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# Environmental Carcinogenesis: *Guest Editorial*

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There can be no denying the fact that one of the most pressing problems of the cancer investigator is the problem of experimental carcinogenesis and its relationship to environmental cancers in the human. Over the past decade entirely too little effort has been devoted to the study of this vital question. It is not surprising, therefore, that Hueper (4) has prepared for this society a most interesting and provocative article on this subject. If its purpose was to stimulate and expand research in the field of carcinogenic mechanisms, it is unfortunate that, in this reader's opinion, it fell so far short of its objective. Its principal deficiency lies in its lack of clear objectives for research or action to guide the cancer investigator. It is vital that anyone who undertakes research in carcinogenic mechanisms and their relationship to environmental cancers in the human recognize the complexities and pitfalls of this subject. It is simple enough to expose animals by one route or another to various chemicals and then sit back and await the development of tumors. If tumors develop in these animals, then the chemical under study is proclaimed a carcinogen, and the world, and in particular industry, is admonished "as a matter of wise precaution to exclude as far as possible" this chemical from the environment of man. Like being opposed to sin, it is a very simple matter to be opposed to the inclusion of unnecessary carcinogens in the environment of man. There are few people who would have the temerity to pronounce openly that they are in favor of either. Yet when one begins to examine one's terms of reference, it is not so easy to arrive at concepts that are agreed to by everyone.

We can all agree that it is appropriate and timely to turn to any scientific principles which offer the hope for a solution to the problem of cancer, whether they be related to the control of infectious disease or the solution of any other problem. One of the first things we have learned about the control of infectious diseases is that it is not necessary to live in a germ-free world. In fact, the overwhelming weight of evidence suggests that not only is this not practical, but it may not even be desirable. Animals which have been reared in a germ-free environment, although larger and longer-lived than those reared in the normal germ-laden atmosphere, are highly susceptible to organisms that otherwise they learn to live with.

The possibility of the existence of biologic adaptation to naturally occurring environmental carcinogens has been acknowledged (4), but it is maintained that the carcinogens of the modern industrial era have all been introduced during a period of a few decades. Nothing could be further from the truth. Benzpyrene and other polyaromatic hydrocarbons, possibly the most significant group of environmental carcinogens, have been with man since the first cave man lit a primitive fire, and possibly even before that (1, 3). Chromates and other metals have been used for centuries. Dyes have been used since before the recorded history of man. Many of these, although of vegetable origin, were chemically similar to synthetic dyes. Plastics and other naturally occurring elastomers have been found in archeological discoveries of ancient civilizations (6). Thyrotropic substances similar to aminotriazole, which caused the cranberry furor not so long ago, occur naturally in rutabagas and other plants. Even the photo-reaction products of present-day Los Angeles smog have undoubtedly been in the environment since before recorded history (3). It is im-

portant to remember that much of what is being accomplished by our modern industrial era has resulted from a study of nature and the development of ways and means of doing rapidly and on a grand scale what nature does slowly and on a minute scale.

Like the definition of sin, the definition of a carcinogen which has significance to the environmental cancer problem is not an easy one. It has been proposed by some that the subcutaneous tissues are suitable under all circumstances for the testing of carcinogenesis. It is necessary to consider this proposition in the light of evidence which says that cobalt, sugar, cholesterol, and plastics, when injected subcutaneously or intramuscularly, cause sarcomas. Cobalt is not only a carcinogen, but also an essential element, being a constituent of the vitamin $B_{12}$ molecule. Sarcomas which are produced from the subcutaneous implantation of plastics do not appear if the size of the plastic is below a critical value, if the plastic sheet has holes punched in it, or if the plastic is introduced in powdered form, but may increase in number if the surface of the plastic is first roughed up by sanding. Certainly, one cannot deny that such materials are carcinogens, in the strict definition of the term, but the important question is, what significance do these observations have to environmental cancers in man. The implication is often left with the reader that these materials "as a matter of wise precaution (be excluded) as far as possible from the environment of man." Does this mean that cobalt should be excluded from the diet of man, or only that metallic powdered cobalt should not be injected subcutaneously into man? Does this mean that plastics should not be used as wrapping material for food, or only that they should not be implanted as solid sheets in the subcutaneous or other mesenteric tissues of man without careful consideration of the possible consequences? The question, therefore, is not whether the subcutaneous tissues should or should not be used for testing carcinogenesis, but rather how will the results of such testing be interpreted? It is in the interpretation of the significance of subcutaneous testing to the whole problem of environmental cancers in man that the meaty and difficult problems lie. These problems cannot be avoided by simply avoiding a discussion of them.

Later, Hueper (4) briefly touches upon another distressing void in our knowledge when he says "the apparent inability of a chemical given by mouth to produce cancers in experimental animals does not justify the conclusion that such a chemical does not exert such an effect in man and thus is not a dietary carcinogen." The reader is left with an uninterpreted statement which leads him only to confusion. Are we, in order to be sure an "epidemic-like occurrence of cancers attributable to an indiscriminate decision made 10–30 years ago" will not occur, to return to the ways of Zinjanthropus (5) man? Certainly, *his* environment contained less carcinogens than our own, and probably less carcinogens than any succeeding generation of man. Undoubtedly, few people seriously believe that civilization should return to this earlier state. If not, then what are the practical rules on which we are to guide our civilization concerning carcinogens in our environment? Perhaps we can attempt to establish a few ground rules which will be applicable, as well as practical.

First, we need vastly expanded research on carcinogenic mechanisms. We need to compare, in *statistically significant numbers* of animals, the results obtained by administering different quantities of carcinogens by different routes—orally, subcutaneously, by skin painting, inhalation, bladder implantation, or other routes. The experiments need to be conducted on a variety of animal species, with compounds in which the statistical epidemiologic data show both a clear-cut positive and a clear-cut negative correlation with cancer production in man. The effort in this direction needs at least to equal that now being devoted to cancer chemotherapy screening. It is probable that at least 10 years will be required before the first significant observations will arise out of these experiments.

Second, we need a vastly expanded program of epidemiological studies in man. These could best be conducted in industry, where the exposures could be measured with accuracy and some hope for the completion of long-term prospective studies exists. These studies will likewise require many years—perhaps 20 or more—and will require investigators cognizant of the statistical-epidemiologic approach, but patient enough to await the completion of their studies before drawing conclusions. If additional study or time is necessary to establish conclusions, then these must be undertaken quietly and with the intent of developing the facts, rather than remonstrating with industrial managements or physicians for withholding facts. Until the data are clear-cut and a solution has been found—i.e., either control of the material or its elimination—publicity through newspapers, congressional committees, or other types of nonscientific releases can hope to accomplish no useful objective. New leads developed in this way should be incorporated into the research programs outlined in the first objective.

Third, until such time as our knowledge in this field has been vastly increased by the above studies, our effort should be to limit, as far as *practical*, not as far as *possible*, exposure to carcinogens by routes in man which the available experimental evidence in animals by comparable routes suggests might present a hazard to man. Naturally, a material that produces malignancies at sites distant from the site of an administered dose must be evaluated differently from materials which produce malignancies only at the site of administration. In addition, materials that produce a profusion of tumors in a variety of species, such as 2-acetylaminofluorene, must be evaluated differently from materials which produce only an occasional tumor in one or two species. In other words, the total available animal data must be carefully *evaluated* in terms of significance including technological contribution, and not simply *listed* or *enumerated*. If such interim decisions are reached in good faith, with neither hysterical over-concern or complacent under-concern, there is little likelihood that an epidemic-like occurrence of cancers will result in 10–30 years.

A reasonable position in this situation has been well expressed by Dubos (2), who says "To demand a certified verdict of safety before accepting a new technological innovation would clearly result in paralysis of the economic and technological progress," and "A society that does not continue to grow through adventure and willingness to take chances is not likely to survive long in the modern world. With regard to health as to all other fields, society must be willing to take the educated and calculated risks inherent in technological civilization. Today, as in the past, willingness to take risks is a condition of biological success."

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