Changing Concepts in Cancer Prevention: Limitations and Implications for Future Research in Environmental Carcinogenesis

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Abstract

While the cause and nature of certain human cancers are known, definitive preventative guidelines still cannot be offered for many types of tumors. This is partly due to the inherent biostatistical and epidemiological limitations involved in the identification and interpretation of complex carcinogenic risk factors and potential low-risk hazards.

Two divergent control strategies have emerged: (a) regulatory programs designed to control or eliminate minute quantities of pollutants in the ambient environment, based on fairly rigid quantitative risk assessment; (b) a biological research effort to understand the fundamental biological mechanisms with the objective of eventually manipulating or intervening in carcinogenesis through chemoprevention or therapy. Apart from more intensified effort on certain already recognized causal factors, current research indicates that the eliminatory approach will have little impact on the cancer burden and that the mechanistic approach, although difficult and slow, represents the most logical alternative. This will require long-term major investments in fundamental research and manpower. This biological approach, however, is largely ignored by the public and legislative bodies concerned with cancer control strategies, partly due to lack of formal input to appropriate national bodies by experts in chemical carcinogenesis. Informed scientists have an important role in ensuring that the public and legislative bodies are aware of current scientific views on carcinogenesis and the need to establish priorities in research.

False facts are highly injurious to the progress of science, for they often endure long; but false views, if supported by some evidence, do little harm, for everyone takes a salutary pleasure in proving their falseness.

Charles Darwin in The Descent of Man, Chapter 21

Early studies on the geographical and temporal variations in cancer incidence in different countries, communities, and migrants, complemented by analytical epidemiological investigations on cultural and occupational cancers, led to the view that most human cancers have a significant environmental component (1). By deemphasizing the role of hereditary factors, such studies have indicated the considerable possibilities of cancer prevention by removal or reduction of exogenous carcinogens in an occupational setting, possibly modification of “life-style” factors (especially use of tobacco, change in diet), or use of vaccines, e.g., hepatitis B and liver cancer. Today there is a general consensus on the identifiable or probable causes of many human cancers and their nature (2-4). In the past, cancer control through elimination of carcinogenic factors has been successful for several types of cancers (2-4).

Nonetheless, despite major epidemiological and laboratory efforts over the last two decades, specific preventative measures cannot be recommended with any certainty for about 50% of cancers in males and 70% in females (2-4). Further, the complexity of environmental risk factors has been demonstrated by recognition of the multitarget nature of carcinogenesis (5, 6) and the numerous modulating factors involved in both humans and experimental models.

Accordingly, the intellectually attractive idea that control of the many animal carcinogens, mutagens, and promoters (both made and natural) in the ambient environment would also significantly reduce the cancer burden (7) has become widespread and has had considerable political impact, especially in view of the perceived slow progress of cancer therapy. However, the role of such ambient chemical pollution as a major factor in human carcinogenesis is now being critically reevaluated (8).

In 1980, Berenblum (9, 10) described several hypothetical approaches to human cancer prevention. These included: the elimination of complete carcinogens; the elimination of possible initiators based on laboratory tests, e.g., mutagens, an approach widely used today by regulatory authorities; and the elimination of various promoting factors during the long latent period of carcinogenesis. In this category, Berenblum clearly included any type of modulating or enhancing factor involved in carcinogenesis. However, based on current research trends, his conclusion was that the most effective approach in the future would be interference in the carcinogenic process rather than the elimination of “incriminating” factors within the environment.

Although a longtime advocate of the traditional eliminatory approach to prevention, I am now convinced that recent progress in biology and carcinogenesis research confirms the essential validity of Berenblum’s views, although they are largely ignored in regulatory policy and public debate. Further, it appears to me that, apart from the application of existing knowledge on the causes of cancer, increasing efforts to reduce cancer based only on such methods may have relatively little impact in reducing the present burden of cancer due to inherent biological, statistical, and social limitations.

This paper briefly summarizes some of the scientific arguments for this thesis. It also attempts to analyze the implications for the public policies of the American Association for Cancer Research in advising on the future direction and priorities of cancer control programs and research strategies.

Role of Epidemiology in Cancer Prevention

Epidemiology has been the major discipline used to test causal hypotheses in human cancer. Such hypotheses have often arisen from chance clinical observation or, less frequently, through systematic investigations in a cultural, occupational, or therapeutic setting or laboratory biosays. The criteria governing such investigations are well known. In general, the multifactorial nature of many cancers and their long induction period require that for a cause(s) to be demonstrable, a reasonable number of persons must be exposed to a carcinogenic risk factor of some potency for some time. No single criterion can establish causality, and the evidence must be evaluated as a whole, including biological plausibility (11, 12).

Modern cancer epidemiology is a sophisticated science, not only relying on traditional ecological and analytical studies (13)
but also using new technologies and concepts developed in the laboratory to analyze complex carcinogenic risk factors (14, 15). However, such studies have well-recognized limitations (11, 12, 16), including: (a) lack of sensitivity; (b) difficulty in discriminating between several plausible risk factors in complex situations where none is key or critical; (c) inability to evaluate the impact of recent exposures; and (d) uncertainties in interpreting “negative” studies or inverse relationships.

Analytical epidemiological studies, even under favorable conditions, usually are insufficiently sensitive to detect cancer increases or decreases below 1:1000, except for certain rare tumors. A “negative study,” even with large numbers, will usually be compatible with a 20% increase in risk (17). The interpretation of “negative” or weak associations in epidemiological investigations requires considerable scientific judgment and expertise (18), as illustrated by studies on low-level radiation (19, 20), socioeconomic factors (21, 22), or dietary inconsistencies (23).

Traditionally, primary cancer prevention has been most successful where a discrete and necessary cause, such as tobacco or a specific chemical exposure, has been identified (2–4). Where carcinogenic risk factors are of considerable magnitude, specific and demonstrable in humans, no serious scientific or social problem usually arises in advising on possible preventative strategies through elimination and control, whether the factor be a discrete chemical or mixture, cultural habit, or virus. In contrast, there is controversy associated with the determination of the significance of low-level potential chemical hazards or the analysis of complex “life-style” and socioeconomic factors. In such cases, the deficiencies of the epidemiological method are most apparent.

Evaluation of Small (de Minimis) Potential Cancer Hazards

In a modern industrial state, apart from certain classical occupations and specific point sources, exposures to many carcinogenic chemicals as identified in animal bioassays usually occur at levels below that at which a carcinogenic effect can be detected by classical epidemiological methods (3, 4, 24). Thus, Hemminki and Vainio (24), in an unique comparative study of the levels of potential environmental carcinogens, have calculated that workplace exposures in Finland are usually below those at which a detectable effect could be anticipated and that most ambient exposures are several orders of magnitude less.

The lack of sensitivity and the inability of the epidemiological method to measure very low (de minimis) risks which represent matters of great public concern pose problems for regulatory bodies which are required both to reduce carcinogenic environmental risks and to justify the effectiveness of their regulations. Thus, they face ever growing lists of many different types of biologically active chemicals in the human environment (both man-made and natural) which cause or enhance tumor formation in animals but for which the impact of humans cannot be detected in vivo or individually by the epidemiological method.

In the United States, the open nature of the regulatory process and the need to avoid the impression of bias has led to pressure to measure numerically such risks by theoretical biomathematical techniques (16, 25–27).

Quantitative Risk Assessment. Quantitative risk assessment as applied to carcinogens implies the use of selected biomathematical models to calculate the probability of a potential cancer risk to humans as a result of exposure to a very low level hazard, usually a chemical. Such models in general attempt to measure risk using very restricted data obtained in animals exposed to high dose levels since adequate human data are rarely available. They are based on simplistic inferences and assumptions as to the nature and variety of carcinogenic mechanisms. Thus, choice of model and the many variables and variances involved in the assumptions, which may be considerable, can modify the conclusions by many orders of magnitude. Further, such conclusions and assumptions cannot and have not been validated by human or animal studies.

Biological problems in relation to simple dose extrapolation are well documented, even when human data are available (16), as illustrated by cigarette smoking. Thus, the carcinogenic effect of the latter is related to the square of the dose but the fourth power of time (28). The relative risk at age 60 for a man smoking 20 cigarettes a day for 20 years is about 1 order of magnitude less than that of a man smoking 10 cigarettes a day for 40 years. Similarly, the high susceptibility of hepatitis B virus carriers to primary carcinoma of the liver as compared to noncarriers (29) makes simplistic dose extrapolation for aflatoxin B1 from rodent studies difficult.

It has been postulated that if the total molecular mechanisms of a specific carcinogenic process were understood, including the probability of each key or limiting step, accurate quantitative extrapolation as to the probability of impact of an exogenous factor could theoretically be made between and within species (16, 26). The feasibility of this concept for very low carcinogenic risk exposures as distinct from pharmacokinetic studies at high doses requires consideration.

Quantitation of Probability of Rare Biological Events. Clinical cancer is now considered the outcome of a multistage process involving a cascade of biochemical and biophysical events within an individual cell and its microenvironment, usually believed to be triggered by one or more exogenous or endogenous factors. Such events include mutation, oncogene activation, gene derepression and promotion, and changes in membrane receptors, as well as the impact of variations in host metabolism, immunological status, etc. (16). However, the nature as well as the relevance of individual events and their probability, including those which are rate limiting or critical, are often unknown.

Since most tumors are monoclonal and only one cell among millions apparently at equal risk gives rise to a clinical cancer, the probability of the total cascade of events leading to transformation and clinical cancer must be exceedingly low. Further, certain individual events, due to their extreme rarity and biophysical nature, can be regarded as intrinsically uncertain from a probabilistic viewpoint. Accordingly, it can be argued that the transformation sequence in an individual cell could be regarded as essentially unique or random.

Peto et al. (30) have calculated for a human at age t years, the probability for a viable epithelial cell becoming transformed on the morrow as about $10^{-23} t^4$, give or take a few powers of 10, and for a mouse, a billion times greater. He points out that for numbers of such magnitude, variations of this degree are of little importance. Little (31) states that in the mouse fibroblast system, the second step in transformation is a rare event occurring with a frequency of $10^9$ or less among initiated cells. He concludes that quantitative expression of transformation in terms of frequency per viable cell is a meaningless and artificial parameter. Klein and Klein (32) suggest that the breakage of a myc-carrying chromosome is due to a randomly occurring mitotic accident. Human cell strains and lines show 300-fold variations in susceptibility to mouse sarcoma virus (33).

If such uncertainties exist in measuring the probabilities of transformation in relatively simple in vitro systems, the diffi-
cancer risks in humans, actuarial data are not and are unlikely an accurate estimate of the probability of an identical accident in the edge of the mechanism of an accident, although complete and homogeneous. Which are unknown, such as human error. Accordingly, knowledge of the total cascade of events in view of the variables, many of which remain poorly understood.

Limited studies in humans predominantly based on cancers in which the strong promoting activity of cigarette smoking is involved have led to the assumption that multiple exposures are synergistic. However, there are considerable in vitro and in vivo data indicating that the action of mixtures are highly complex. Thus, while in vitro studies suggest that most genotoxic mutagenic mixes are considered to be additive (38), inhibitory as well as synergistic effects can be found and can sometimes be explained mechanistically. There are few data, in vivo or in vitro, on the effects of multiple modulating factors or mixtures, however, at very low levels of exposure.

These complexities suggest that in calculating the probability of cellular transformation through knowledge of individual biological events, the situation may be analogous to forecasting the probability of a very rare accident, such as an airplane crash or nuclear core meltdown, based on analysis of mechanisms of previous accidents. After an accident, many contributing events may be identified. Some will usually be found to be unique, others trivial and unanticipated. The nature and sequence may differ from accident to accident and often no individual factor will be found to be a critical or a key determinant. Thus, it is usually impossible to assign a meaningful numerical probability to the total cascade of events in view of the variables, many of which are unknown, such as human error. Accordingly, knowledge of the mechanism of an accident, although complete and presenting a logical sequence, does not necessarily permit an accurate estimate of the probability of an identical accident in the future unless a major critical and necessary event, such as the failure of a major component, can be identified and its probability measured. In contrast, an actuarial risk, i.e., the number of deaths per 100 million passenger miles, can be measured from experience, as can the relative frequency of general classes of accident. Unfortunately, however, for low cancer risks in humans, actuarial data are not and are unlikely to become available due to the insensitivity of the epidemiologic method. Thus, the assumption that more intensive epidemiological studies will permit better quantitation of such risks may not be true.

In conclusion, biomathematical models essentially represent value judgments and thus, despite their increasing mathematical sophistication, are unlikely to contribute more objective measurements of carcinogenic risks despite detailed knowledge of molecular events since the probability of most individual events cannot be verified. This limitation is inherent in the rarity of the series of events and not on their biological or physical nature. It is doubtful, moreover, that in the present political climate, the necessary megamouse experiments to test the validity of such complex models will ever be initiated. The ED01 experiment (i.e. based on the minimum dose necessary to produce 1% of tumors in the experimental animals) illustrated rather than resolved the many difficulties and uncertainties in interpreting low-level risk laboratory studies; nor, for ethical and logistic reasons, are meaningful observational studies in humans feasible (39). Many biologists would accordingly accept Berenblum's (40) contention that, "In view of the great complexity of the carcinogenic process, it seems clear that there cannot possibly be a straightforward, direct correlation with carcinogenesis considered as one single parameter. Nor are the available biological data adequate, even if this were theoretically possible."

These arguments apply only to low risk quantitative assessment and in no way negate the great value of pharmacokinetic and molecular mechanistic studies for defining chemoprevention and therapeutic approaches or as a basis for making scientific judgments on the characterization of a potential cancer risk factor. Thus, for example, pharmacokinetic data may provide a biological explanation for the different neoplastic as well as toxicological responses between species (41).

Complex Carcinogenic Risk Factors: Epidemiologic Considerations

If the epidemiological identification of discrete carcinogens originating in the external environment presents difficulties, these are nonetheless recognizable as foreign to the human organism. Yet current evidence suggests that perhaps one-fourth to one-half of cancers in occidental males and females, respectively, are influenced by natural constituents of diet and by chemicals which are "normal" cell products or metabolites but the mechanistic and modulating roles of which remain poorly understood.

Where complex, subtle, and often ill-defined carcinogenic risk factors are involved, their analysis by epidemiological techniques may often be difficult and subjected to both biological and statistical limitations. However, serendipitous clinical or systematic observational studies in patients on drug therapy have generated useful etiologic hypotheses as to the biological nature and role of certain carcinogenic risk factors such as hormones (e.g., estrogens in endometrial cancer or prolactin in breast cancer, etc.) (42). Nonetheless, the analysis and evaluation of complex life-style risk factors such as diet have proved unexpectedly difficult (23, 44).

Associations between certain foods, macronutrients, and specific cancers have been demonstrated, e.g., high fat and breast cancer, low fiber intake and colon cancer, but these are seldom strong and sometimes inconsistent (45, 46). In contrast to the recent decrease in heart disease in North America, due probably in part to the major dietary changes that have occurred over the last 40 years, no comparable changes have been observed in the incidence of cancer of the breast, uterus, colon, and prostate, although they are widely believed to be diet related and the dietary trends long established. The decline in stomach cancer in many countries has been attributed to increased use of dairy products, fruit, and vegetables, and changes in food preservation, including increased refrigeration, antioxidant use, and decreased use of salt or a reduction in intragastric N-nitroso compound formation. Studies on dietary nitrates have been inconsistent with simple V nitroso hypotheses and suggest more complex interactions (47). If such uncertainties apply to major dietary components or cancers, which have been extensively studied, the difficulty of isolating the carcinogenic or anticarcinogenic impact of the many biologically active chemical microconstituents in the diet, natural or man-made, by epidemiological studies in humans is obvious (8).

Large-scale population prospective cohort studies based on
detailed dietary analysis are logistically expensive and often prove to be uninformative. The Framingham heart study is unlikely ever to be repeated and unfortunately many potential parameters of interest to oncologists were not included in the original protocol. The interplay between dietary, hormonal, and socioeconomic factors in humans (2, 4) complicates evaluation of individual risk factors. Thus, high-fat diets, late pregnancy and high living standards, all risk factors in breast carcinoma, usually occur in the same segments of the population.

Ecological correlation studies between countries and communities are frequently attempted. Although usually considered hypotheses-generating or "fishing" expeditions, such studies have unfortunately tended to become increasingly used for drawing definitive causal associations, despite their well-recognized limitations and frequent inconsistencies, since the individual may not be identified with his diet of many years earlier (23).

After an extensive review, the National Academy of Sciences (43) could only conclude that while accepting that most major cancers are influenced by diet, "the data are not sufficient to quantify the contribution of diet to the overall cancer risk or to determine the percent reduction in risk that might be achieved by dietary modifications." Accordingly, recommending unequivocal guidelines requiring major and possibly unnecessary changes in a pleasurable cultural habit are difficult.

Unfortunately, experimental dietary studies usually imply gross dietary changes or the administration of specific nutrients at almost pharmacological levels, which may not reflect the more subtle changes likely to be involved in human carcinogenesis. It seems unlikely that traditional observational studies will further resolve these difficulties or facilitate discrimination between populations unless specific dietary or other lifestyle characteristics can be better defined. Accordingly, it is logical that major research efforts be directed to defining such risk factors more objectively, using approaches based on biochemical and molecular epidemiology.

Individual Susceptibility and Prevention

Investigations on migrants, while emphasizing the predominance of environmental factors, do not exclude important interactions between genetic and environmental factors (48, 49) and a number of syndromes have been identified associated with increased cancer risks (50). Major conceptual contributions in molecular cytogenetics have been made by Knudson (48). He points out that inherited susceptibility depends on genetic changes in somatic cells, such as activated protooncogenes, deficient repair of genetic damage, fragile sites, or oncogene mutation or recessive oncogene mutation, etc. (48, 50). His studies on retinoblastoma are somewhat unique in that the theoretical calculations are in accord with the observed frequency of first mutation and later tumor development in affected individuals.

If susceptibility depends on one or two key gene loci, analysis and identification through modern cytogenetic or biochemical techniques may be possible, such as susceptibility to breast cancer in ataxia-telangiectasia heterozygotes (51) or bladder cancer in individuals deficient in N-acetyltransferase. However, if multiple genes are involved, susceptibility will be polygenic and may appear random and difficult to analyze meaningfully in a large population, especially where several environmental factors of uncertain impact may be involved. Thus, for example, an individual with even a 50-fold increase in susceptibility due to recessive gene would be very difficult to detect in an epidemiological study (49). Such studies are subject to the same biostatistical limitations as occur with multiple interacting risks of low probability. Accordingly, it should not be assumed that sequencing the human gene or the identification of sensitive individuals (52) will necessarily provide feasible preventative approaches through environmental control for many cancers. However, identification of individuals susceptible to tobacco smoke or evidence of ability to metabolize or detoxify chemicals occurring in the work environment would of course have major implications for specific cancers.

Future Developments in Epidemiology and Prevention

For the reasons given above, there would appear to be definitive limitations to cancer prevention based only on traditional eliminatory approaches, whether related to low level chemical exposures or isolated dietary changes. However, epidemiological investigations will continue to provide important contributions to cancer control.

Traditional Studies

The differences in cancer experience which are found between various countries (1) and communities (53, 54) indicate that theoretically, major possibilities for prevention still exist. Thus, the black male in San Francisco has double the risk of developing cancer as compared to his countryman of Japanese ethnic origin (54). Furthermore, significant differences between certain religious groups, specific occupations, and the general United States population are well known. Available data suggest that many of these differences are partly related to known causes, including tobacco (4) and socioeconomic conditions (21) for which classical eliminatory approaches are feasible (55). Priority, of course, should continue to be given to the control of such cancers.

While improved public health measures in most modern states make it unlikely that many new strong carcinogens will enter the environment in the future, such a possibility cannot be excluded. Furthermore, well-recognized "old" chemical hazards may surface unexpectedly in new "high-tech" industries and in inadequately supervised small plants, notably in third world countries. It is probable that epidemiological studies will continue to identify unusual variations in cancer incidence and to investigate potential causal associations as illustrated by domestic radon gas. These observations justify routine monitoring surveillance studies, especially where excessive exposures are suspected. Such activities essentially represent the cancer equivalent of the routine public health surveillance carried out for communicable diseases.

For the reasons above, notably lack of sensitivity, many such studies will be "negative," especially where exposures are several orders of magnitude lower than in an occupational setting, as around waste disposal sites (56), irrespective of whether cancer or some biomarker is used as an end point. Thus, they must be interpreted with care and not be undertaken without reason since, unfortunately, spurious causal associations or random cancer clusters may lead to unnecessary public concern which will not always be allayed, even by well-conducted epidemiological studies.

Developments in Biochemical and Molecular Epidemiology

The value of integrating laboratory investigations into epidemiological studies has long been recognized (1, 2, 57, 58) and
motivated the direction of the early program of the International Agency for Research on Cancer. Studies in the 1950s and 1960s were predominantly related to identifying virus markers, hormonal patterns, or tissue analysis for suspected carcinogens, e.g., dichlorodiphenyldichloroethylene. Today, elegant and sensitive laboratory techniques such monoclonal antibodies, DNA hybridization probes, rapid screening test techniques, etc., permit the direct or indirect identification, measurement, and evaluation of multiple cellular processes in in vivo and in vitro systems (14, 15, 59, 60) in addition to modern analytical chemical methods (61). Harris (60) has examined the possible use of in vitro models utilizing human tissues and cultures to permit increased understanding of the processes controlling growth, differentiation, and neoplastic transformation in human cells, including carcinogen metabolism, DNA damage and repair, and the role of oncogenes. Nonethless, major difficulties still remain in attempting extrapolation of carcinogenic data and knowledge of mechanisms from laboratory animals to humans and from heterogeneous populations to individuals. The complexities of relating transformation to a single defined agent are well illustrated by Duesberg (62) for the retroviruses.

In vitro neoplastic transformation in human cells is difficult and may possibly be intrinsically different from transformation in rodent cells (60). However, the study of growth differentiation in normal and neoplastic human epithelial cells and the hypothesis of selective clonal expansion and the potential repression of carcinogenesis by many techniques in culture do suggest theoretical possibilities to intervene in key mechanisms critical to transformation and tumor induction.

At present, great interest in molecular epidemiology is focused on biomarkers. These are of many types. Some might be best described as specific predictors of neoplasia or preneoplasia, others as indicators of increased susceptibility to cancer or exposures to exogenous carcinogenic agents. Considerable hope is being placed on their employment in epidemiology since they theoretically can provide guidelines, not only to molecular mechanisms but also to potential carcinogenic triggers (14, 15). Thus, carcinogens such as aflatoxin B1 can be activated to form carcinogenic DNA adducts in cultures of human tissues. Other biomarkers include onecogenes, antionecogenes, membrane changes, growth factors, hormonal receptors, enzymes, micronuclei, etc. (14, 15, 59, 63-69). Carcinogenic metabolites may also prove informative such as intragastric or intraoral formation of N-nitroso compounds (47, 70). Chromosomal abnormalities are frequent in human cancers and may be specifically associated with certain tumor types, but their specific biological relevance and significance are usually not known (71). Similar limitations relate to the detection and evaluation of transforming genes in tumors.

From the viewpoint of identifying exogenous factors, there are significant variations relative to carcinogen metabolism, DNA damage, and repair in somatic activities that may occur in various tissues of individuals and outbred animals which are of significance in inferring biological extrapolation to low doses (60). The value of a specific biomarker requires that it be demonstrated to predict a specific end point, e.g., tumor or defined preneoplastic lesion, or provide a measure or index of previous exposure to a specific chemical (14, 69) or virus (72). This is true whether it reflects a key molecular event or is a surrogate measure. The extreme sensitivity of the methods used in the identification of molecular markers, however, subjects their evaluation to the same biostatistical limitations inherent in studying any low level discriminator. It may prove difficult to evaluate a single biomarker, i.e., a DNA adduct, as predicting cancer or exposure to a very low level chemical risk in the presence of many confounding adducts due to other ambient carcinogens of equal plausibility. While DNA adducts are receiving great attention, DNA damage obviously reflects only one aspect in a complex process. Thus, while it is possible to measure carcinogenic DNA adducts in cells of individuals exposed to carcinogenic chemicals and chemotherapeutic agents, it is unlikely that they will necessarily be quantitative predictors of cancer risk, even though they measure "DNA lesions considered to be important in carcinogenesis" (60). Inconsistencies between adduct formation, transformation, and cancer induction have also been reported (67-69).

Biomarkers, however, can offer useful information in a number of situations, including: (a) possible identification of a suspected high-risk group in an occupational setting, whether the marker relates to a specific chemical (14, 64, 66), biological agent, or metabolite; (b) provide objective support for a "negative" epidemiological study where the "exposed" population shows no quantitative differences from an unexposed population in terms of the suspected factor(s); (c) identification of metabolic variations indicative of individual susceptibility to a xenobiotic chemical (14, 70); and (d) the comparative evaluation of potential carcinogenic mechanisms in humans.

There are, however, ethical problems in informing an individual as to his possession of a marker of uncertain significance when no practical benefit can be offered. Further, where invasive techniques are required, their use may not necessarily be without risk. For the above reasons, the view that biomarkers provide a definitive breakthrough to the investigation of suspected low level potential carcinogenic risks, for example, associated with toxic waste deposits or water or air pollution, and thus offer new eliminatory approaches may be premature.

Interventive Strategies

It is obvious that major changes in diet, cultural, or sexual habits may prove difficult to implement and may be socially unacceptable in large populations unless the latter are convinced of unequivocal benefit at the individual level. As argued above, current epidemiological and laboratory fundamental research increasingly indicates that many human cancers of unknown etiology arise from multiple interactions involving both host and environment, the individual and critical components of which may prove difficult to identify. However, progress in fundamental research increasingly offers possibilities for eventual control of cellular mechanisms or modulating factors involved in transformation and cancer induction through interference ("a spanner in the works") (10, 14, 73-76) rather than by the elimination of a single Life-style factor or an ambient chemical pollutant. Intervention implies both chemopreventive and chemotherapeutic approaches.

Concepts and developments in chemoprevention were recently reviewed in this journal (37, 76). Studies of endocrine-dependent tumors have suggested a number of possibilities through hormonal control, and the impact of oral contraceptives on ovarian and endometrial cancers is well known (75). Further, the development of some form of drug therapy mimicking the critical determinants of first pregnancy or late menarche that could retard or prevent many breast cancers appears theoretically feasible, provided that such a therapy would be adequately tested and be socially acceptable in healthy populations. Viruses may be necessary determinants for certain cancers, e.g., hepatitis B virus in primary liver carcinoma in Africa.
or human papilloma virus in cervical cancer (72). Vaccines offer an obvious approach to active intervention for such cancers and are being tested.

While there are many hypotheses for cancer control through changes in the dietary environment, such as the administration of retinoids and antioxidants or modification of fat and fiber intake, their effectiveness remains to be established.

It is anticipated that epidemiology will contribute to such efforts through well-executed, integrated laboratory and field studies and rigorously controlled clinical intervention trials of chemopreventative technologies, vaccines, etc. Such trials require considerable logistic and technical effort and should not be undertaken lightly. Thus, the attempt of the International Agency for Research on Cancer to reverse esophageal cancer by dietary supplements in China showed no effect after 1 year. Despite the major further effort involved, further follow-up is clearly required before the negative results can be accepted.

Epidemiological studies must not only be directed to the identification of carcinogenic factors but also give greater attention to inverse relationships and the characteristics of populations at a low risk to cancer, including socioeconomic factors, with a view to seeking clues to inhibitory mechanisms. On the other hand, if chemoprevention through modest dietary or therapeutic manipulation is shown to be impractical, then chemotherapy represents the most logical alternative. Both approaches are dependent on essentially similar lines in basic carcinogenesis research.

General Comments

There is a large group of cancers in humans for which major causes and consequent preventative strategies are well defined. However, there still remains much neoplastic disease with a significant environmental component for which no unequivocal guidelines for prevention can be given due to the inherent biological and biostatistical limitations to identifying controllable etiological factors. Two divergent strategies have developed for the control of such cancers. First, there are large regulatory programs based on fairly rigid quantitative risk assessment designed to control or eliminate the evergrowing number of potential carcinogens, mutagens, and promoters usually present in minute quantities in the ambient environment. In contrast, the biological approach attempts to analyze the molecular and mechanistic biological base of transformation and modulation with the objective of eventually intervening actively in the carcinogenesis process.

The past effectiveness of control measures on occupational cancer and the ecological benefits of much regulatory activity are unquestionable. However, it is important to distinguish between environmental controls for ecological reasons and those enacted to reduce cancer risks. Exact figures are difficult to obtain, but calculations of the direct or indirect costs of environmental controls indicate enormous financial expenditures and estimates ranging up to several per cent of the gross national product have been reported (77). Such controls are often enacted on the premise that they will significantly reduce the human cancer burden. Irrespective of the exact cost, it is not unreasonable to regard this expenditure as a large if not the largest national effort ostensibly directed to cancer control. Its effectiveness and relevance to health as distinct from the ecological component should be accordingly critically examined.

Despite intense epidemiological efforts, the list of carcinogenic chemicals and occupations established in humans has not expanded significantly in the last 15 years although the number of carcinogens, mutagens, and enhancers (both man-made and natural) identified in animal bioassays continues to grow. Moreover, there is little objective evidence as distinct from theoretical calculations that regulation of minute quantities of ambient pollutants has had a significant impact on the overall burden of cancer in recent years apart from classical high-risk occupational and point source situations (2-4). Exposures to most chemicals of concern began during and after World War II and sufficient time should have elapsed by now to show some impact. Nevertheless, the emotive nature of cancer as a disease has led to the argument that one cannot wait for “dead bodies” before enforcing regulatory controls irrespective of their effectiveness. This argument is meaningless for de minimis risks, since it is impossible to prove the negative. On the other hand, it has great weight among the public and among many well-intentioned people with limited scientific experience in chemical carcinogenesis as illustrated by the California Safe Drinking Water and Toxic Enforcement Act of 1986, adopted by Proposition 65.

The use of quantitative risk assessment as a surrogate measure of the danger of potential ambient carcinogens has been discussed. Despite lack of confirmation and known limitations, definitive claims are made by some as to the exact number of cancers that are or will be caused by an exposure or will be prevented as a result of certain regulatory actions (78). Such claims confuse prudent control of unnecessary exposures to potential risks with actual cancer prevention.

While molecular mechanistic studies may not necessarily contribute to the establishment of generic guidelines to measure cancer risks of low probability, they are of inestimable value in risk characterization. Thus, competent scientists, using data on type of carcinogen exposures, pharmacokinetics, comparative metabolites, etc., can often provide sound opinions as to the probable significance to humans of potential carcinogenic hazards which can be used for prioritization and to distinguish the trivial from the significant, even when the data are incomplete. Such judgments may be more meaningful and scientifically less subjective than theoretical estimates based on biomathematical models. The latter, however, can provide legitimate input to the analysis of complex interactions and their operation, but mathematical elegance cannot substitute for reality and scientific judgment. The question is still essentially under what conditions a suspected factor, e.g., vinyl chloride or unsaturated fat, constitutes a hazard to humans. Thus, at some point we must rely on scientific judgment as to the triviality or significance of a risk, and such judgment must remain the essential ingredient of any rational public health policy.

As discussed above, developments in cellular biology (including molecular epidemiology) indicate the possibility through identification of key mechanisms of directly or indirectly inhibiting or interfering in carcinogenesis (through either chemoprevention or cure). Such research represents the logical outcome of Berenblum’s concepts (10) and has been emphasized by the AACR Public Affairs Committee report (76) and the present National Cancer Institute program (79).

Unfortunately, such concepts which are widely accepted by many oncologists are almost completely ignored by regulatory or legislative bodies in their perception of cancer control strategies. More formal input to the public arena by scientists with recognized expertise in chemical carcinogenesis would appear to be essential to ensure that such complex and important

1 The abbreviation used is: AACR, American Association for Cancer Research.
scientific issues involved are adequately discussed.

Role of the AACR

As a general rule, the national professional societies within a country contain the majority of recognized scientists in a specific discipline. The AACR remains the traditional professional and academic society for chemical carcinogenesis, although today many epidemiologists, virologists, cellular biologists, etc., involved in carcinogenesis may belong to other societies. In determining to what extent policies directed to controlling chemical cancer risks in the United States are influenced by the AACR, I have reviewed formal input by members to some bodies.

In 1983, a committee of the National Research Council was charged to report on the management of risk assessment in the federal government with emphasis on the role of chemicals in cancer (25). There was one member of the AACR among the committee members and one among the 35 external advisers. No other recognized leader in molecular biology or carcinogenesis appears to have been formally involved. The recent National Academy of Science report on the impact of pesticide contamination which emphasized that a high risk existed had only one member of AACR among its 16 associates (78). These important conclusions were based on biomathematical models, the basis of which was not critically examined. The Environmental Protection Agency is the lead body in regulating carcinogenic hazards in the ambient environment in the United States. Only 1 of the 58 members of the Scientific Advisory Board in June 1986 and only 2 of the 7 members of the subcommittee on Carcinogenicity Guidelines were listed as members of the AACR. Of 19 members of the influential interagency committee reviewing the nature of chemical carcinogenesis in 1985 (16), only 3 were AACR members. The few AACR members mentioned clearly do yeoman service, inasmuch as the same names recur. Obviously there is considerably more input by AACR members to regulatory activities as advisors, etc. However, this contribution is difficult to evaluate because they cannot be identified as responsible for the final report.

Whether these bizarre observations reflect a failure by the agencies to recruit formally from the society or an unwillingness by academic scientists to be involved in an area which they may regard as political, nonscientific, or trivial is a matter for speculation. Certainly the subject of risk assessment, although emphasized by regulators as a major “new science” on which to base cancer policy, is generally ignored by oncologists. The Environmental Protection Agency stated that only 4 of the 62 comments received for its guidelines for carcinogenic risk assessment were from academic institutions (26).

These comments are not meant to disparage scientists from other disciplines, who are well represented and whose competence in carcinogenesis may be equal to or greater than that of members of the AACR. Nor is it clear that regulatory policies would be changed since considerable scientific judgment has been exercised despite use of models, at least in some cases (80). Nonetheless, the question remains as to why there is so little formal input by members of the AACR in a scientific area of such major public concern.

Conclusions

The need to apply and intensify the control of known causes of cancer, especially tobacco and chemicals in the workplace, is obvious. However, current research indicates that there are limitations to cancer control through regulation or simplistic control of life-style factors. In contrast, such research offers the possibility of developing feasible techniques to interfere actively in carcinogenic mechanisms. Such techniques will be based on fundamental and basic research and appear to me to represent the most logical scientific method to reducing the burden of human cancer in the future. Where chemopreventative strategies are lacking, therapy seems to be the logical alternative, and both depend on fundamental molecular research. This view offers no immediate short-term success but rather a long-term commitment in manpower and funding. Despite clearly defined goals and targets, there is no certainty as to the time frame or effectiveness of individual projects. This fact, based on current knowledge, although disappointing, must be accepted but is difficult to convey to the public, legislative bodies, and public interest groups who are inexperienced in the complexities and needs of modern biology. Consequently, immediate control of putative environmental carcinogens at minute levels or recommendations for major changes in “life-style,” including dietary patterns, have considerably greater public appeal irrespective of effectiveness or necessity. Over the last two decades, moreover, such approaches have developed large constituencies in industry, academia, toxicological laboratories, and government as well as among environmental activists. Thus, major public resources and efforts are directed predominantly to detecting but not to evaluating environmental hazards. According to the Conservation Foundation (81), “tens of billions of dollars are being invested to comply with environmental standards but little, comparatively, is being invested to improve the scientific basis for the standards.”

Such efforts are operating outside the usual norms of scientific scrutiny to determine effectiveness, intellectual content, and financial justification. Accordingly, it may not be surprising to find that a recent government-sponsored task force established to recommend on research in environmental health policy seriously suggested that the usual statistical restraints in evaluating environmental agents should be relaxed in the name of prevention (Ref. 27, p. 288).

While differences in opinion as to the direction of research are part of the normal development of science, fear of cancer among the public may have undue impact on the direction of cancer control at the legislative level. However, if the arguments presented above are valid, much of this national effort expended in the name of cancer control is directed to strategies which are both costly and apparently ineffective. The danger of emphasis on the benefits of certain control measures based on quantitative risk assessment lies not in their intent and irrelevance but in their false accuracy. This may maximize trivial risks, cause unnecessary public concern, and thus divert limited resources away from more effective cancer control strategies and other more important national social and health goals.

Holland (82) has emphasized that “cancer research is less dependent on individual breakthrough than on steady progress over a number of years.” The fact that this progress has been apparently slower and less spectacular than originally hoped does not mean that the war against cancer is being lost, as frequently announced, but rather that the biological problems are more complex than anticipated in 1970 (83). Moreover, such lack of progress in no way negates the statement of Elizabeth Miller (84) that cancer control strategies must be based on scientific knowledge and methods. These require intellectual integrity and scholarship. It is postulated that the direction of current cancer research control activities should be...
of concern to members of the AACR and that the challenge posed by Shear in his presidential address (85) as to whether the AACR will accept a stronger role in the public arena can no longer be ignored. Failure to do so may distort the issues by encouraging attacks on the opinions of respected scientists sponsored by those unfamiliar with scientific developments (86).

References

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