conclusions of the committee. One more statement of the committee concerning this consistency is thought provoking. Concluding on the demonstrated consistency of all epidemiological studies the committee notes:

> "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 constitutional genetic characteristic or one acquired early in life, which will be discussed later in section, Constitutional Hypotheses." (Page 182)

We have already seen that it is not so difficult to conceive of a universally acting bias in this situation. For instance, the fact that cigarette paper might contain carcinogenic agents or the fact that smoking may be an aspect of a general style of life which might be considered unhealthy would both be biases which could act universally on all populations.

The Strength of Association

The committee states on page 183:

> "In essence, then, a relative risk ratio measuring the strength of an association provides for an evaluation of whether this fact is important in the production of a disease."

We see here complete reliance on the mortality ratio. Also I doubt whether a number of statements really can be deduced from the papers by Cornfield which are alluded to by the committee. The committee is satisfied it has demonstrated strength of association because smokers develop lung cancer 9 to 10 times as frequently as do non-smokers.

Within this discussion the reference to a dose response association between amounts smoked and the mortality ratio is somewhat out of place. This dose response ratio is not always obtained and is somewhat open to question and certainly it should not belong in the section discussing strength of association.

The Specificity of the Association

The discussion on this point is again confusing. The committee in some ways is unable to differentiate the specificity of the association from the

strength of the association. One fails to see the point of the criterion entirely.

This confusion is by no means alleviated by reference by the committee to special insight and understanding.

> "Another aspect of specificity requires some insight." (Page 184)

The committee takes notice of the fact that the overall effect of cigarette smoking has been criticized.

> "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. In a sense this viewpoint is an exaggeration for not all of the specific disease mortality ratios in excess of 1.0 are large enough to warrant secure judgments on the strength of the association and of causal significance." (Pages 184-185)

This point has already been discussed sufficiently. Therefore, the conclusion of the committee, namely:

> "Actually, the findings of 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." (Page 185)

is a peculiarly naive statement.

Temporal Relationship of Associated Variables

This criteria seems to amount to the fact that as long as somebody dying from lung cancer has smoked first rather than after his death the temporal relationship of associated variables is demonstrated. Another point the

committee raises here is that premalignant changes have been observed in the lung of smokers, but as the committee notes itself, no evidence has thus far been brought forth to indicate that the initiation of the carcinomatic process in a smoker who develops lung cancer antedates the onset of smoking.

Coherence of the Association

According to the committee this criterion concerns itself with the association of known facts and natural history and biology of the disease with respect to the association between smoking and cancer. The actual evidence quoted here seems to have little to do with biological and natural history of disease. Rise in lung cancer mortality is mentioned with time. As has been repeatedly pointed out, there has been a disease and environmental change in the last few decades in this country which cannot be accounted for by the increase in cigarette smoking. Sex difference, urban rural differences, or social economic gradients do not bear on biological necessity. The two items which seem to have some merit are the dose response relationship with the amount smoked of which some if weak evidence exists and the localization of cancer in relation to type of smoking. In fact, the localization of cancer with respect to type of smoking is the strongest evidence brought forth by the committee relating specifically tobacco to cancer.

In summary, the committee's application of its own criterion of causality is confusing. Only two of the five criteria have any merit at all. The only thing accomplished by use of these criteria is to create a false

impression of evidence falling into place according to a logical schema.

Conclusion

From a cooly reasoned point of view one should not confuse the judgment of the Advisory Committee to the Surgeon General with the scientific process by which statements of fact are established. The problem of science versus public health is more than a fine point of distinction. The action oriented attitude underlying, by necessity, a public health evaluation of any evidence constitutes a definite bias as far as the scientific decision process is concerned. Such a bias may and apparently has influenced the judgment of the committee in evaluating evidence and presenting its conclusions.

For the same reasons, any critical attack on the report is immediately vulnerable to accusation of self interest. After all, the committee is on the side of the angels. It not only evaluates the evils of tobacco scientifically but also protects the common good against their effects. Yet for the benefit of the future value of public health pronouncements, the report ought to be put in its proper perspective. It is doubtful whether this can be done by any assembled panel of experts. Any divergent conclusion reached by another committee would be exactly that--another conclusion. Moreover, the advisory committee is cloaked in the mantel of the surgeon general's office and thus its findings carry more weight than those of independent reviewers or of opposing panels.

Fortunately, questions of fact are not decided by committees, whether they are assembled by government, private, or professional agencies.

The scientific process provides its own system of proof that prevails despite majority opinions or the notions of hardened experts. The work of the committee has pointed to those areas in which research efforts must be expended so that the relation between smoking and health can be clarified. The research outline appended to this review indicates the area of most important immediate clarification.

APPENDIX

Outline Of An Experimental Design To Test For Certain Confounding Factors In Smoking and Health Studies

Introduction

The conclusions concerning the effect of smoking on health stand and fall with the acceptability of current epidemiological studies. These studies, as summarized in the report Smoking and Health, appear to show that smokers have a higher mortality from many diseases than do non-smokers. Despite their shortcomings and despite the failure of animal studies to show any harmful effects due to tobacco smoke, these studies have been officially accepted as conclusive evidence linking smoking with a variety of diseases.

In my review of the report Smoking and Health I pointed to a number of major errors committed by earlier reviewers of the available data and repeated by the advisory committee to the Surgeon General. Of special relevance here are:

1. The analysis of the epidemiological data must consider with equal attention the alternative hypotheses that both the smoking of cigarettes and groups of diseases have a common cause which determines that an individual shall become a smoker and also that he shall be predisposed to other diseases. Despite some lip service to this credo, Smoking and Health considered and rejected only one alternative hypothesis, namely, that genetic and constitutional factors predispose the individual to smoking and lung cancer. However, there are other underlying factors which may cause disease and also induce smoking as a side effect. (See below)
2. By the report's use of mortality ratios and by wrongly singling out some diseases as caused by smoking but not others the impression was

created that the main effects of smoking are excess deaths due to lung cancer. I have pointed out as has Berkson that this ranking is largely an artifact of the statistic used, namely, of the mortality ratio. It is impossible for the mortality ratio of death due to coronary diseases to be large in the population of smokers. If limitations of the mortality ratio are corrected, then the largest effects of smoking become deaths due to circulatory causes (2), (23). However, while the largest difference between smoker and non-smoker mortality may be in circulatory causes, the difference in death rates between smokers and non-smokers includes almost all causes.

One alternative hypothesis that seemingly can account for the differences in mortality, especially for circulatory causes, and at the same time also explain the association of most of these deaths to smoking is that smoking and non-smoking is an index or sign of a "Style of Life", or a "Style of Personal Hygiene". This style of life may be viewed as a system of actions, behaviors, and habits which are inconsistent with good health and long survival. As a syndrome, these behaviors may include such features as over-eating, irregular food intake, non attention to irritating properties of food, irregular rest periods, overweight, lack of regular exercises, occasional over exertions, excessive drinking of alcoholic beverages, non avoidance of stress situations, high levels of aspiration, and so on, as well as smoking.

There is a large amount of evidence which makes this hypothesis very reasonable.

Several studies reported that heavy smokers also drink alcoholic beverages excessively (9), (16), (18). Friedman's type A men (the coronary type) tend to be heavy smokers (8). Smokers are said to be more easily angered and to eat more when under stress (25). They have been reported to marry oftener, to change jobs more frequently and to be more often hospitalized (14). The concentration of serum cholesterol has been found to be slightly higher in smokers than in non-smokers (4, 5, 11, 19, 24) although some studies have found no relationship (1, 12). One investigator found also not only that serum cholesterol was higher in smokers than in non-smokers but also that it remained higher in those who stopped smoking (7). Smokers also have higher heart rates than non-smokers (3). One study found an excess of smokers who were 30 per cent overweight and the subjects who were 40 per cent or more overweight were all regular smokers. Also the non-smokers had a greater frequency of individuals with 10 per cent or more underweight than did the smokers (25). Smokers not only have certain physical characteristics that would make them appear to be candidates for some diseases especially of the circulatory system, but their psychological characteristics are in line with the hypothesis advanced here. The general picture emerging from all studies is one of smokers tending to live faster and more intensely and to be more socially outgoing. Studies, using behavioral rather than psychological tests support this picture (6, 18). Most studies support the contention that neuroticism defined, among others, by the existence of anxiety states, nervousness, somatic symptoms, unusual restlessness in terms of jobs and residence,

is indeed associated with smoking habits (13, 14, 17, 20). Other relevant evidence includes the large differences between the mortality of smokers and non-smokers when compared by marital status, educational levels, use of tranquilizers, and degree of exercise (Page 100, Table 18, Smoking and Health).

All the references cited above are included in the report on Smoking and Health as well as others that would indicate that smoking may be a response to frustration and failure to achieve status (10) and may be accompanied by impulsive and rebellious behavior (15, 18, 21). In short, a picture quite in harmony with our hypothesis of differences in style of life emerges both in physical and in psychological terms. (The wording of the conclusions in each of the references quoted here are taken almost verbatum from Smoking and Health).

While such a hypothesis seems eminently reasonable its test is somewhat more difficult. A research design is outlined here and certain suggestions are made which not only make a crucial experiment possible but are also capable of unambiguous execution.

The Research Design

Summary Outline

The proposed study consists of two parts.

In Part I, a large sample of individuals is classified as to style of life and smoking. Classification is based on medically acceptable criteria and on those aspects which are known to be associated with groups of

degenerative and other diseases. Information on the subject's medical history also is obtained if possible. The data are analyzed for association between style of life and smoking. The hypothesis tested is that style of life is a variable very much confounded with smoking. (It should be pointed out that this hypothesis has already been tested in part by the many studies listed above and apparently found to be valid.) Part I of the study should demonstrate rigorously that stylesof life or of personal hygiene are confounded with smoking.

Part II will follow the sample for a period of time and accumulate data on mortality and morbidity. These data will then be examined for association between style of life and mortality and smoking and mortality from different causes. The hypothesis tested will be that excess mortality of segments of the population is accounted for by their styles of life.

Construction of Style of Life Indexes:

These indexes will be devised by a special committee composed of a wide variety of medical specialties. It will list types of behavior and habits known or suspected to be associated with mortality of specific kinds (such as circulatory causes, ulcers, cirrhosis of the liver, etc.)

Subjects:

Subjects of the study ideally should be drawn from a large random sample of the population at large. However, because of the magnitude of the study and its ultimate comparison to existing data, the population could be limited to white males. Expenses and difficulties for follow up may demand a further restriction of this population to certain groups which are more

easily found and followed. Such groups would be organized populations found in industry, governmental agencies, universities, fraternal and other organizations.

Large industrial populations have many advantages. They are reasonably representative of the total population of white males and can be followed with relatively small expenditures. The same is true for educational institutions which represent a large segment of American Society. Fraternal and social organizations are probably highly selective in many ways as to socio economic and special interest. (This is one of the severe criticisms leveled at data now used to establish the relation between smoking and mortality.) This selection may make itself felt in style of life. Governmental agencies (such as the Army or Post Office) may be selected also for types of work and with it limit styles of life more narrowly than would be true in samples selected from a broad band of American Industry.

A random sample of the population could be used to test hypotheses for Part I of the study only. Such a sample could be obtained through the use of county housing records and sampling locations could be chosen by a random process. If nomore than interviews are attempted, such a population sample should give ample evidence on the confounding of style of life with smoking hypothesis. However, the type of verification of the indexing through medical records as can be done for industrial population is not possible with such a sample. It may be well to include a relatively small random sample with the follow up population to be used only for Part I of

the study.

Numbers of observations will be determined by the kind of populations obtained. Because of the small frequencies of some diseases the number of observations should not be less than 120,000 man years at risk if the sample population is over 45 years of age. This number may be obtained by following a population of 75,000 men for two years assuming an 80 per cent follow up as a minimum. Follow up may reasonably be expected to be 90 to 95 per cent with modern methods of locating individuals.

While the estimate of 120,000 man years at risk is a minimum estimate the actual requirements may be higher if the age composition of the population tends toward or includes younger groups. If the cooperation of large industrial and university groups can be secured it will not be difficult or costly to extend the sample to its appropriate size.

Methods

For Part I of the study, subjects will be interviewed by a trained nurse. Personal and family history will be obtained as well as a broad information on history of diseases including those of the immediate family. The index of style of life will be completed as well as another commonly used scaler for state of health (such as parts of the Cornell Medical Index). Subjects will be questioned closely as to smoking history. When possible, the medical records of the subject will be examined for significant medical events. This will be feasible for many large industries that keep fairly good records and from industrial insurance companies associated with these industries.

To eliminate the bias introduced because subjects are in a good state of health at time of sampling, the population on record some time prior to the beginning of the study could be used. If the study were to start in July 1965 one could define the population at risk as that which was on the industry's record on July 1964 or 63, etc. A number of individuals will have died by then but their number may be used to assess the selection bias from which previous epidemiological studies have suffered.

For Part II of the study the original population will be surveyed constantly. If industrial populations are used, this surveillance is relatively simple. Lists of drop outs can be obtained weekly or monthly from company records and information on morbidity and mortality from union, insurance, and death benefit records. Much of this information is now automated and easily to come by providing adequate cooperation of relevant agencies are obtained.

Subjects which drop out of sight completely have to be traced. I have found a number of procedures useful in a variety of similar studies in which the follow ups have proven most effective.

1. Search through internal revenue central offices for the last known address of the taxpayer subject.
2. Notification through O.A.S. if person is still on record as receiving old age or other benefits.
3. Search through death certificates of state offices of vital statistics.

In addition searches can utilize Board of Educations, Health Departments,

Credit Bureaus, the Post Offices, City Directories, and many other sources.

Whenever a death is found, a copy of the death certificate will be obtained. If possible records of major morbidity (i. e. requiring hospitalization or more than 30 daysoff stay in the home) will be kept.

At the end of the study period, each subject will be classified with respect to state of health and this classification correlated with the style of life index and smoking history as well as with other relevant information.

Analysis of Results

For Part I of the study, the subjects will be divided by indices of style of life, other medical information, and smoking. Correlations of amount smoked with style of life index will be obtained. Degree of confounding will be assessed between smoking and style of life variables.

For Part II mortality (and if possible morbidity) for the style of life groupings will be examined and compared with that of smoking-non-smoking categories.

While the analyses mentioned above are crucial, a number of other answers to interesting questions may be obtained. The extent of analysis will depend on the variety and suitability of data.

Significance of Results

The report Smoking and Health fails to take account of what has been defined here as style of life as a common factor underlying both smoking and disease frequency. Yet strong evidence, contained in the report itself, points to the existence of such a factor.

Analysis of Part I of the suggested study will counter the weight of this report if it shows confounding between style of life and smoking. On the other hand, if such confounding should not appear, then the conclusions of the report will be in no way modified. Thus, from point of view and self-interest of the sponsors, nothing is to be lost and much to be gained from Part I of the study alone.

I have repeatedly mentioned that considerable evidence already exists on style of life differences between smokers and non-smokers and that this evidence is quoted in the Surgeon General's report. However the report does not adequately consider the confounding hypotheses pursued and fails to organize the material relating to style of life in the fashion done here and in my review of the report. Also, the report contains a morass of biases, assumptions, and irrelevancies which make any direct attack on already existing data fruitless and frustrating. In addition, the data existing now are fractionary. Only parts of the style of life index as suggested here have been tested and these parts are found in a large number of studies. Only a study that concentrates all phases of style of life into one population will be able to challenge the report with any hope of success. Finally, the suggested study will introduce new evidence into the controversy. The old evidence and its flaws have been discussed ad nauseum and probably little is gained from viewing it from still another perspective.

Part II of the study will be a contribution to our knowledge of disease etiology regardless of its outcome with respect to smoking. The relation of many characteristics of life, behavior, and habit to subsequent disease will

be clarified. Many of these relations have been suspected heretofore and evidence on their existence will be of immeasurable value to practical medicine.

Analysis of the data may result in a number of possible clear cut conclusions which may or may not brand smoking as a cause of some diseases. However it is most unlikely that all of medical experience will be reversed and that behaviors and habits known to be inimical to health will be shown to have no effect on morbidity and mortality. With respect to the effect of smoking, the following two outcomes may be expected reasonably:

1. Smoking combined with a style of life inimicable to health increases risk of death from some diseases in excess to what these risks may be for the same style of life without smoking. On the other hand, some styles of life lead to an increased risk of death from some disease irregardless of whether or not smoking is part of the behavior pattern. For some diseases smoking and style of life are confounded such that no independent conclusion on the effect of smoking is possible. Finally some diseases are related neither to style of life nor to smoking.
2. Style of life with or without smoking is related to patterns of death from all diseases. The effect of smoking is completely confounded with styles of life.

Of these two, the first outcome would appear to be the more reasonable expectation according to present state of knowledge. A finding, such as contained in Smoking and Health namely, that smoking and smoking alone causes various kinds of diseases and is the major factor in excess mortality

is unlikely to occur. If it does it would be an important contribution to medicine since valuable clues to survival must then be contained in the act of smoking or its by products. However, the likelihood of the latter even is unfortunately (or fortunately) almost nonexistent.

One other point needs to be discussed. We have proceeded so far from the proposition that the effect of style of life will make itself felt predominantly on death from circulatory diseases, ulcers, cirrhosis of the liver and other causes not connected with cancer --either of the lung or of other locations. One possible outcome of the study could be that, after clearing out the confusing underbrush of irrelevant disease, a clear association between smoking and cancer may remain.

If this should be the case, this study would make an important contribution to the etiology of cancer since it would clearly indicate a source of carcinogenes which can not be detected by animal studies. Concentrated effort in this area may lead to breakthroughs in our understanding of causes of the malignancies in man. However an equally important contribution would be made if cancers too can be shown to be related to style of life rather than smoking. Actually the latter is the more likely outcome of Part II. It is reasonable to expect that some behaviors are such that they expose individuals to wider sources of irritations of physical or chemical nature. Also the failure to produce cancer in laboratory animals that respond readily with malignancies when exposed to known carcinogenes make it unlikely that smoking is a primary and independent cause of cancer.

In essence then, the proposed study should not only clear the air as

far as the problem of smoking and health are concerned but also will constitute a considerable contribution of the industry to public health and welfare. Perhaps the latter aspect is the most valuable by-product for the industry. As long as an industry fails to show major concern with the health aspects of its products it will be and should be subject to stringent government regulations. Industries such as lead or petroleum that have constantly investigated medical aspects of their processes and products have never been subject to unreasonable public health procedures.

Execution

The present state of affairs, reinforced if not created by the Surgeon General's report, is such that the tobacco industry will need help and cooperation from many sources. Also to obtain cooperation from industry and other suppliers of data will require a certain amount of professional pressure. Therefore I suggest the following steps be undertaken to initiate this study.

1. Appointment of a central committee with the mission of supervising the preparation and execution of the study and take responsibility for the report. This committee should contain individuals who are prominently concerned with scientific methodology, some ought to be involved with the various sides of the smoking controversy, the A.M.A., the Public Health Service, industrial medicine, and statistical as well as epidemiological studies. The following names are suggested as desirable possibilities:

J. Berkson	Chief, Biometry and Medical Statistics Mayo Clinic Rochester, Minnesota
A. L. Cochran	Professor Medical Research Council Epidemiological Research Unit 4, Richmond Road Glamorgan, South Wales, Great Britain
J. A. D. Cooper	Dean of Science Northwestern Medical School Chicago, Illinois
M. DeBakey	Professor of Surgery Baylor University School of Medicine Houston, Texas
E. C. Hammond	Director, Statistical Research Department American Cancer Society
M. Kac	Professor, The Rockefeller Institute New York
L. Lasagna	Director of the Division of Clinical Pharmacology Johns Hopkins Hospital Baltimore, Maryland
R. Miller	Chief, Epidemiological Branch National Cancer Institute National Institutes of Health Washington, D. C.
J. Neyman	Professor and Director, Statistical Laboratory University of California Berkeley, California
E. Saenger	Professor of Radiology College of Medicine University of Cincinnati Cincinnati, Ohio
R. Seltser	Associate Professor of Epidemiology John Hopkins University Baltimore, Maryland

J. Yerushalmy	Professor of Biostatistics School of Public Health University of California Berkeley, California
Representation from	Surgeon General and Public Health Service
" "	A.M.A.
" "	Insurance Companies

2. This committee should be composed such that it can obtain official committments of cooperation from the A.M.A., The Industrial Medical Association, the Public Health Service, and other agencies.
3. Execution of the study could proceed through a university department equipped to handle it or could be shared by two universities that have the means and facilities to bring the study to a successful conclusion. Outstanding candidates are the departments of industrial or environmental medicine at Cincinnati, Pittsburgh, and Harvard in this order.
4. The committee should obtain a moratorium on public statements by all interested parties until all the data are in and analyzed.
5. The tobacco industry commits itself to put all funds necessary for the study at the disposal of the committee and then steps out of the study.

Duration of the Study

The committee could be formed and formalize its job within six months. Eight months should be allowed to obtain the necessary cooperations and acquire staff. The study itself and analysis of data need take no longer than three years so that four and one half years between initiation and

publication of results may be expected to elapse.

Conclusion

The design and suggestions for execution of the study are open to some modifications. Obviously the final methods and procedures as well as cost will be dictated by a number of factors so that this presentation should be considered purely as a working proposal and rational for the ambitious and necessary task outlined here.

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