Some Thoughts on the Epidemiology of Cancer*

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The aim.—The ultimate goal of man in respect to human health is to prevent disease. Progress in the field of infectious diseases has clearly demonstrated what can be achieved in this regard. Similar advances can be made in respect to noncommunicable diseases, such as cancer. It is toward this end that epidemiological research is directed. Its aim is to contribute to our understanding of the causation of cancer and to set forth measures leading to its reduction, if not its elimination.

Proof of causation.—In using the term causation, it is pertinent to clarify its meaning. In the present state of knowledge a causative factor of cancer is not a necessary one but one that increases the risk for developing cancer. It is also evident that multiple factors may effect the development of cancer. It is mere semantics whether we call such a factor causative, associated, contributory, or related to cancer, as long as it can be established that, in its absence, the incidence of cancer is reduced.

In respect to causative factors we recently proposed three postulates which, when fulfilled, are regarded to establish the causative nature of such factors (1). Historically, such proof has been established for a variety of occupational tumors, proof accepted by the majority of scientific opinion. What has been less commonly accepted is the fact that many cancers affecting the general population are similarly related to environmental factors.

The first postulate states that “The greater and more prolonged the exposure to the factor, the greater the risk of the population involved.” Retrospective as well as prospective studies have been used to evaluate the role of environmental factors in the development of cancer in man. Such studies have shown that the risk of developing cancer of the respiratory tract increases the greater the amount of tobacco consumed, that the risk of skin cancer increases the greater the amount of sunlight exposure, that the risk of cervical cancer increases the poorer the degree of penile hygiene, that the risk of oral cavity cancer increases with excessive tobacco and alcohol consumption, and that the risk of upper alimentary cancer increases in Swedish women with an increase in dietary deficiencies—to cite just a few examples of general environmental factors related to cancer.

It is clear that in such studies all possible environmental factors need to be investigated so as to avoid possible biases and to untangle possible interrelated variables. The greater the differences found the less likely it is that an error or bias exists. In some instances the factor has been so important as to be responsible for a majority of a given group of cancer cases.

The second postulate states that “The epidemiological pattern should be consistent with the distribution of the factor.” The geographical distribution of cancer is one of its most fascinating aspects not only for industrial groups but for whole populations. This applies not only to countries of markedly different living standards where the age distribution, medical care, and available statistics may vary greatly, but also for countries of similar medical standards. Such differences clearly indicate environmental factors, once racial factors have been ruled out. We have investigated such divergent differences as the high incidence of cervical cancer among Hindus and the low rate among Jewish women; the high rate of oral cavity cancer in India and the low rates among Indians in the Fiji Islands; the relatively high rate of esophagus cancer among Irish Catholics and the relatively low rates among Jews; the high rates of stomach cancer in Japan, Iceland, Yugoslavia, and Costa Rica and the decreasing rate in the United States; the low rates of breast and prostate cancer in Japan and the high rates in the United States; the high rates of oral cavity cancer among Swedish women and relatively low rates of

American women; and the low rates of lung cancer in Japan and the high rate in the United States (Chart 1). For the epidemiologist the world indeed is his laboratory. In some instances environmental factors have been clearly established; in others the search has not as yet given fruitful results. In any case, it is pertinent that the geographical distribution of factors be consistent with the frequency of the cancer.

The third postulate states that "a removal or a reduction of the factor for a given population should be followed by a reduction in the incidence of disease." This happenstance has been clearly shown by occupational cancers. Preventive measures in industry have long shown that certain industrial cancers can be avoided. The chimney sweep cancer serves as a classical example. Similarly, it has been demonstrated that ex-smokers have a lower risk of developing lung cancer than those who continue to smoke, that Japanese and Eastern Europeans who immigrated to the United States have less stomach cancer than the people of their own countries, that nonchewing Indians in the Fijis have less mouth cancer than their people in India, and that improved diets have reduced the risk of oral cavity cancer in Swedish women. It is clear that the postulates have been fulfilled in many instances.

It has been often suggested that what is needed to establish proof of a cancer cause in man is experimental evidence. A fully planned experiment would not be feasible for humane reasons alone, but it must be apparent that man himself provides the experimental setting. Epidemiology is indeed a study of human experimentation.

Laboratory evidence.—As noted, no statement has been made so far in regard to laboratory studies as proof for a given factor to produce cancer in man. Such studies cannot prove that a factor can cause cancer in man. They can suggest, they can define its mechanism, they certainly can support human data, but they cannot establish proof—a proof which depends solely on human evidence. This thought is not to deny the importance of chemical and biological studies in carcinogenesis, a field in which our group is heavily engaged (2). The major purpose of biological and chemical experimentation is to study the mechanism of a given carcinogenic process and to interpret the findings in line with human data. In the field of tobacco carcinogenesis, for instance, we are striving to account for the established tumorigenic activity in animals in chemical terms and then to alter the process in such a way as to reduce the established activity. If a practical product can thus be obtained, a long-term follow-up study in...
man upon its introduction is still necessary in order to prove its effect.

Much of the experimental work has had its human counterpart, but clearly some has not. It is important that we decide how to interpret animal results. Are epithelial cancers more specific than sarcomas? Is there a threshold for carcinogens which, from a theoretical point of view, seems unlikely, but from a practical point of view seems to apply? Should public health measures be taken on animal evidence alone, or should human data in addition be required?

Some uniform guide lines in respect to laboratory findings should be formulated. At the moment, we tend to be most cautious and ban substances because of experiments involving tissues and dose levels quite unlike those encountered by man and in the absence of human data, while ignoring findings in respect to other substances where the evidence on all these points is substantially greater. Scientific evidence should know only one set of truths. I would agree that, if a given substance has produced cancer in animals and if such substance is not essential to man, a cautious point of view is to control its use, in spite of the absence of human evidence.

Although certain laboratory studies clearly follow human findings, others do not. It may be said that any experiment can contribute to our understanding of carcinogenesis which, however, can be obtained as well from the study of substances to which man is exposed. More experimental groups should work in this direction. Tobacco smoke, for example, is being studied by relatively few groups in view of its significance in human carcinogenesis. Alcohol, well established to increase the risk of cancer in the upper alimentary tract, has been but little studied; and smegma, suspected to play a role in the development of cancer of the cervix and penis, has received relatively little attention either biologically or, particularly, chemically. We should pay increased attention to carcinogens to which man is exposed and utilize similar tissues in which a given cancer occurs in man. Such studies cannot only increase our understanding of carcinogenesis, but above all help to interpret the human findings and suggest preventive measures. Animal and chemical findings in our present knowledge need to be interpreted within the framework of the human setting.

We shall not review the epidemiology of lung cancer except to cite it as an example from a general point of view. The only asset of the lung cancer epidemic has been that it has focused attention on environmental cancer research. Rarely have so many studies of retrospective, prospective, pathological, biological, and chemical nature been focused on one subject. The lung cancer issue has focused attention on general environmental factors as distinguished from industrial ones. It has stimulated research in the biological and chemical sciences and has attracted increased attention to preventive measures in regard to cancer. It has unfortunately also revealed man's nature to refuse to recognize facts that are unpleasant and to circumvent evidence that he would like to ignore. But as always in life, scientific proof will prevail, and this indeed is one of the great assets of science itself.

Preventive measures.—Preventive measures based upon available and accepted evidence must be the concern of every physician and every scientist. Just as the physician must warn against unnecessary exposure to infectious agents, so he must stand in respect to carcinogenic substances.

Standards need to be established along the lines outlined here. They should be neither so loose as to incriminate any substance that can produce a tumor unrelated to the type occurring in man and utilizing doses far in excess to human exposure, nor so strict that they could never be fulfilled. Once the evidence is regarded as established, it becomes the duty of every physician to become acquainted with the data so that he can properly instruct himself as well as his patients. The outlook in this regard is promising, as well shown from results obtained for occupational tumors; the outlook should be even more rewarding in respect to general environmental factors, because so many more people are affected.

I like to conclude with a hypothetical example based upon available epidemiological data from countries where satisfactory death rates exist. If the incidence of respiratory cancer in the United States were as low as in Japan, if the incidence of cervical cancer among American women were that of the women in Israel, it is clear that a considerable number of lives could be saved. In these instances, available data have tended to establish a causative relationship between environmental factors and the development of these cancers. In other areas marked differences in the incidences of different cancers exist, but the reasons remain unknown. The different rates of cancer of the colon, breast, prostate, and stomach in the United States and Japan are most intriguing and require additional study. Present evidence suggests that environmental rather than racial factors are also important in respect to these cancers.

Thus, whereas for some cancers we do not know the precise preventive factor, for others we do. It is for the former that we need to extend our epi-
Epidemiological studies, together with correlated laboratory investigations, can add to our understanding of carcinogenesis. It is in the direction of prevention, however, that there lies epidemiology's greatest contribution. This is true regardless of what the basic cause of cancer may be. The history of medicine clearly demonstrates that preventive measures often precede the ultimate understanding of the pathogenesis of disease by many years. As said at the onset, the ultimate goal of man in respect to human health is to prevent disease. The success experienced in the field of infectious diseases can be duplicated in respect to cancer. Present evidence clearly indicates that this goal is not a theory, is not a dream, but is a reality.

REFERENCES

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