Letters

Chemical Carcinogenesis

In a recent editorial "Cancer phobia" (31 July, p. 473), Philip H. Abelson criticizes the use of animal carcinogenicity tests as a basis for decisions about human exposure to chemicals. He comments that "comparatively little effort has been devoted to studying the mechanisms of chemical carcinogenesis." This ignores the major research effort of the past few years which has established that one mechanism of chemical carcinogenesis is induction of mutations that "activate" the protooncogenes of mammalian genomes. An elegant demonstration of this mechanism was the in vitro activation of a protooncogene by benzopyrene diol epoxide, a mutagenic metabolite of cigarette smoke (*1*). Another vivid demonstration is the tumorigenesis associated with expression of activated oncogenes in transgenic mice (*2*). A third important line of evidence comes from the isolation of activated oncogenes from human tumors (*3*). Clearly, human DNA is susceptible to chemical mutagenesis that can activate protooncogenes.

The prudent course, in view of this knowledge, is to place the highest priority on eliminating human exposure to mutagenic chemicals. Since oncogene activation can play a role in tumorigenesis in experimental animals, it would also be prudent to eliminate exposure to known animal carcinogens. This policy may unnecessarily eliminate some animal carcinogens that are not human carcinogens. However, the economic cost of such errors appears to be a reasonable price for a policy that applies current knowledge to the goal of minimizing the incidence of cancer. To permit continued exposure to mutagenic chemicals is to take unnecessary and indefensible chances with the public health.

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Abelson suggests that the public has been misinformed by the results of chemical carcinogenesis studies in animals, particularly rodents. The reasons Abelson gives for the "dubious relevance" of these animal studies for humans can be broadly grouped as follows: (i) Animal studies are flawed because of the use of "massive" doses, inbred strains, supersensitive species, and questionable end points (liver tumors); and (ii) risk assessments are flawed because they rely on animal data ("animals are not humans") and linear extrapolation. Finally, Abelson suggests that an inordinate amount of money is devoted to "testing" as compared with the understanding of carcinogenic mechanisms.

True, in laboratory experiments animals may be exposed to chemicals in greater amounts than those to which humans are normally exposed, but past occupational exposures in at least three important instances (asbestos, benzene, and 1,3-butadiene) are not different from the amounts used in laboratory experiments. However, this approach [the use of a maximum tolerated dose (MTD)] is well justified on scientific bases (*1*) and is no different from the approach used for the study of other biologic or toxic end points. The primary purpose of such studies is hazard identification, that is, to identify those chemicals most likely to present a potential hazard to humans. It takes an unusually high exposure of cigarette smoke to cause cancer in laboratory animals (as compared with humans) (*2*). Does this mean the studies are not relevant? If cigarette smoke were an "unknown," would one assume tobacco was safe because the dose to animals was higher than the average human receives? In the case of many chemicals, animals are able to detoxify hundreds or even thousands of times faster than humans do (*3*), and to get an equivalent dose to the target tissue in such a case would require much more of the chemical in animals. Also the use of 50 animals per dose group can only detect cancer occurring at a relatively high incidence and, therefore, the effect in animals needs to be optimized. The reason the MTD was initially used in chemical carcinogenesis studies at the National Cancer Institute was because the developers of these studies found that cancer did not occur in rodents with *known* human carcinogens at doses below the MTD (*4*).

Exposure of animals used in carcinogenesis studies for their "lifetime" is, in fact, the exception rather than the rule. In most of these studies the animals are not exposed until 4 to 8 weeks of age and the exposure is terminated after 18 to 24 months, a point at which most (70 to 80%) of the animals are still alive.

The relevance of mouse liver tumors to humans and to risk assessment in general is commonly misunderstood. An increase in the incidence of mouse liver tumors alone (without other tumor effects) has been used in fewer than 10% of chemical carcinogenesis studies to classify a chemical as a carcinogen (*5*). Also, oncogene studies suggest that mouse liver tumors have important features in common with human tumors (*6*). While liver cancer is comparatively uncommon in the U.S. population, the incidence is indeed high in other areas of the world (*7*). Additionally, a liver tumor response in the laboratory animals is highly logical, since the liver is the major organ in animals and in humans for metabolism (activation or detoxication) of many xenobiotic chemicals and, in such cases, the metabolic products (proximate carcinogen) would be higher in the liver.

The use of inbred animals in biomedical research is common practice. In toxicity studies one attempts to control for a myriad of variables including diet, temperature, water, and infectious disease, as well as the genetics of the experimental animal, to minimize extraneous factors that could possibly confound the results of the study.

The most appropriate method of extrapolating animal data to humans is a matter of ongoing debate and research. While no single mathematical model is universally recognized as the most appropriate for low dose extrapolation in carcinogenesis, models involving linearity have been supported, for example, when uncertainty exists regarding the mechanisms of carcinogenic action (*8*). Similarly, in the absence of other information it also seems prudent for public health reasons to assume that humans are at least as sensitive to cancer induction from an unknown chemical as the most sensitive species. It is important to protect that segment of the population most prone to cancer development from exposure to chemicals, and to protect those most highly exposed occupationally.

It is not correct to state that little effort has been devoted to studying the mechanisms of chemical carcinogenesis. In our own institute (the National Institute of Environmental Health Sciences, National Institutes of Health), for example, a large portion of our "testing" budget is devoted to the understanding of mechanisms of toxicity, including carcinogenicity. In addition, two-thirds of our intramural effort and extramural (grants to universities) budget would be classified as mechanistic research (*9*). Other institutes likewise allocate significant amounts of their budgets to the study of biological mechanisms.

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The Candidates' Budgets

The time has come to reconsider the scientific method for selecting presidents. In response to the editorial by Daniel E. Koshland, Jr. (19 June, p. 1501), I wrote letters to each of the 14 most likely presidential candidates (seven Democrats and seven Republicans) requesting that they consider the preparation of a federal budget to provide voters with a discrete measure of candidates platforms. The experiment had the advantage of sampling the entire population as of July 1987. The letters suggested that the candidates consider the previous year's budget as a control and report only the significant differences between their budget and the control. Embellishments regarding the potential benefits to the presidential campaign process and the appropriateness of these measures were included, and Koshland's editorial was cited.

Today is the bicentennial of our Constitution, and nearly 2 months have passed since the letters were submitted to our presidential candidates. The raw data include responses from two of the 14 candidates, or 14%. These data deliver a crushing blow to the hopes that the majority of presidential candidates are concerned with "we the people." It is also noteworthy that Republican candidates unanimously chose not to take part in the experiment.

The two Democratic candidates who responded were Michael Dukakis and Paul Simon. The letter from Governor Dukakis' staff was concise (two paragraphs); it stated that my request could not be reasonably fulfilled and that such a specific proposal would not accurately reflect an actual Dukakis budget in 1989. In addition, it said that this request would not provide an accurate representation of "underlying program tradeoffs." Finally, it said that Dukakis would prefer to be judged on his past record and on his statements of purpose for the future. The letter from Senator Simon stated that the request would be considered very seriously. He went on to point out his support for "education, productivity, peace, and justice."

These observations indicate that a number of candidates may proclaim love of mother because it costs nothing, but only a small minority might sell their Porsche to support her in the manner to which she has become accustomed.

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Human Control

Judith Rodin's article, "Aging and health: Effects of the sense of control" (19 Sept. 1986, p. 4770), reviews empirical studies indicating that the psychological construct "sense of control" can have strong effects on biological variables ranging from physiological changes to mortality. Because of the importance of this research for behavioral and natural scientists in the health and human sciences, and because theoretical and empirical work on control is at such a pivotal juncture, we believe it is important to address two substantive areas in Rodin's article that require further clarification.

Although the data Rodin cites are promising, they emanate primarily from laboratory and institutional settings. It is unclear how effectively these techniques can be generalized to less structured and more complex environments. On the basis of research with clinical populations suffering from impairments of control [for example, eating disorders; substance abuse; stress related disorders; Type A behavior (*1*)], we believe there are limits to the effectiveness of self-control strategies [for example, biofeedback, behavioral self-control, meditation, progressive relaxation (*2*)] and that relapse and lack of compliance are frequent (*3*). Future research needs to assess the differences, if any, between control-enhancing interventions offered by the environment and "self-control" strategies generated by the individual as well as the limits of their effectiveness (or adverse effects) in both clinical and normative populations.

Rodin's article highlights the lack of uniform, operational terminology in research on control. The use of different terms, with variable meanings, suggests the critical need to systematically address the construct of control theoretically and conceptually. We believe what is needed is a theory-driven research model, based on clarification of semantics and efforts toward developing a unifying theory of control. Examples of some important clarifications and issues not addressed in Rodin's article include the following: (i) the relationship between "sense of control" and actual control; (ii) whether "sense of control" is most effectively generated by self-control behaviors, control enhancing interventions, or belief that a benevolent other has things in control (*4*); and (iii) the negative effects of an "illusory" sense of control caused by unhealthy defenses and denial.

Further, since many major events (such as death) (*5*) and minor events (for example, daily hassles) (*6*) cannot be controlled, it is necessary to make the critical distinction between altering what we can directly control (a mastery model) and dealing with what we cannot control and to which we can only hope to respond well (a coping model) (*7*). Finally, equating control with active efforts to alter or change, or to use restraint to refrain from altering or interfering, may reflect a limiting, culture-bound definition. Other cultures conceptualize control in terms of yielding, acceptance, and letting go (*8*). More of a "sense of control" may be gained from letting go of active control (acceptance) than continuing efforts to try to change that over which we do not have control.

Without an effort at more clinically rigorous investigation and clarification of terms and constructs, we may be significantly limiting our understanding of and approaches to human control.

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