RESEARCH AND DEVELOPMENT IN CARCINOGEN CONTROL

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There are two questions fundamental to the prevention of cancer by limiting or preventing exposure to carcinogenic agents: 'Which agents present a hazard?' and, if this is answered in the positive, 'Who, in consequence, is at risk?' Both of these questions have been the subject of research, in respect of particular substances and exposures, for more than half a century. Answers to these questions have the potential to reduce cancer-associated mortality and morbidity; however, the means of finding answers remains limited when considered against the background of progress in other fields of health research. This article describes which agents pose a carcinogenic hazard, who is at risk, and the future prospects of research in and development of carcinogen control.

WHICH AGENTS POSE A CARCINOGENIC HAZARD?

When presented with the question 'Which agents pose a carcinogenic hazard?' one assumes that the answer must involve a list. However, the answer to the question is not to be found in a list, and an understanding of why 'lists' of chemical carcinogens are a problem is fundamental to both the public health and the research aspects of carcinogenesis.

The most authoritative assessments of carcinogenicity data—the International Agency for Research on Cancer's (IARC) *Monographs on the Evaluation of Carcinogenic Risks to Humans*—arose because in the early 1970s the IARC was asked by governments from around the world to list known carcinogens. It became apparent that definitive biological criteria to generate such a list (both in respect of determining compounds to be on or off the list) were not available. Rather, the IARC initiated a program to evaluate carcinogencity data for any given agent, using a protocol that ensured that all relevant findings were taken into account. While the *Monograph* series has given rise to 'lists' these were secondary to the individual evaluations and depend on the interpretation (sometimes disputed in individual cases) of the individual data sets.

The means of identifying carcinogens has not changed markedly over the last fifty years. During this time, understanding of the mechanism by which agents cause malignant transformation has moved from reference to tumours in particular animals to the structure and effect of altered gene sequences.[2] Operationally, knowledge has only marginally altered the generalisation that evidence of carcinogenicity is drawn from appropriately designed epidemiological studies and testing of chronic toxicity in animals. Insight regarding a chemical of unknown biological potential can be gained using 'short term tests' for carcinogenicity, most commonly based on mutations of specifically-developed ultrasensitive strains of bacteria; or otherwise involving mutation or transformation of mammalian cells in culture.[3] Tests are generally based on simulating the metabolism of carcinogens so that reactive intermediate products, capable of becoming bound to DNA, are formed in the presence of sensitive bacteria or other 'indicator' populations. While occupying a vital niche, for example, in toxicological evaluation of new drugs, short term test data are supplementary to epidemiological and animal testing data with respect to agents to which humans are already exposed. Finally, it must be acknowledged that, for the majority of specific chemicals, reliance is placed on animal studies, since the occurrence of human exposure to the agent in question—say, a specific pesticide—at high concentration and in the absence of other compounds, is rare.

Despite these generalizations, which concern all carcinogens, data for each compound must be considered on its merits. In some instances the findings are clear: for example, 1,3-butadiene, tris(2,3-dibromo-propyl) phosphate and 2,4-diaminotoluene present a carcinogenic hazard to humans and their use in children's sleepware and in hair dyes has been controlled; likewise sodium fluoride is not carcinogenic and its addition to water supplies is therefore appropriate.

Carcinogenicity data for other compounds, however, are far from clear, and there are plenty of examples that indicate that once relevant studies have been completed, an understanding (and a basis for action) does not necessarily follow. For example, exposure to trichloroethylene is associated with an increased risk of tumours at different sites, or with no increased risk, depending on the occupational context studied;[4] causation of lymphoma by chloro-phenoxy herbicides may be inferred from agricultural and forestry work findings, but studies based on exposure to these compounds have generally failed to confirm this hypothesis, and dioxin (2,3,7,8-tetrachlorodi-benzodioxin) appears to increase risk of cancer generally without being characterised as causing a particular tumour type. In all instances, the corresponding experimental data do not clarify the picture.

Apart from short-term tests, research has not contributed greatly to the assessment of putative carcinogenic hazards. Regarding electromagnetic fields, research data are

unhelpful.[5] In this context, as in the testing of chemicals, it was supposed that artificially transferring genetic material from one animal species to another might provide an improved vehicle for chronic testing, but this hope has yet to be realised. And, for the purpose of elucidating specific mechanisms that account for increased risk of cancer in people occupationally exposed to complex mixtures of agents, novel effective methodologies have not emerged.

WHO IS AT RISK?

Regarding exposure to a specified carcinogen, the facile answer to the question 'Who is at risk?' is "Whoever is exposed'. The dimensions of the category 'exposed' have increased markedly through the achievements of research. Such research addresses limitations inherent in the use of broad indicators to identify persons at increased risk by comparison with a wider comparative population. Thus the populations exposed to toxins produced by the fungus *Aspergillus flavus* (aflatoxins) growing on peanuts and maize, which causes liver disease (and especially cancer of the liver), are those living in tropical Africa and Asia.

Sometimes the carcinogen under consideration implicitly suggests who is at risk: painters and paint manufacturers are exposed to paint solvents; asbestos workers are exposed to asbestos. However, the limitations of such statements are well recognised: administrative staff at a paint factory may never come into contact with paint, while demolition workers (rather than asbestos workers) may have the highest exposure to asbestos.

Nothwithstanding their limitations, broad categories will continue to usefully identify persons at risk. Thus, accumulation of lipophilic pesticides in breast milk may result in the newborn being exposed to relatively high concentrations of carcinogens: a scenario meriting intervention without waiting for direct evidence of harm. Other broad categories of individuals at risk include those who are immunocompromised by, for example, HIV infection or the administration of immune-suppressing drugs.

Finally, a separate body of evidence indicates that not all circumstances of carcinogen exposure result in increased risk. So far as is known, cigarette smokers receive 10 times the amount of benzene as non-smokers,[6] but do not appear to suffer a commensurate increased risk of leukaemia.[7] Ingestion of water containing asbestos derived from piping does not appear to present the hazard posed by respired asbestos. Indeed, the current reporting of a recognised carcinogen such as acrylamide, which is produced in some foods prepared at a high temperature, may be characterised as alarmist. However, if a new route of exposure can identify a higher risk than previously recognised, publicity of relevant observations is justified. Research has contributed little in this context.

Quantitation of individual exposure to many carcinogens is assessable. Elucidation of relevant metabolic pathways has allowed detection of indicative compounds in body fluids. Much more significantly, and subject to on-going study, patterns of mutation attributable to specific carcinogens mark the interface between exposure and mechanistic analysis. Thus, patterns of mutation attributable to aflatoxin, benzo[a]pyrene, or ultraviolet radiation, not only indicate that a relevant exposure has occurred but provide insight into the mechanism of cancer causation [8]. Mutation is the commonest specific genetic alteration exhibited in human malignancy. Such insight is gained from studying tumours, and does not provide any simple immediate means of prevention. However, some progress is being made on the use of genetic information to indicate people at risk from environmental carcinogens. Intense effort has been directed toward the relationship between carcinogen metabolism (assessed genotypically or phenotypically) and risk of malignancy. Differences in risk are sometimes indicated, but variation is not so marked as to have public health implications.[9]

FUTURE PROSPECTS

In common with virtually every area of medical science, understanding of carcinogenesis is certain to be affected by advances in molecular genetics: we are in the postgenomic era. The recent publication *Cancer Cell* epitomises the focus of molecular analysis on the biology of malignancy.[10] Discovery of a 'new gene' that is crucial is unlikely. But the capacity of available technology, such as microarrays (that is, matrices in which cDNA corresponding to 10,000 or more individual genes are 'arrayed' so that the expression of each gene may be evaluated relative to expression of the same gene in some reference context) to assess thousands rather than one or two genes on a single analysis, may change beyond recognition the identification of people at risk from a specific hazard. At the level of public health policy, the exploitation of chemoprevention—whether based on pharmaceuticals or micronutrients—has a limited history but continues to provide an opportunity for action outside the frame of simply 'preventing exposure'.[11]

CONCLUSION

Environmental factors that influence cancer are known to include diet, certain infections and some behaviours. Nonetheless, causation of cancer by specific substances has been, and will remain, a singular opportunity to prevent malignancy. Hopefully, the design and implementation of such preventive measures will continue to be assisted by progress in research.

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