Medicine as an art demands constant evaluation, weighing new treatments against old practices, benefits against risks, successes against failures. On occasion, the evidence leads to different conclusions. Nowhere is this more evident than in the management of the cancer patient.

OPINIONS will present the views of specialists on a wide spectrum of controversial subjects. It is hoped that the frank expression of ideas will provide a framework within which our readers may form their own opinions.

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WARNING: FALSE CANCER CLAIMS MAY BE HAZARDOUS TO YOUR HEALTH

In the fall of 1974, a rash of newspaper and magazine headlines claimed that contaminants discovered in the lower Mississippi Valley drinking water were associated with a grave risk of cancer. One accompanying illustration, playing upon the story's shock-value, showed the face of a man drinking a glass of water, and was captioned: "Will he get cancer?"

It is highly unlikely that the trace contaminants of drinking water would pose specific risks of cancer in the general population. Yet these unfounded claims, sensationalized in the media, have greatly alarmed the public. We can say that environmental factors cause about 80 percent of all human cancers, and this knowledge is grounded in both epidemiologic and experimental data. The major human cancers are due to our lifestyle, among which cigarette smoking and diet, especially high-fat, low-fiber foods and mode of cooking, are key elements.

When the public is informed of newly found environmental cancer hazards, it is imperative that the information be supported by definitive documentation. Scare tactics are counter-productive. If baseless assertions continue, society will only become deafened to bona fide evidence of real carcinogenic hazards. Valuable research funds and time will be diverted in useless investigations, and efforts to focus on the key causes and prevention of major human cancers will be neglected for lack of resources.

The stories dealing with the "carcinogenic" contaminants in the Mississippi River were spun before any scientific evidence had even establish what that drinking or river water contained. Scientists in the fields of chemical carcinogenesis and cancer etiology were left wondering as to the nature and basis of the problem. Months after the announcements had alarmed the general public, a paper appeared in Science, but it merely listed the chemicals found in the water of that region; its tables gave no information concerning the amounts of those chemicals. The carcinogenicity of the agents was implied, but not specifically discussed in relation to the publicly announced cancer hazard. Buried in the text was a statement that the salient contaminant was

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chloroform, and that it was present at the level of three parts per million. Chloroform had been shown to induce liver tumors in mice in about 1945. While I was at the National Cancer Institute, additional tests on this and other chlorinated hydrocarbons had been started under my direction; however, detailed and carefully evaluated results of these tests were not available at the time of the publicity.

Most chemical carcinogens have one or more specific target organs. No agent is known which leads to a generalized increase in diverse tissues. Yet, the implication of the publicity about contaminants in water was that these contaminants served to increase the cancer risk at diverse sites for people using such water. This is scientifically unsound extrapolation. Aflatoxin, for example, causes cancer mainly in the liver in many experimental species and is strongly suspected of doing so in man. Aromatic amines in an occupational setting have led to cancer in the urinary bladder in man and in most experimental species in which these same chemicals were tested, although in mice they also led to tumors of the liver. The fact that this is so probably stems from the specific biochemical transformation required to convert procarcinogens to the ultimate active forms. The required enzymes are probably similarly located in organs across species lines, although admittedly, more research in this area is necessary. Nonetheless, if chloroform and other such chlorinated hydrocarbons did cause cancer in man, the preferred site would be the liver or kidney. These are among the rare cancers of man in the United States.

Not all carcinogens are alike. The mold toxin and aflatoxin B\textsubscript{1} causes liver cancer in rats even at one part per billion in the diet; the flavoring agent safrole requires 2000 to 5000 parts per million, a considerable difference! Yet the FDA has banned safrole, but has set a tolerance of 15 parts per billion for aflatoxin B\textsubscript{1}. The latter is a sound practical decision, for setting a "zero tolerance," for foods with aflatoxin B\textsubscript{1} would require a ban on many of our foods! Thus, the FDA also tacitly underwrites the existence of "no effect" levels even for powerful carcinogens.

The other question is whether chemicals which are carcinogenic in experimental animals at high dose levels can actually lead to cancer in man in trace amounts even when present for an entire life span. All known chemical carcinogens have a classical pharmacological dose response. The higher the dose, the higher the cancer yield and the shorter the latent period, and vice versa. To be sure, there are synergistic effects like inhalation of asbestos and smoking of cigarettes where the asbestos enhances manyfold the risk due to smoking alone. Nevertheless, it is most unlikely that the trace contaminants of drinking water or river water would be associated with specific carcinogenicity in the general population. In this instance, the press reports thoroughly frightened the public. This does not mean we should not clean up our rivers and water. This is an urgent aim, meritorious for its own sake. But we should not have to use a cancer scare to reach this goal.

Misguided concern about the relationship of certain food additives to cancer is yet another case where facts were grossly misrepresented and funds needlessly spent. When a study performed abroad found that the food dye Red #2 had a "carcinogenic effect," well-meaning but ill-informed lay groups exerted pressure on the United States Food and Drug Administration (FDA) to re-examine the data in their hands. The foreign investigation claimed to have obtained evidence for carcinogenicity in a test where the treated animals developed cancer in different target sites, mostly in the endocrine-sensitive organs such as pituitary, gonads and uterus. In a lifetime study, the control animals reportedly had no cancer. This is a most unusual finding: the cancers seen in the experimentally treated group were the ones normally present in aged untreated controls. Yet these were the results which apparently caused the FDA to set up another expensive research project to re-test this dye, even though in the mid-1950's, FDA scientists of excellent standing and repute had conducted a test series involving large numbers of mice and rats, and had concluded that this dye presented no
cancer hazard. But these were discounted in favor of clearly specious findings in an attempt to assuage the fears that unfounded publicity had aroused in the American people.

In the field of azo dye carcinogenesis, a considerable number of studies on structure-activity correlation have been performed by many scientists and, in particular, in the laboratory of the Millers at the University of Wisconsin. The general conclusion was drawn that substitution of polar groups or of solubilizing groups like hydroxy, carboxy, and especially sulfonate, uniformly decreased, and in the latter instance abolished, the carcinogenic effect. Pure Red Dye #2 has the structure of an azo dye with sulfonic acid substitution on the aryl rings on both sides of the azo bond. On the basis of what is known in the field, it seems unlikely, therefore, that this polar, water-soluble azo dye or its metabolites should be carcinogenic. This was also the conclusion of the extensive FDA studies performed in 1954-1956.

However, the FDA went to the trouble of performing one more test series. For various reasons, this series was inadequately supervised and poorly conducted. Yet, the data generated were evaluated mathematically and the conclusion was drawn that excess cancers were seen in female animals. These cancers were not at specific target sites. They were not in organs affected by known carcinogenic azo dyes for which many structures have been examined. They were, instead, in organs where neoplasms are often seen in aged animals. Given such random distribution of cancers, one is entitled to ask: Why does it affect only female rats and not males? In fact, males treated with Red #2 had a lower disease incidence than untreated males. Yet, all of this information taken together was used by administrative and legislative authorities, and boards of scientists and physicians, to rule that insufficient evidence existed to declare Red Dye #2 a safe dye. It was, therefore, banned. The public must have been relieved that government authorities had protected it from a grave risk of cancer!

Dr. F. Ingelfinger, the editor-emeritus of the New England Journal of Medicine, in an editorial on the "cancerophobia" being induced in the public, indicated that too many claims for cancer hazards, which eventually are found wanting, immunize and make the public resistant to what might be valid, proper and real cancer hazards. Thus, the efforts to control cancer, which are the concern of all in the field of cancer and medical research, are rendered ineffective. The public will ignore any statements if they come too often and do not discriminate between claims based on sound evidence and those which are flimsy.

It is important that when the public is alerted, the alert have the backing of authoritative, reliable documentation. It is important that when scientists go to Federal or State agencies in order to modify the environment through regulatory and legislative action, that their evidence be strong and irrefutable. It is important that the interpretation of the existing literature rest on a sound foundation and not represent frivolous imagination. It is important to construct protocols for new studies, which consume a good fraction of our limited resources for medical research, so that such studies, if successful and properly conducted, will actually contribute knowledge which can be used to reduce human cancer risk. Finally, it is important that we emphasize and deliberately foster public action on those cancer risks which are already well defined, such as those seen in occupational settings and, most urgently, those due to our lifestyle, such as the smoking of cigarettes, the consumption of diets high in fat and low in fiber, and other conditions which are epidemiologically and experimentally fully documented as real cancer hazards.

Let us not waste time and effort, and delude the public and ourselves through irrelevant busybody actions. Let us, rather, concentrate on what is important to all mankind—the effective prevention and control of cancer.

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