Current Status of Experimental Chemical Carcinogenesis and Its Applications to Human Cancer Risk

William Lijinsky

Chemical Carcinogenesis Program, Frederick Cancer Research Center, Frederick, Maryland 21701

Abstract

The history of chemical carcinogenesis is a record of the observations of physicians and epidemiologists of the relation between the occurrence of uncommon cancers in humans and the exposures of those people to certain chemical agents. In parallel with some of these findings, experimental animal models were developed to imitate the findings in humans. From these experimental studies has been obtained most of the information we have about the mechanisms of chemical carcinogenesis. Many of the biochemical studies have focused on liver cancer which might be an inappropriate general model for chemically induced cancer, liver cancer being comparatively rare in humans. It is not known to what extent exposures to any particular chemical carcinogens are responsible for the major human cancers, and the agents responsible for most of them are not known. It is probable that many noncarcinogenic chemicals act as promoters of carcinogenesis, and among these alcohol can be included as an important contributor.

There seems to be no doubt that carcinogenic chemicals make a significant contribution to the risk of cancer in humans. Whether the risk is greater from chemical carcinogens of industrial origin, from those which result from diet or other habits, or from those formed endogenously is debatable at the moment. However, it is important to consider the role of chemical carcinogens in increasing the human cancer risk because presumably we can do something about it. By reducing exposure to such carcinogenic agents, we can help prevent cancer by lowering the risk.

Only in the case of lung cancer in cigarette smokers has there been convincing evidence that an environmental chemical agent is a major contributor to a type of cancer affecting large numbers of people. For the remainder of the cancers which occur in 1 in 4 of the population, there is no good explanation or cause to which they can be attributed.

It might be supposed that most human cancer is a result of exposure to a multitude of carcinogenic agents over a long period of time; their combined action resulting, in susceptible individuals, in cancer of the types which we commonly observe. These types of cancer in humans are mainly of epithelial origin and differ from the cancers most commonly seen in animals that have not been exposed to chemical carcinogens.

It would be wise then to reduce our risk of cancer by limiting or eliminating our exposure to carcinogens. To do this we must be able to identify those carcinogenic agents to which we are exposed. Means have been developed and are still being developed for determining that a given substance is carcinogenic to animals and, by only a small extrapolation, is likely to be a contributor to the risk of cancer in humans. The problem is complicated by the possibility or probability that some substances might be promoters of carcinogenesis although they themselves are not cancer-causing. Alcohol might well be one such agent. The process of cancer promotion is no better understood than that of cancer initiation, which is to say that it is a process of which we are profoundly ignorant.

The history of chemical carcinogenesis goes back to the announcement 200 years ago by Pott, an English surgeon, of a connection between the occurrence of scrotal cancer, a rare tumor, in men who had been chimney sweeps and their exposure to coal soot. Thus began the study of occupational and environmental carcinogenesis, although it was more than a century until the next significant observation, that of Rehn (1895) who remarked on the frequent occurrence of another rare cancer, bladder cancer, in workers in the synthetic dye industry. He called this cancer "aniline cancer," although we now know that the agent was not aniline but one of several other aromatic amines which are bladder carcinogens in humans as well as in experimental animals. In these cases, as in almost all others connecting human cancer with exposure to certain types of chemical carcinogens, the significant observation was made by an alert physician. A brief summary of the important landmarks in chemical carcinogenesis is given in Table 1.

More complex epidemiological studies have indicated that exposure to certain types of asbestos, especially when combined with cigarette smoking, leads to enormously increased incidences of lung cancer. The high incidence of colon and breast cancers in western countries has been related to a large intake of animal fat. Esophageal cancer and possibly liver cancer in certain areas of the world have been related to the consumption of certain alcoholic drinks. In neither of the last 2 cases nor with cigarette smoking have all the responsible carcinogenic agents been identified. However, our past experience in chemical carcinogenesis has guided our choice of methods for the evaluation of the contribution of environmental carcinogens to human cancer risk. A brief description of some of these findings, which might be useful, is given below.

The polynuclear hydrocarbons have been referred to previously and comprise the most extensively studied group of carcinogens. The best known carcinogen among them is benzo(a)pyrene, a fluorescent carcinogenic hydrocarbon first isolated from coal tar (3). A large number of carcinogenic hydrocarbons have been isolated from coal tar and are present in most organic pyrolysates, such as cigarette smoke and engine exhausts. Considerable progress has been made in elucidating the mechanism of carcinogenesis by some of these compounds although by no means is the problem solved. The smallest polynuclear hydrocarbon that is carcinogenic is 9,10-diethyl-anthracene, and the largest is dibenzo(a,b)pyrene. The
chemical structural specificity compatible with carcinogenic activity is quite marked. The most notable feature of this group of carcinogens is their restricted carcinogenic action. They are very effective carcinogens in mouse skin (but not equally effective in all strains) and in the lungs of hamsters, in which quite high doses are needed to elicit lung tumors. They are not very effective in the skin of hamsters or rats and are completely inactive in guinea pig skin although humans are obviously susceptible. In other species and organs, they are largely ineffective.

One interesting feature first noted with polynuclear hydrocarbons is that a very small dose of a carcinogen, insufficient in itself to give rise to tumors, can so change some cells as to make them susceptible to the action of a noncarcinogenic "promotor," which causes tumors to appear. This 2-stage process of "initiation" and "promotion" was investigated by Berenblum and Shubik (2), and the concept has been applied to many types of carcinogenesis although sound evidence for it is restricted to the case of mouse skin. There is little indication that this process is duplicated in the skin of other animal species. There is also scant evidence for the existence of a 2-stage process of carcinogenesis in other organs and tissues although a multistage process seems theoretically likely. The evidence for the action of promotors in the lung is small although widely accepted. On the other hand, the recent work of Kitagawa et al. (4) and Pitot et al. (11) has indicated that phenobarbital can act as a promoting agent in the liver of rats treated with low doses of carcinogens. This suggests that ethanol might act by a similar mechanism as a tumor promoter for human liver.

Since so many types of chemical compounds have been shown to be carcinogenic in humans and in experimental animals, it is reasonable to assume that the cancers seen in humans are the result of the compoundung of a large number of relatively small exposures to compounds that increase the cancer risk. It seems probable that there is at least an additive effect of one exposure to a carcinogen with another; there is possibly in some cases even a synergistic effect although evidence for this is weak. Therefore, one approach to reducing the incidence of cancer is to eliminate or reduce as many of these exposures as possible. To this end, a large number of chemicals to which there is extensive human exposure have been tested for carcinogenicity in animals. In addition, many compounds structurally related to others of known carcinogenic activity have been tested in an attempt to gain information about the mechanism of carcinogenesis by these compounds. So far, there has been only limited success in this effort, and details of the mechanism of carcinogenesis by even one carcinogen still elude us.

The main classes of carcinogens are listed in Table 2. With the exception of the N-nitroso compounds, all of them show a strong species specificity; that is, only one or 2 species, respond and others are refractory. This is well illustrated by the aromatic amines, some of which (2-naphthylamine and benzidine) induce bladder cancer in dogs and in humans at apparently somewhat smaller doses. They give rise to bladder tumors in hamsters only at much higher doses and fail to induce bladder tumors in rats, although they do often cause liver tumors in rats and mice. In guinea pigs they appear to be noncarcinogenic. Similarly, the aflatoxins are extremely potent liver carcinogens in rats, are perhaps slightly active (at very high doses) in monkeys, and are noncarcinogenic in mice, but there are strong indications that in some parts of the world ingestion of aflatoxin-contaminated food is associated with an increase in liver cancer incidence.

The N-nitroso compounds are an interesting group of carcinogens since they show a great diversity of target organs in which tumors of various types are induced, depending on the species, the route of administration, the frequency of dose, and so on. However, no species has been found resistant to the action of nitrosamines, and it is unlikely that humans are the sole exception. Therefore, it is perhaps significant that several N-nitroso compounds have been found in the environment, often at very low concentrations, and that they can be
formed by reaction of secondary and tertiary amines with nitrite, especially readily in acid solution, as in the mammalian stomach (5, 6, 7). The recent report of the presence of nitrosamines in beer might be important (12), even though the concentrations are low, because of the large quantities of beer drunk. Many nitrosamines cause liver cancer and tumors of the esophagus in experimental animals which might have a bearing on the reported association between drinking of alcoholic beverages and esophageal cancer (in the Calvados region of France) and of liver cancer in other areas. The number of carcinogens inducing liver tumors of similar type in rats is large and diverse including nitrosopyrrolidine, nitrosodi-η-propylamine, dimethylaminoazobenzene, aflatoxin B₁, and acetylaminofluorene. It is difficult to imagine that these could act by a common mechanism.

The following are some of the common characteristics of chemical carcinogens which have been observed in studies made with experimental animals: there is a long latent period; small frequent doses are more effective than are single large doses; they usually do not act by direct contact and require activation; ingestion is often the most effective route of administration; and there is an increased response to higher dose rates, i.e., a higher proportion of cancers and shorter latent period. Similar characteristics have been found in chemicals known to be carcinogenic in humans. These characteristics are well illustrated by the extensive studies that have been conducted with N-nitroso compounds during the past 2 decades and that have led to an increased understanding of the significance of the results of chronic testing of carcinogens in animals. The most notable characteristic of the N-nitroso compounds is their pronounced organ specificity, the explanation of which is probably rooted in differences of metabolism or activation in one organ versus another. Most of the biochemical studies have been conducted in rat liver which is not an important target of most nitrosamines, nor is the liver an important site of formation of human tumors. Therefore, the relevance of most of the past and present studies can be questioned. On the other hand, it is most difficult to carry out metabolic studies in an organ which is as small and muscular as is the esophagus. Consequently, most of our information about the carcinogenicity of N-nitroso compounds is phenomenological and circumstantial.

Even in the rat the findings are very confusing since the strain of rat can make a large difference in the response to a given N-nitroso compound. For example, while nitrosodiethylaniline and nitrosotetrahydropyridine induce liver tumors in Sprague-Dawley rats, both compounds induce only tumors of the esophagus in our Fischer rats; in parallel with this, the potent liver carcinogen nitrosodimethylamine is much less effective in inducing tumors in Fischer rats than in Sprague-Dawley rats. This suggests that the effectiveness of these nitroso compounds in inducing liver tumors is related to the capacity of the liver for metabolizing them and that this capacity is lower in Fischer rats than in other strains. In support of this, the Fischer rat is less susceptible to liver damage by hepatotoxic N-nitroso compounds (and perhaps by other hepatotoxins) than is the Sprague-Dawley rat, liver microsomes from which, coincidently, are much more effective in activating compounds to bacterial mutagens (in the " Ames" test) than are liver microsomes from Fischer rats. These results suggest that liver cell damage is intimately involved in liver carcinogenesis and that liver-damaging agents (which include ethanol) might be equally important as liver carcinogens in the formation of the liver cancer. In support of this was the finding that simultaneous treatment of Sprague-Dawley rats with the hepatotoxin carbon tetrachloride and nitrosodimethylamine increased the number of hepatocellular carcinomas induced, compared with nitrosodimethylamine alone, which gave rise only to angiosarcomas of the liver (13).

The type of tumor induced by a given nitrosamine depends on the species to which it is administered and often on the dose, frequency of treatment, and route of administration. While the esophagus is the most common site for induction of tumors in rats, this is not so in Syrian hamsters or guinea pigs; in the latter, the liver appears to be the organ most susceptible to the action of carcinogenic nitrosamines. One example of the differences in response of various species to a nitrosamine is 2,6-dimethylnitrosomorpholine which induces esophageal tumors in rats (of several strains), liver tumors in guinea pigs, and tumors of the pancreas in Syrian hamsters. This compound exists as a mixture of 2 conformational isomers of which the cis isomer is a weaker carcinogen than the trans isomer, the minor component of the mixture.

Another example is nitrosomethyldodecylamine which induces bladder tumors in rats of several strains [although the Fischer rat appears to be more susceptible than is the Sprague-Dawley rat (8)] and in Syrian hamsters (1) but induces liver tumors in guinea pigs. On the other hand, nitrosomethylundecylamine, with one carbon atom less in the chain than does nitrosomethyldodecylamine, induces no bladder tumors in rats but instead induces liver and lung tumors (10). There are many other instances which illustrate the difficulty of extrapolating findings in experimental animals to evaluations of the action of carcinogens in humans.

Other problems in such extrapolation are apparent from what we know of carcinogenesis in animals. Among these are large differences in the dose-response curves between one nitrosamine and another even in the same species and when the target organ of the carcinogen is the same, for example, the esophagus (9). Nor, in spite of the commonly stated probability, has there been sound evidence of a synergistic effect of one carcinogenic nitrosamine with another; the most that has been observed is an additive effect. Therefore, while carcinogenesis studies in animals tell us a good deal about patterns of carcinogenic action and something about mechanisms of carcinogenesis, the etiology of cancer in humans is so complex because of the multitude of exposures to carcinogens and agents which modify carcinogenesis that the possible influence of alcohol in human cancer cannot be discounted even though experimental evidence is so far limited.

References

W. Lijinsky


Current Status of Experimental Chemical Carcinogenesis and Its Applications to Human Cancer Risk

William Lijinsky


Updated version  Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/39/7_Part_2/2887

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.