DISCUSSION

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I want to state at once and emphatically that I am not a statistician. Hence, I am not at all competent to comment upon Dr. Dorn's paper on the technical level of the professional statistician. This fact was pointed out to your committee at their first approach, and I also took the liberty of suggesting at least five other persons whom I considered far better qualified for the present assignment. However, since your Chairman was quite insistent that I should make this appearance, I warned him that my comments would necessarily be those of an amateur and non-specialist.

My personal orientation is essentially that of the experimentalist and my reflections upon these figures that Dr. Dorn has presented therefore tend naturally to revolve around their meaning and challenge to the man in the laboratory.

It is, of course, not fair and proper to dwell unduly upon the relatively minor indications of these figures where the small numbers of cases available for analysis reduce the reliability of the correlations. Nevertheless, there are a good many individual points where the figures seem to suggest contradictory, irrational or difficultly credible conclusions. Dr. Dorn has called attention to some of these but a few others may perhaps be mentioned in passing. For example, the data seem to indicate that cigarette smokers, as a group, die of stomach cancer more often than non-smokers. Yet, the light smokers show a higher mortality from this disease than medium smokers, and medium smokers a higher mortality than heavy ones. One wonders whether an extrapolation of the trend line would indicate some level of very heavy cigarette smoking at which the mortality from stomach cancer would equal or fall below that for non-smokers. Data from other studies have already shown that the mortality from stomach cancer in general has been declining for a number of years during a period in which cigarette smoking was increasing sharply. In view of the fact that a great deal of the extraneous material inhaled into the lungs is eventually swept out by the flow of mucous, received into the mouth and swallowed, the figures for stomach cancer seem to present an anomalous picture.

A similar situation appears to exist in the case of cancer of the kidney.

Also, the higher mortality of cigarette smokers who reduced their levels of smoking as compared to those who continued at their former rates, appears anomalous, unless the reduction was indeed due to poor health as postulated.

Another puzzling point is that so large a number of cigars, eight or more, must be smoked daily before any effect upon the mortality ratios is found.

However, as I have stated, comment should properly be concentrated upon the largest and most pronounced trends and relationships that have been reported. The most remarkable observation in this study as well as in its predecessors is the great difference between cigarette smokers on the one hand and cigar or pipe smokers on the other, with respect both to total mortality rates and the mortality from a number of individual diseases. Our knowledge of the chemical composition of pipe and cigar smoke as compared to that of smoke from cigarettes is still quite inadequate for the kinds of comparisons that are indicated by these striking statistical differences among various types of smokers. We do know that pipe and cigar tobaccos tend to run higher in nicotine content than the usual blends of cigarette tobaccos.(1) It is reasonable to suppose that nicotine absorption is of the same order for pipe and cigar smokers as for smokers of cigarettes. Studies on this point are under way which may help in the interpretation of the statistical comparisons.

Very deficient also is our present information on the relative biological activity of these several different types of tobacco smoke. A few studies have reported activity for cigar smoke condensates comparable to that of cigarette smoke condensates as measured by the skin reactions of sensitive mouse strains.(2) Comparisons of this kind, however, have been delayed and handicapped by a lack of reliable and particularly of rapid bio-assay methods sufficiently standardized to be capable of interpretation. A great deal of work is currently under way in the effort to provide better assay techniques for use in the resolution of such questions.(3) There is also a great dearth of information about the mechanics of smoking by users of pipes and cigars, as well as about the kinds of differences that exist among cigarette

smokers in their methods of smoking. The greatest question attaches to the problem of inhalation since this would presumably affect actual physiological dosage of smoke.(4) While it is easy to assume that cigarette smokers inhale more often and more deeply than the users of pipes and cigars, and to assume that inhalation differences account for the statistical differences in disease and mortality statistics, we actually have very little information on this point.

Dr. Dorn's figures tend strongly to reinforce the conviction that fuller knowledge of the comparative chemistry of these several smokes, better methods of bio-assay, and improved knowledge of smoking mechanics, particularly with respect to smoke inhalation, may provide the answers to some key questions. I would be doubtful whether inhalation practices can ever be studied adequately by questionnaire methods. Better information seems likely to be provided by direct mechanical measurements of mouth and chest movements, and perhaps by assay of body fluids for metabolites of nicotine or other smoke ingredients that may serve as indicators of the degree of overall smoke contact with the tissues.

All the problems mentioned above are either included in the present program of the Scientific Advisory Board to the Tobacco Industry Research Committee or are in some stage of planning.(3) Solutions to these problems should provide tools eventually capable of showing whether the statistical comparisons of pipe and cigar smokers to cigarette smokers present a truly anomalous picture or whether they can be given a rational and coherent interpretation. It would not seem to me that further statistical observations alone could carry us much closer to a final solution.

The question has been raised many times before whether and to what extent the psychological and physiological make-up of individual persons may determine whether they remain non-smokers or whether they adopt the use of pipes, cigars or cigarettes. In a society where the opportunities and inducements to use these products are virtually universal, the determinants of use or non-use, and the choice of form might be expected to reflect prominently the family and group mores as well as such psycho-physiological factors. The latter might be expected also to play a role in determining the frequency and manner of smoking within the several categories of tobacco use.

Evidence of personality differences among heavy smokers and non-smokers has been found by Heath in an analysis of data collected, largely by him, over a period of many years on a group of Harvard students.(5) Some indications of sociological factors in smoking patterns have been provided by McArthur in a further analysis of those data.(6) Such data suggest that the various patterns of smoking are not distributed among the population at random but that they tend to select various types from among the general population and thus to separate groups that may have differing inherent life and disease expectancies. Similar evidence of selection has been provided by Sir Ronald Fisher through study of identical and non-identical twins. He found that identical twins are far more often similar in their smoking habits than non-identical twins even though reared apart in different environments.(7)

Further evidence along such lines has been published by Dr. Caroline Bedell Thomas from a study of the medical students at the Johns Hopkins University. After first establishing to her satisfaction that certain cardiovascular conditions show a familial tendency, she has shown that young men with a family history of such conditions are more often smokers than those lacking such a history.(8) Although these young men do not now have any disease of the heart or arteries, it is presumed that they constitute a selected group that may eventually show a high incidence of disease in this category. Of course, if that time arrives, the relatively heavy cigarette smoking of this group will show a correlation with the disease incidence. I do not suggest, naturally, that this relationship furnishes the complete explanation for the observed correlations.

Dr. Dorn's data on the association of smoking with ulcer of the stomach and duodenum are especially interesting to me on account of the experimental studies that have recently been conducted in this field. He shows a ratio of actual to expected deaths from these diseases among regular cigarette smokers of 2.83, which reflects one of the relatively strong associations. While the etiology of ulcer cannot be said to be fully understood, it is widely considered that gastric hypersecretion and hyperacidity are important contributory factors especially since direct control of these conditions is often effective in palliation. The effects of cigarette smoking on gastric secretion have been studied rather extensively in several experimental studies of human subjects

in projects sponsored by our Scientific Advisory Board.(9) In general, no significant differences have been found between the responses of persons with an ulcer history and those lacking such a history. Indeed the smoking of cigarettes by subjects in either category produced no significant changes in the several gastric functions that were measured including volume, density, viscosity, acidity or pepsinogen content of the secretions or gastric motility. The absence of significant response to nicotine absorption, therefore, fails to sustain any hypothesis that smoking contributes directly through physiological action to the etiology of ulcers. The observations tend rather to recall the prevalent concept that ulcer is an anxiety or stress disease containing a strong psychosomatic component. If this is truly the case, one wonders whether the statistical association of smoking and ulcer may not prove to be due to the fact that the candidates for ulcer are selectively inclined to seek solace from smoking to a greater degree than the average population.

According to Dr. Dorn's statistics, cirrhosis of the liver shows an even stronger association with cigarette and cigar smoking than ulcer. This is a disease now widely, if not generally, believed to be related to nutritional deficiency, particularly to the lack of nutrients providing labile methyl groups, in the presence of relatively high calorie intake. Cirrhosis has long been associated with alcoholism and the hypothesis that it might be caused primarily by the direct action of some alcohol metabolite was formerly in vogue. At present the concensus appears to be that the consumption of alcohol has no direct causal relation to liver cirrhosis. The association is regarded to be indirect and to reflect the fact that alcoholics often neglect to consume diets adequate in choline and other methyl donors to balance the calorie content of their alcohol consumption.

Since an association between heavy smoking and heavy alcohol consumption has also been reported by several investigators, it would appear likely that the association of smoking with liver cirrhosis may be removed by a still further step from a direct causal relation to this disease. Discussion of cirrhosis recalls the recent study of Trieger and his collaborators on cancer of the tongue.(10) In a series of about one hundred cases, the factors of malnutrition, syphilitic infection, local irritation, alcohol consumption and smoking were studied. The salient observation of this team was that a combination of three or more of these factors was found in a large majority of the tongue cancer cases. In only a small minority of cases was a single factor such as smoking found to be present alone. If tobacco use had been the only factor studied, this research would have appeared as still another in which an association between tobacco use and a disease was reported. In actuality the study placed some emphasis upon the prevalence of incipient cirrhosis as a factor in mouth cancer and implied that smoking might function as a non-specific minor contributing influence through local irritation.

I have dwelt somewhat upon these several diseases because they all illustrate cases where the initial statistical association has received some degree of elucidation through experimental study or additional statistical data. Several of them illustrate the usual complexity of etiological pictures and in some the association with tobacco use has been shown to be indirect, incidental or accidental. The moral is that statistical association alone is not able to indicate whether a specific factor is actually a part of the causal complex or to distinguish between a direct and major factor and one that is involved in an indirect, incidental or accidental manner. The distinction will usually have to come, in the end, through direct experimental investigation that can trace out the etiological picture step by step.

This brings us to the consideration of lung cancer, which though it accounts for far less mortality than the cardiovascular diseases, stands out as the disease which, according to Dr. Dorn's ratios, shows by far the greatest difference in incidence among the smokers and non-smokers of cigarettes. Nevertheless, a striking feature of the statistics is that the great majority even of the heaviest smokers do not develop the disease, whereas some non-smokers do. These facts alone appear to me to constitute quite incontrovertible evidence of the complex nature of the etiology of this disease. Evidently some unknown series of factors, either extrinsic, intrinsic, or both, must be combined in the proper manner to permit development of the condition designated as primary bronchogenic carcinoma.

These several factors may be likened to the elevations and depressions on the key to a modern lock. A whole series of such elevations and depressions must be aligned in the proper order and must have the proper relative dimensions if the key is to turn in the lock. So it is with the numerous etiologic factors that enter into the web

of causation of any disease. It is unlikely that many of the elevations and depressions in the key to lung cancer have as yet been identified or evaluated, and it is certainly reasonable to suppose that interaction of factors is involved. Influences which are incapable of producing the disease when acting singly, may well do so when operating synergistically.

There has been much rather pointless semantic debate over the relationship between statistical associations and the concept of causation. The practical issues, however, seem to me to be actually rather clear. The universal objective is to find the simplest, most effective, and also cheapest and least disturbing method of interrupting the etiologic chain and obtaining effective prevention of lung cancer or reduction in incidence.

Malaria has been associated for centuries with the proximity of stagnant water. Even when the disease was erroneously considered to be "caused" by inhalation of poisonous miasma (whence the name), some degree of control was attained occasionally by draining a swamp or by removal to higher ground. It is conceivable that malaria might even have been eradicated by heroic measures along such lines, but this proved hardly practical.

When the role of the female Anopheles mosquito was explained as a vector, more effective control became available through spraying stagnant water with oil and later with insecticides to kill the mosquito larvae. Complete understanding of the role played by the plasmodium paved the way for better chemotherapy with consequent reduction in the reservoir of human sources for infection of the mosquitoes. Still later, the more detailed study of mosquito behavior revealed their habit of alighting on a nearby surface for a siesta immediately after every meal of human blood. This knowledge revealed the efficacy of spraying all house walls in endemic areas, with insecticides to destroy potentially infectious mosquitoes before they can leave the premises. This method of control promises to be the one which may finally bring the total eradication of malaria within the realm of practical possibility for the first time in history.(11)

It is obviously pointless to debate the relative degree to which swamps, mosquitoes or plasmodia should be designated as the "causes" of malaria. The point is that as the total web of causation has been elucidated step by step, the control measures have correspondingly improved progressively, in simplicity, practicality and efficacy.

It is well known that pellagra was long ago associated with the consumption of corn, that is maize, as a staple food. For a long time debate continued as to whether this deficiency disease was due to an infection or to a poison in the grain. It is reported that the prevalence of pellagra in certain parts of France actually led to a ban on the growing of maize in that country. This measure is reputed to have been successful in the sense that pellagra diminished or disappeared. In the light of present knowledge, however, the story has a tragic aspect, since a very valuable economic crop was lost to the farmers and a potentially valuable food was sacrificed on account merely of an inadequate understanding of the etiology of pellagra. Now we know that a simple dietary supplement to supply niacin or tryptophane would easily have eradicated the disease and preserved the values of maize cultivation. The moral of these stories should be obvious.

When the statistical relation between cigarette smoking and lung cancer was first reported, it was reasonable to assume as a primary working hypothesis, that some one or more of the various known chemical carcinogens or close relatives of these might be present in cigarette smoke at levels of biological consequence. The search for such agents has now been continued so long in the hands of so many able investigators and with such meager results that many scientists no longer believe it likely that tobacco smoke exerts any significant effect as a direct or specific carcinogen for human tissues. The universal failure to produce lung cancers in animals by simple smoke inhalation reinforces this point of view. Many investigators now expect to find that if tobacco smoke exerts any significant effect in the complex of cancer etiology it will prove to be of a non-specific, indirect, accidental or synergistic character in combination with many others. In the elucidation of such effects and in the search for a satisfactory point d'appui for control, the laboratory and clinic must certainly be primary arenas of activity henceforth.

It seems to me very unfortunate that some of the popular magazines nevertheless have seen fit to publicize the "carcinogenic substance" theory so prematurely, vigorously and sensationally, as to create a strong public demand for supposedly remedial measures which are actually of a wholly uncertain efficacy.

In my opinion, the clue hunt has only begun, and certainly needs to be continued and intensified. Through the Veterans Administration hospitals, the national health agencies have access to a relatively

large number of lung cancer cases. I hope that opportunity will be found to search the medical and personal histories of these patients very exhaustively for any common elements that may be revealed. Dr. Walter Finke(12) and Dr. Sheldon Sommers(13) have already made fruitful approaches along such lines. The discovery of common elements among lung cancer victims should provide additional clues for test and verification in the clinic and laboratory as possible factors in the causal complex. Identification of such contributory factors may well provide a simple and effective method of control or prevention.

Bibliography

1. Garner, W.W. The Production of Tobacco. Philadelphia, 1951. p. 430ff.

2. Croninger, A.B., Graham, E.A., and Wynder, E.L. Experimental Production of Carcinoma with Tobacco Products V. Carcinoma Induction in Mice with Cigar, Pipe and All-Tobacco Cigarette Tar. Cancer Research, 18, 1263 (1958).

3. Little, C.C. 1958 Report of the Scientific Director. Tobacco Industry Research Committee. New York (1958).

4. Schwartz, D., and Denoix, P.F. L'enquête française sur l'étiologie du cancer broncho-pulmonaire. Rôle du tabac. Sem. Hôp. Paris 33, 424 (1957).

   Todd, G.F. Tobacco Manufacturers' Standing Committee, Research Papers, No. 1. Statistics of Smoking. London (1958).

5. Heath, C.W. Differences Between Smokers and Nonsmokers. A.M.A. Archives of Internal Medicine, 101, 377 (1958).

6. McArthur, C., Waldron, E. and Dickinson, J. The Psychology of Smoking. J. Abnormal and Social Psychology. 56, 267 (1958).

7. Fisher, R.A. Lung Cancer and Cigarettes? Nature 182, 108 (1958).

   Fisher, R.A. Cancer and Smoking. Nature. 182, 596 (1958).

8. Thomas, C.B. Familial and Epidemiologic Aspects of Coronary Disease and Hypertension. J. Chronic Dis. 7, 198 (1958).

9. Cooper, P. and Knight, J.B., Jr. Effect of Cigarette Smoking on Gastric Secretions of Patients with Duodenal Ulcer. N.E.J. Med. 255, 17 (1956).

   Cooper, P., Stein, H.L., Moore, G.F. and Harrower, H.W. Effect of Cigarette Smoking on Excretion of Uropepsin and Concentration of Plasma Pepsinogen. R.I. Med. J. 40, 215 (1957).

   Cooper, P., Saltz, M., Harrower, H.W. and Burke, D. Effect of Cigarette Smoking on Dissolved Gastric Mucins and Viscosity of Gastric Juice. Gastroenterology 33, 459 (1957).

   Cooper, P., Harrower, H.W., Stein, H.L. and Moore, Goldwyn F. The Effect of Cigarette Smoking on Intragastric Balloon Pressure and Temperature of Patients with Duodenal Ulcer. Gastroenterology 35, 176 (1958).

10. Trieger, N., Weisberger, D., Ship, I.I. and Taylor, G.W. Cirrhosis and Other Predisposing Factors in Carcinoma of the Tongue. Cancer, 11, 357 (1958).

11. World Health Organization. Malaria Eradication. Geneva (1958).

12. Finke, W. Chronic Pulmonary Diseases in Patients with Lung Cancer. New York State J. Medicine 58, 3783 (1958).

13. Sommers, S.C. Host Factors in Fatal Human Lung Cancer. A.M.A. Arch. Path. 65, 104 (1958).