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Commentary

Multifactorial Carcinogenesis: Implications for Regulatory Practice

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The last decade has seen increased recognition of the complexities of carcinogenesis, with significant implications for cancer control and prevention. No attempt will be made in the present paper to discuss in depth the molecular and biological nature of multistage carcinogenesis, as these aspects are adequately covered by other papers. Rational regulation, however, will depend on some understanding of their mechanisms.

Early attempts by authorities to regulate and control disease were directed to communicable diseases such as smallpox, plague, leprosy, etc. In view of the very inadequate understanding of basic mechanisms, regulations were essentially pragmatic, being based on empirical observation. Nonetheless the successful control of these diseases has had a major impact on public health policy and scientific attitudes to the prevention of chronic disease, including cancer, by regulation of defined hazards. These attitudes were reinforced by the successes in cancer prevention and control through the identification of major occupational and drug hazards, and of the danger of such cultural habits as cigarette smoking, betel chewing and ethanol ingestion. Today, effective public health regulations and guidelines have been promulgated for a number of defined risks in many states. Accordingly, cancer control has tended to be considered only in the context of a single predominant initiating factor, e.g., 2-naphthylamine, although the role of promotion in cigarette smoking in lung cancer had already been emphasized in the early 1950s (*1*).

It had long been clear, however, that many human cancers could not readily be ascribed to a single predominant carcinogenic stimulus and that many other factors were involved, including diet and behavioral and cultural patterns (*2*). Thus, observations in the South African Bantu demonstrated that cancer patterns differed very significantly from those within industrial countries, and that many cancers could not all be readily explained by then current hypotheses. While confirming the influence of environment as a total concept, it was emphasized that "way of life" was also involved (*3*). Nonetheless, although well documented by the 1940s (*4*), the concept of two-stage or multistage carcinogenesis tended to be neglected. More recently, the importance of modulating stimuli has received attention as analytical studies in humans have demonstrated an association with certain "carcinogenic risk factors" related to behavior and diet. This is a convenient term for many lifestyle-associated risks. Such risk factors are believed to reflect modulating stimuli which effect not only initiation but also promotion and inhibition (*5-7*). These are now being investigated as described by others at this meeting.

The question therefore arises as to what extent the principles adopted for control of well defined carcinogenic hazards, chemical or physical, are equally effective for the prevention of those cancers possibly related to the interactions of the many exogenous and endogenous factors involving initiation, cocarcinogenesis, promotion, progression, inhibition and modulation. This is an area in which there still remains considerable confusion as to terminology, since the basic mechanisms are poorly understood at the molecular level. Further, classical epidemiology and experimental approaches do not offer satisfactory possibilities for pragmatic prevention, at least in theory. For convenience, the present discussion will use the terms "initiation" and "promotion" with the connotation developed from the mouse two-stage model, recognizing their inadequacies in biological terms, since this model no longer adequately reflects current views on carcinogenic mechanisms.

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Aims of Legislation and Regulation

There is an extensive literature on this subject, and some of the problems have been recently summarized by Campbell (*8*). Fredrickson (*9*) has described the difficulties in reaching a consensus even among scientists, especially where they are uncertain as to degree of risk and mechanisms. In general, while the objectives of certain legislative regulations may appear obvious and based on common sense, implementation may give rise to scientific and socioeconomic problems of enormous complexity. Ideally, regulation should meet the following requirements.

Regulation should be effective and efficient, leading to reduction in the hazard. It is important, moreover, that its effectiveness should be clearly perceived. This requires that the degree of risk can be measured and defined, and that effect can be demonstrated. Unfortunately, the latter may not be practical where the risk is very low or where only the potential of risk exists.

If possible, regulation should be consistent and not arbitrary or subjective. This requires conformity with widely recognized political and scientific norms. A consensus may not exist with ill-defined generic risks as compared to defined and measurable risks. Thus, while there is no real conflict between the scientific data and public health policy, for most major occupational or drug hazards, there may be wide variations of opinion as to the degree or even existence of a potential risk as determined from experimental or *in vitro* data. Further, the effectiveness of public health strategy in relation to exposures to multiple low levels of human or animal carcinogens is subject to uncertainty. In such cases regulation is often *ad hoc* or pragmatic and tends to be based on other certain criteria in addition to scientific considerations. Where international acceptance is sought, the scientific data base should have been published in the appropriate peer-reviewed literature, although national governments, of course, have the right to use material from any source in making decisions.

Regulations should be feasible. Thus, they should be acceptable, both to the general population and to the limited segments of society to which they may be applied. For example, where attempts have been made to control pleasurable cultural habits, e.g., cigarette smoking and alcohol consumption, general acceptance by the population has been limited, leading to double standards in public health policy.

Regulations should be capable of being modified with new knowledge to reduce potential conflict with the scientific community. This flexibility should be inherent in the regulation as originally legislated.

Regulations should not be counterproductive, in the sense that they distort perspectives and priorities, nor should they give a false sense of security. They should not replace a smaller hazard by a greater risk. Thus the risk of dying from myocardial infarction in postmenopausal women who are not treated with estrogens may be greater than the risk of dying from endomentrial cancer (*10*). It is also important for scientists to remember that very minor cancer hazards shoud not be overemphasized to the detriment of control of other health or ecological hazards which may be of greater importance to the community.

In conclusion, the above comments imply that regulations require that the hazard and degree of risk can be defined and measured. The important question of risk/benefit analysis will not be discussed.

Role of Modulators in Multistage Carcinogenesis: Implications for Control of Generic Risks

It is necessary to classify carcinogens as genotoxic and nongenotoxic (*11*). The former group are believed to interact directly or after activation with cellular DNA and lead to irreversible damage to genetic material of some magnitude. Most are mutagens. The nongenotoxic stimuli are believed to operate through epigenetic mechanisms and not interact directly with cellular nucleic acids. It is possible both types of stimuli may operate indirectly by triggering cancer-associated genes. In terms of the classical two-stage model, a complete carcinogen is assumed to have both initiating and promoting action. Some carcinogens are described as incomplete initiators, in the sense that they lack promoting action, and it is postulated that their effects are largely dependent on the latter. These distinctions are based largely on limited animal models. The molecular mechanisms which basically would distinguish incomplete from complete initiation as well as the early stages of promotion from initiators remain the subject of investigation and conjecture especially since common mechanisms remain to be demonstrated between different models, e.g., skin (*12, 13*) and liver (*14*). Furthermore, many other factors, some of which are under genetic control, have now been identified as modulating cancer development in man and animals, e.g., procarcinogen activators or inactivators require that a much wider conceptual base be utilized than consideration of only initiation promotion. It is thus

evident that the classical two-stage model, although representing a major conceptual advance at the time, is insufficient to explain the complex mechanism involved in carcinogenesis including progression.

As already mentioned, the greatest successes in cancer prevention have been related to the identification and control of strong carcinogenic stimuli, e.g., alkylating agents and such cultural habits as cigarette smoking. In some cancers, however, the effect of a promoting agent may be so strong that it can be identified and regarded for practical purposes as a "nongenotoxic" carcinogen, in which case preventive action may be possible, e.g., postmenopausal estrogen medication and carcinoma of the endometrium.

Lifestyle Cancers

Despite intensive effort, there has been comparatively little progress in identifying and controlling the casual factors responsible for approximately 40% of cancers in males and 80% of those in females. These cancers are largely those of the gastrointestinal tract and of the endocrine or endocrine-dependent organs, e.g., breast, prostate, uterus. Many of these latter have been associated with certain carcinogenic risk factors related to lifestyle. The term "lifestyle"—in addition to including obvious cultural habits, e.g., cigarettes—also covers diet, e.g., lack of fiber, and behavioral and cultural patterns, e.g., age at first pregnancy and degree of sexual activity. There is considerable circumstantial evidence to indicate that such carcinogenic risk factors may reflect the interaction of numerous modulating factors, e.g., enhancers, promoters, inhibitors, enzyme activators, as well as the *milieu interieur*, e.g., gastric acidity, bacterial flora. While modulating stimuli may eventually be defined more objectively in biochemical terms and their relative importance evaluated, the importance of such research in humans is only now beginning to be recognized as discussed by Wynder (*15*). Where strong initiating stimuli cannot be identified it is possible to postulate that, while certain events causing severe genetic damage may occur frequently in man or animal, either spontaneously or due to endogenous or exogenous exposure to initiators, such damage is either incomplete or lethal. Accordingly, in the former case potent enhancing or modulating factors would be pivotal to cancer expression. Theoretically, such factors, if potent and definable, could be identified and evaluated by standard epidemiological studies. Unfortunately, such situations are rare in humans, and techniques to identify "spontaneously initiated" cells in man are not available. The type of lesions, for example as observed in latent carcinoma of the prostate and cervical-carcinoma *in situ*, for example, as compared to invasive and metastasizing cancers is unknown. However, the existence of spontaneous initiation is consistent with the observations of Yuspa and Morgan (*16*), Haynes et al. (*17*), Scherer and Emmelot (*18*) and others in experimental models, but its nature remains a subject for speculation. On the one hand, it may be the equivalent of background mutation (*19*) and be due to failure of DNA repair, decontrol of oncogenes, viruses, genetric factors, etc. (*11*). On the other hand, it may reflect long-term exposure of the target cell to numerous potential initiators and mutagens, both exogenous and endogenous—e.g., *N*-nitroso compounds, epoxides of cholestrol—to which the target cell is exposed within the body. Endogenous formation of such compounds are now accepted as demonstrated and are theoretically identifiable and measurable. However, in view of the vast number of compounds possibly involved and since the effect of each day may be insufficient to be complete and to permit measurement of its additive or inhibitory effect, the possibilities of individual identification and control in humans would appear minimal. Where cancer expression is dependent equally on numerous environmental but ill defined modulating factors of very low potency, there is no certainty that these will be more easily identified or permit the development of meaningful preventive strategies. Accordingly it may be preferable to concentrate research effort on the nature and role at the molecular level of "spontaneous" initiation and modulating factors, since control may prove eventually more practical through external intervention, e.g., chemoprevention based on understanding of mechanisms.

Implications for regulation

The above comments carry significant implications in developing rational legislation and regulations to meet the guidelines given above. First, where the role of a modulating factor is so predominant as to permit it to be identified and measured, practical prevention may be possible, i.e, control of postmenopausal estrogens and cancer of the endometrium, cigarette smoking and lung cancer. Thus, control of cigarette smoking is a base for rational public health policy irrespective of the relative importance of initiative or promotive effect of cigarette smoking. On the other hand, there is little evidence to indicate that such strong promoting factors as DDT and phenobarbitol in the rodent have any cancer-enhancing effect in humans, nor that their control has had a significant impact.

In complex situations where individual modulating factors, although clearly associated with cancer development cannot be measured or defined, e.g., types and quantity of fat, calorie intake, fiber content, etc., generic control through legislation would appear impossible.

Thus, in conclusion, I believe that there are at present insufficient data to permit promulgation of generic regulation in terms of cancer-enhancing factors that would meet the requirements indicated above, Further, in the immediate future it is unlikely that such information will be obtained and Thus decisions must be made on an *ad hoc* basis. Further, it should be noted that many modulating factors, notably hormonal and dietary, may be important in maintaining health. This means that consideration of such factors only in terms of cancer and not in terms of total adverse health effects may be imprudent (*20*) as for the case of postmenopausal estrogen therapy discussed above.

Conclusion

For over 40 years the role of modulating factors has been accepted, and it is distressing how little additional information has been acquired that has proven of unequivocal value in cancer prevention. However, with more sophisticated approaches both in the laboratory and in the field, it may now be feasible to study the modulating aspects of carcinogenesis more effectively. Nonetheless, in examining the role of epidemiology in this field, we could find only mention of "promotion" in six of over 1300 studies described in the 1981 IARC Directory of ongoing epidemiological research. This would suggest that this area is being inadequately studied or that epidemiologists are considering "carcinogenic risk factors" in a much wider context than the classical two-stage model.

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