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Letter to the Editor

Cancer Prevention, Rodent High-Dose Cancer Tests, and Risk Assessment

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We have recently reviewed the causes and prevention of cancer with an emphasis on mechanism.[1] The major causes of cancer are smoking, dietary imbalances, chronic infections leading to chronic inflammation, and hormones.[1] Past occupational exposures might cause a few percent of current human cancer, a major part being asbestos exposure in smokers. The age-adjusted cancer death rate in the U.S. for all cancers combined has declined 14% since 1950 (excluding lung cancer, 90% of which is attributable to smoking), while life expectancy has increased,[1] which may in part be due to better diet.[2] The idea that there is an epidemic of human cancer caused by synthetic industrial chemicals is not supported by either toxicology or epidemiology. Though some epidemiologic studies find an association between cancer and low levels of industrial pollutants, the studies do not correct for diet, which is a potentially large confounding factor; moreover, the levels of pollutants are low and rarely seem plausible as a causal factor when compared to the background of natural chemicals that are rodent carcinogens.[3]

Chronic inflammation from chronic infection such as hepatitis B and C viruses, *Helicobacter pylori*, and schistosomiasis is a major cause of cancer worldwide. Chronic inflammation releases oxidants (HOONO, H_2O_2, HOCl) that both stimulate cell division and are mutagens.[1] Inflammation from noninfectious agents also contributes to cancer, e.g., asbestos and lung cancer,[4] sunburn and melanoma.[5]

Diet has a major impact on the degenerative diseases of aging such as cancer, which have, in good part, an oxidative origin.[2] Dietary antioxidants, such as Vitamins C and E and carotenoids, may play a major role in minimizing oxidative damage; however, much of the world's population consumes inadequate amounts of them.[2] Insufficiency of dietary antioxidants causes the same oxidative damage to DNA as radiation.[2] The main source of dietary antioxidants is fruits and vegetables. The quarter of the American population that eats the least fruits and vegetables has over twice the rate of most types of cancer as the quarter eating the most, as shown by about 200 epidemiological studies that are remarkably consistent.[1,2,6] Thus, a high percentage of the American population is eating insufficient fruits and vegetables (5 portions a day is advised), particularly the poor. A deficiency in the vitamin folic acid (whose source is fruits and vegetables) is common and causes chromosome breaks, cancer, brain damage, and heart disease.[7] We have shown that the chromosome breaks from folate deficiency, which could contribute to the other pathologies, are due to massive uracil incorporation into human DNA, resulting in nicks and breaks during repair.[7] Hypomethylation due to folate deficiency could contribute to cancer as well.[8]

Seventh-Day Adventists—who generally do not smoke, drink heavily, or eat much meat but do eat a diet rich in fruits and vegetables—have an overall cancer mortality about half that of the general U.S. population and live several years longer.[2]

The Importance of Cell Division in Mutagenesis and Carcinogenesis

Endogenous DNA damage from normal oxidation is enormous. The steady-state level of oxidative damage in DNA is over one million oxidative lesions per rat cell.[2] Thus, from first principles, the cell division rate must be a factor in converting lesions to mutations and thus cancer.[9] Raising the level of either DNA lesions or cell division will increase the probability of cancer. Just as DNA repair protects against lesions, p53 guards the cell cycle and defends against cell division if the lesion level gets too high.[1] If the lesion level becomes still higher, p53 can initiate programmed cell death (apoptosis).[10,11] None of these defenses is perfect, however.[1] The critical factor is chronic cell division in stem cells, not in cells that are discarded, and is related to the

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total number of extra cell divisions.[12] Cell division is both a major factor in loss of heterozygosity through nondisjunction and other mechanisms[13,14] and in expanding clones of mutated cells.

Half the Chemicals Tested in Rodents Are Carcinogens

Chronic cell division is plausible as the major reason that more than half the chemicals are classified as carcinogens when tested at the maximum tolerated dose (MTD) in standard rodent cancer bioassays.[9,14,15] As currently conducted, rodent bioassays provide inadequate data to estimate human risk at low dose. Sixty percent of the chemicals tested in both rats and mice are carcinogenic; even among the known nonmutagens, 49% are positive (among the mutagens, 78% are positive).[15] The high positivity rate is consistent for synthetic chemicals, natural chemicals (99.9% of the chemicals humans are exposed to are natural),[3,15,16] natural pesticides, chemicals in roasted coffee; moreover the proportion positive has not changed through the years of testing.[14,17] Half the drugs in the *Physician's Desk Reference* that report animal cancer test results are carcinogenic.[18] The Innes series of tests in 1969 of 119 synthetic chemicals, mainly the commonly used pesticides of the time, is frequently cited as evidence that the proportion of carcinogens among all untested chemicals is low, as only 9% were judged positive. We have pointed out that these tests were quite deficient in power compared to modern tests,[17,19] and we have now reanalyzed Innes by asking whether any of the Innes-negative chemicals have been retested using current protocols. We found that 34 have been retested and 16 were carcinogenic, again about half.[20]

Cell Division and the High Positivity Rate in Bioassays

What are the explanations for the high positivity rate in high-dose animal cancer tests? We have rejected bias in picking more suspicious chemicals as the major explanation for the results for numerous reasons.[17,19] One explanation for a high positivity rate that is supported by an ever increasing array of papers is that the MTD of a chemical can cause chronic cell killing and cell replacement in the target tissue, a risk factor for cancer that can be limited to high doses.

Tissues injured by high doses of chemicals have an inflammatory immune response involving activation of recruited and resident macrophages[21–27] (e.g., phenobarbital, carbon tetrachloride, TPA). Activated macrophages release mutagenic oxidants (including peroxynitrite, hypochlorite, and H_2O_2), as well as inflammatory and cytotoxic cytokines, growth factors, bioactive lipids (arachidonic acid metabolites), and proteases. This general response to cell injury suggests that chronic cell killing by high dose animal cancer tests will likely incite a similar response, leading to further cell injury, compensatory cell division and therefore increased probability of mutation.

Thus it seems likely that a high proportion of all chemicals, whether synthetic or natural, might be "carcinogens" if run through the standard rodent bioassay at the MTD, but this will be primarily due to the effects of high doses for the nonmutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens.[9,14,28] *Ad libitum* feeding in the standard bioassay can also contribute to the high positivity rate,[29,30] plausibly by increased cell division and decreased apoptosis due to high caloric intake.[9,30,31]

Correlation Between Cell Division and Cancer

Many studies on rodent carcinogenicity show a correlation between cell division at the MTD and cancer. Cunningham *et al.* have analyzed 15 chemicals at the MTD, 8 mutagens and 7 nonmutagens, including several pairs of mutagenic isomers, one of which is a carcinogen and one of which is not.[32–42] They found a perfect correlation between cancer causation and cell division in the target tissue: the 9 chemicals increasing cancer caused cell division in the target tissue and the 6 chemicals not increasing cancer did not. A similar result has been found in the analyses of Mirsalis,[43] e.g., both dimethylnitrosamine (DMN) and methyl methane sulfonate (MMS) methylate liver DNA and cause unscheduled DNA synthesis (a result of DNA repair), but DMN causes both cell division and liver tumors, while MMS does neither. A recent study on the mutagenic dose response of the carcinogen ethylnitrosourea concludes that cell division is a key factor in its mutagenesis and carcinogenesis.[44] Chloroform at high doses induces liver cancer by chronic cell division.[45] Formaldehyde causes cancer at high doses, primarily through increases in cell division.[12] PhIP, a mutagenic heterocyclic amine from cooked protein, induces colon tumors in male rats, but not in female rats; the level of DNA adducts in the colonic mucosa was the same in both sexes, however, cell division was increased only in the male, contributing to the formation of premalignant lesions of the colon.[46]

Therefore, there was no correlation between adduct formation and these premalignant lesions, but there was between cell division and lesions. Extensive reviews on rodent studies[8,9,14,47–49] document that chronic cell division can induce cancer. There is also a large epidemiological literature reviewed by Preston-Martin, Henderson and colleagues[50,51] showing that increased cell division by hormones and other agents can increase human cancer.

The Natural Background

The vast bulk of chemicals ingested by humans are natural. For example 99.99% (by weight) of the pesticides Americans eat are naturally present in plants to ward off insects and other predators.[3,16,20] Of the 59 natural pesticides that have been tested, 33 are rodent carcinogens.[3,20] Reducing exposures to the 0.01% of ingested pesticides that are synthetic is not likely to reduce cancer rates.[3] Synthetic pesticide residues in the U.S. diet rank low compared to the background of natural chemicals in the diet, when human exposures to rodent carcinogens are ranked according to an index of possible carcinogenic hazard.[3,20]

Cooking food generates thousands of chemicals.[3,52] There are over 1000 chemicals reported in a cup of coffee. Only 26 have been tested in animal cancer tests and 19 are rodent carcinogens; there are still a thousand chemicals left to test.[3,20] The amount of rodent carcinogens consumed as pesticide residues in a year is less than the known amount of rodent carcinogens in a cup of coffee.[3] This does not mean that coffee is dangerous, but that animal cancer tests and worst-case risk assessment should not be considered true risks because data on high doses cannot be extrapolated to low doses without information on mechanism of carcinogenesis for each chemical.

Risk Assessment

In regulatory policy, the "virtually safe dose" (VSD), corresponding to a maximum, hypothetical cancer risk of 10^{-6}, is estimated from bioassay results using a linear model. To the extent that carcinogenicity in rodent bioassays is due to the effects of high doses for the nonmutagens, and a synergistic effect of cell division at high doses with DNA damage for the mutagens, then this model is inappropriate. Moreover, as currently calculated, the VSD can be known without ever conducting a bioassay: for 96% of the NCI/NTP rodent carcinogens, the VSD is within a factor of 10 of the ratio MTD/740,000.[53] This is about as precise as the estimate obtained from conducting near-replicate cancer tests of the same chemical.[53] The recent report of the National Research Council, *Science and Judgment in Risk Assessment*,[54] as well as the EPA's draft document *Working Paper for Considering Draft Revisions to the U.S. EPA Guidelines for Cancer Risk Assessment*[54] recommend changes that can improve the risk assessment process, such as incorporating consideration of dose to the target tissue, mode of action, and biologically based dose–response models, including a possible threshold of dose below which carcinogenic effects will not occur.[54]

Conclusion

Taking cell division into account will make priority setting in cancer prevention more effective.[28] For example, regulatory policy aimed at reducing tiny exposures to synthetic rodent carcinogens[3] has confused the public about what factors are important for preventing cancer,[1] and has diverted enormous resources from more important health risks.[1,7,19,55,56]

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