DRUG METABOLISM REVIEWS, 30(2), 201-223 (1998)

THE PREVENTION OF CANCER

BRUCE N. AMES*
University of California
Barker Hall
Berkeley, California 94720

LOIS SWIRSKY GOLD
E. O. Lawrence Berkeley National Laboratory
Berkeley, California 94720

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I. CANCER TRENDS

Cancer death rates overall in the United States (after adjusting for age and excluding lung cancer due to smoking) have declined 16% since 1950 [1,2]. The types of cancer deaths that have decreased since 1950 are primarily stomach, cervical, uterine, and colorectal. The types that have increased are primarily lung cancer (90% is due to smoking, as are 35% of all cancer deaths in the United States), melanoma (probably due to sunburns), and non-Hodgkin's lymphoma. Overall, from 1991 to 1995, cancer death rates have declined 2.6%, including declines for lung cancer for men and breast cancer for women [3]. A similar downward trend in cancer mortality has been seen in Europe since 1988 [4]. (Cancer incidence rates are also of interest, although they should not be taken in isolation, because trends in the recorded incidence rates are biased by improvements in registration and diagnosis [2,5].)

Cancer is one of the degenerative diseases of old age and increases exponentially with age in both rodents and humans. External factors, however, can markedly increase cancer rates (e.g., cigarette smoking in humans) or decrease them (e.g., caloric restriction in rodents). Life expectancy has continued to rise since 1950. Thus, the increases in observed cancer deaths (not adjusted for age) reflect the delayed effect of earlier increases in smoking and increased life expectancy [2,5].

II. IMPORTANT CAUSES OF HUMAN CANCER

Epidemiological studies have identified the factors that are likely to have a major effect on reducing rates of cancer: reduction of smoking, improvement in diet (e.g., increased consumption of fruits and vegetables), and control of infections [6]. We [6] estimate that diet accounts for about one-

third of cancer risk, in agreement with the earlier estimate of Doll and Peto [2], and we discuss diet in the next section. Other factors are life-style influences on hormones, avoidance of intense sun exposure, increased physical activity, reduced consumption of alcohol, and occupational exposures.

Because cancer is due in part to normal aging, to the extent that the major external risk factors for cancer are diminished (smoking, unbalanced diet, chronic infection and hormonal factors) cancer will occur at a later age, and the proportion of cancer caused by normal metabolic processes will increase. Aging and its degenerative diseases appear to be due in good part to the accumulation of oxidative damage to DNA and other macromolecules [7]. By-products of normal metabolism—superoxide, hydrogen peroxide, and the hydroxyl radical—are the same oxidative mutagens produced by radiation. Oxidative lesions in DNA accumulate with age, so that by the time a rat is old, it has about 66,000 oxidative DNA lesions per cell [7]. Mutations also accumulate with age. DNA is oxidized in normal metabolism because antioxidant defenses, although numerous, are not perfect. Antioxidant defenses against oxidative damage include vitamins C and E and carotenoids, most of which come from dietary fruits and vegetables.

Smoking contributes to about 35% of U.S. cancer, about one-quarter of heart disease, and about 400,000 premature deaths per year in the United States [8]. Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus, and possibly colon. Tobacco causes even more deaths by diseases other than cancer. Smoke contains a wide variety of mutagens and rodent carcinogens. Smoking is also a severe oxidative stress and causes inflammation in the lung. The oxidants in cigarette smoke—mainly nitrogen oxides—deplete the body's antioxidants. Thus, smokers must ingest two to three times more vitamin C than nonsmokers to achieve the same level in blood, but they rarely do. Inadequate concentration of vitamin C in plasma is more common among single males, the poor, and smokers.

Men with inadequate diets or who smoke may damage both their somatic DNA and the DNA of their sperm. When the level of dietary vitamin C is insufficient to keep seminal fluid vitamin C at an adequate level, the oxidative lesions in sperm DNA are increased 250% [9–11]. Smokers also produce more aneuploid sperm than nonsmokers [12]. Paternal smoking, therefore, may plausibly increase the risk of birth defects and childhood cancer in offspring [9,10]. New epidemiological evidence suggests that all types of childhood cancer are increased in offspring of male smokers [13].

Chronic inflammation from chronic infection results in the release of oxidative mutagens from phagocytic cells and is a major contributor to cancer [6,14]. White cells and other phagocytic cells of the immune system com-

bat bacteria, parasites, and virus-infected cells by destroying them with potent, mutagenic oxidizing agents. The oxidants protect humans from immediate death from infection, but they also cause oxidative damage to DNA, mutation, and chronic cell killing with compensatory cell division [15] and thus contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation. Chronic infections cause about 21% of new cancer cases in developing countries and 9% in developed countries [16].

Endogenous reproductive hormones play a large role in cancer, including cancer of the breast, prostate, ovary, and endometrium [17,18], contributing to as much as 20% of all cancer. Many life-style factors such as lack of exercise, obesity, and reproductive history influence hormone levels and therefore risk [17–20].

Genetic factors play a significant role in cancer and interact with life-style and other risk factors. Biomedical research is uncovering important genetic variation in humans.

Occupational exposure to carcinogens can cause cancer, although how much has been a controversial issue: A few percent seems a reasonable estimate [6]. The main contributor was asbestos in smokers. Exposures to substances in the workplace can be high in comparison with other chemical exposures in food, air, or water. Past occupational exposures have sometimes been high and therefore comparatively little quantitative extrapolation may be required for risk assessment from high-dose rodent tests to high-dose occupational exposures. As occupational cancer is concentrated among small groups exposed at high levels, there is an opportunity to control or eliminate risks once they are identified.

Although some epidemiologic studies find an association between cancer and low levels of industrial pollutants, the associations are usually weak, the results are usually conflicting, and the studies do not correct for potentially large confounding factors like diet. Moreover, the exposures to synthetic pollutants are small and the low concentrations do not seem plausible as a causal factor when compared to the background of natural chemicals that are rodent carcinogens [21]. Even assuming that the Environmental Protection Agency's (EPA) worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that EPA could prevent by regulation would be tiny [22].

III. PREVENTING DIET-RELATED CANCER

Consumption of adequate fruits and vegetables is associated with a lowered risk of degenerative diseases, including cancer, cardiovascular disease, cataracts, and brain dysfunction [7]. Over 200 studies in the epidemiologi-

TABLE 1

Review of Epidemiological Studies on Cancer Showing Protection by Consumption of Fruits and Vegetables

Cancer site	Fraction of studies showing significant cancer protection	Relative risk (median) (low vs. high quartile) of consumption
Epithelial		
Lung	24/25	2.2
Oral	9/9	2.0
Larynx	4/4	2.3
Esophagus	15/16	2.0
Stomach	17/19	2.5
Pancreas	9/11	2.8
Cervix	7/8	2.0
Bladder	3/5	2.1
Colorectal	20/35	1.9
Miscellaneous	6/8	—
Hormone dependent		
Breast	8/14	1.3
Ovary/endometrium	3/4	1.8
Prostate	4/14	1.3
Total	129/172	

Source: Ref. 23.

cal literature have been reviewed that show, with great consistency, an association between lack of adequate consumption of fruits and vegetables and cancer incidence [23–25] (Table 1). The quarter of the population with the lowest dietary intake of fruits and vegetables compared to the quarter with the highest intake has roughly twice the cancer rate for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix, and ovary). Only 22% of Americans met the intake recommended by the National Cancer Institute and the National Research Council [26–28]: five servings of fruits and vegetables per day. When the public is told about hundreds of minor hypothetical risks, they lose perspective on what is important: Half the public does not know that fruits and vegetables protect against cancer [29].

A. Micronutrients in Fruits and Vegetables Are Anticarcinogens

Antioxidants in fruits and vegetables may account for some of their beneficial effect as discussed above. However, the effects of dietary antioxidants

are difficult to disentangle by epidemiological studies from other important vitamins and ingredients in fruits and vegetables [24,25,27,30].

Folate deficiency, one of the most common vitamin deficiencies, causes chromosome breaks in human genes [31]. Approximately 10% of the U.S. population [32] is deficient at the level causing chromosome breaks. In two small studies of low-income (mainly African-American) elderly [33] and adolescents [34], nearly half were folate deficient to this level. The mechanism is deficient methylation of uracil to thymine, and subsequent incorporation of uracil into human DNA (4 million/cell) [31]. During repair of uracil in DNA, transient nicks are formed; two opposing nicks cause a chromosome break. Both high DNA uracil levels and chromosome breaks in humans are reversed by folate administration [31]. Chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans [31]. Folate deficiency also damages human sperm [35], causes neural tube defects in the fetus, and is responsible for about 10% of U.S. heart disease [31].

Other micronutrients are likely to play a significant role in the prevention and repair of DNA damage and, thus, are important to the maintenance of long-term health. Deficiency of vitamin B_{12} causes a functional folate deficiency, accumulation of homocysteine (a risk factor for heart disease) [36], and misincorporation of uracil into DNA [37]. Strict vegetarians are at increased risk of developing a vitamin B_{12} deficiency [36]. Niacin contributes to the repair of DNA strand breaks by maintaining nicotinamide adenine dinucleotide levels for the poly ADP-ribose protective response to DNA damage [38]. As a result, dietary insufficiencies of niacin (15% of some populations are deficient [39]), folate, and antioxidants may act synergistically to adversely affect DNA synthesis and repair. Diets deficient in fruits and vegetables are commonly low in folate, antioxidants, (e.g., vitamin C), and many other micronutrients, and result in significant amounts of DNA damage and higher cancer rates [6,23,40].

Optimizing micronutrient intake can have a major impact on health. Increasing research in this area and efforts to improve micronutrient intake and balanced diet should be a high priority for public policy.

Fruits and vegetables are of major importance for reducing cancer: If they become more expensive by reducing use of synthetic pesticides, cancer is likely to increase. People with low incomes eat fewer fruits and vegetables and spend a higher percentage of their income on food.

B. Calories or Protein Restriction and Cancer Prevention

In rodents, a calorie-restricted diet, compared to *ad libitum* feeding, markedly decreases tumor incidence and increases life span, but decreases

reproduction [41,42]. Protein restriction, although less well studied, appears to have similar effects [43]. Darwinian fitness in animals appears to be increased by hormonal changes which delay reproductive function during periods of low food availability because the saved resources are invested in maintenance of the body until food resources are available for successful reproduction [44,45]. Lower mitotic rates are observed in a variety of tissues in calorie-restricted compared to *ad libitum* fed rodents [46,47], which is likely to contribute to the decrease in tumor incidence [48]. Although epidemiological evidence on restriction in humans is sparse, the possible importance of growth restriction in human cancer is supported by epidemiologic studies indicating higher rates of breast and other cancers among taller persons [26]; for example, Japanese women are now taller, menstruate earlier, and have increased breast cancer rates. Also, many of the variations in breast cancer rates among countries and trends, over time, within countries are compatible with changes in growth rates and attained adult height [49]. Obesity in postmenopausal women is a risk factor for breast cancer [20,26; see above].

IV. DOES LOW-DOSE EXPOSURE TO SYNTHETIC CHEMICALS THAT ARE RODENT CARCINOGENS MATTER?

Of the chemicals humans ingest, 99.9% are natural. The amounts of synthetic pesticide residues in plant foods are insignificant compared to the amount of natural pesticides produced by plants themselves [50,51]. Of all dietary pesticides that humans eat, 99.99% are natural: They are chemicals produced by plants to defend themselves against fungi, insects, and other animal predators [50,51]. Each plant produces a different array of such chemicals. On average, Americans ingest roughly 5000–10,000 different natural pesticides and their breakdown products. Americans eat about 1500 mg of natural pesticides per person per day, which is about 10,000 times more than they consume of synthetic pesticide residues.

Even though only a small proportion of natural pesticides has been tested for carcinogenicity, half of those tested (35/64) are rodent carcinogens, and naturally occurring pesticides that are rodent carcinogens are ubiquitous in fruits, vegetables, herbs, and spices [52] (Table 2).

Cooking foods produces about 2000 mg per person per day of burnt material that contains many rodent carcinogens and many mutagens. By contrast, the residues of 200 synthetic chemicals measured by the Food and Drug Administration (FDA), including the synthetic pesticides thought to be of greatest importance, average only about 0.09 mg per person per day [50,52]. The known natural rodent carcinogens in a single cup of coffee are

TABLE 2

Carcinogenicity of Natural Plant Pesticides Tested in Rodents (Fungal Toxins Not Included)

Carcinogens $N = 35$	Acetaldehyde methylformylhydrazone, allyl isothiocyanate, arecoline · HCl, benzaldehyde, benzyl acetate, caffeic acid, catechol, clivorine, coumarin, crotonaldehyde, cycasin and methylazoxymethanol acetate, 3,4-dihydrocoumarin, estragole, ethyl acrylate, *N*2-γ-glutamyl-*p*-hydrazinobenzoic acid, hexanal methylformylhydrazine, *p*-hydrazinobenzoic acid · HCl, hydroquinone, 1-hydroxyanthraquinone, lasiocarpine, *d*-limonene, 8-methoxypsoralen, *N*-methyl-*N*-formylhydrazine, α-methylbenzyl alcohol, 3-methylbutanal methylformylhydrazone, methylhydrazine, monocrotaline, pentanal methylformylhydrazone, petasitenine, quercetin, reserpine, safrole, senkirkine, sesamol, symphytine
Noncarcinogens $N = 28$	Atropine, benzyl alcohol, biphenyl, *d*-carvone, deserpidine, disodium glycyrrhizinate, emitine · 2HCl, ephedrine sulphate, eucalyptol, eugenol, gallic acid, geranyl acetate, β-*N*-[γ-*l*(+)-glutamyl]-4-hydroxymethylphenylhydrazine, glycyrrhetinic acid, *p*-hydrazinobenzoic acid, isosafrole, kaempferol, *d*-menthol, nicotine, norharman, pilocarpine, piperidine, protocatechuic acid, rotenone, rutin sulfate, sodium benzoate, turmeric oleoresin, vinblastine

These rodent carcinogens occur in absinthe, allspice, anise, apple, apricot, banana, basil, beet, broccoli, brussels sprouts, cabbage, cantaloupe, caraway, cardamom, carrot, cauliflower, celery, cherries, chili pepper, chocolate milk, cinnamon, cloves, cocoa, coffee, collard greens, comfrey herb tea, corriander, currants, dill, eggplant, endive, fennel, garlic, grapefruit, grapes, guava, honey, honeydew melon, horseradish, kale, lemon, lentils, lettuce, licorice, lime, mace, mango, marjoram, mushrooms, mustard, nutmeg, onion, orange, paprika, parsley, parsnip, peach, pear, peas, black pepper, pineapple, plum, potato, radish, raspberries, rhubarb, rosemary, rutabaga, sage, savory, sesame seeds, soybean, star anise, tarragon, tea, thyme, tomato, turmeric, and turnip.

Source: Ref. 52.

about equal in weight to an entire year's worth of carcinogenic synthetic pesticide residues, even though only 3% of the natural chemicals in roasted coffee have been tested for carcinogenicity [21]. (See the article by Gold et al. in this issue.) This does not mean that coffee is dangerous, but rather that assumptions about high-dose animal cancer tests for assessing human risk at low doses need reexamination. No diet can be free of natural chemicals that are rodent carcinogens [52].

A. Why Are Half of the Chemicals Tested in High-Dose Animal Cancer Tests Rodent Carcinogens?

Approximately half of all chemicals—whether natural or synthetic—that have been tested in standard animal cancer tests are rodent carcinogens [53,54] (Table 3). We have rejected bias in picking more suspicious chemicals as the major explanation for the results for numerous reasons [55,56].

In standard cancer tests, rodents are given chronic, near-toxic doses, the maximum tolerated dose (MTD). Evidence is accumulating that it may be cell division caused by the high dose itself, rather than the chemical per se, that is increasing the cancer rate. Endogenous DNA damage from normal

TABLE 3

Proportion of Chemicals Evaluated as Carcinogenic

Chemicals tested in both rats and mice	330/559	(59%)
Naturally occurring chemicals	73/127	(57%)
Synthetic chemicals	257/432	(59%)
Chemicals tested in rats and/or mice		
Natural pesticides	35/64	(55%)
Mold toxins	14/23	(61%)
Chemicals in roasted coffee	19/28	(68%)
Innes negative chemicals retested[a]	16/34	(47%)
Drugs in the *Physician's Desk Reference*	117/241	(49%)

[a]The 1969 study by Innes et al. [112] is frequently cited as evidence that the proportion of carcinogens is low, as only 9% of 119 chemicals tested (primarily pesticides) were positive in cancer tests on mice. This test, although not a random group of chemicals, was primarily picked on the basis of use at a time when the ability to identify carcinogens was poor. However, these tests lacked the power of modern tests [54]. We have found that of 34 of the Innes negative chemicals that have been retested using modern protocols, 16 were positive [54], again about half.

Source: Ref. 54.

oxidation is enormous. The steady-state level of oxidative damage in DNA is about 66,000 oxidative lesions per old rat cell [7]. Thus, from first principles, the cell division rate must be a factor in converting lesions to mutations and, thus, cancer [57]. 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 becomes too high [6]. If the lesion level becomes still higher, p53 can initiate programmed cell death (apoptosis) [58,59]. None of these defenses is perfect, however [6]. The critical factor is chronic cell division in stem cells, not in cells that are discarded, and is related to the total number of extra cell divisions [60]. Cell division is both a major factor in loss of heterozygosity through nondisjunction and other mechanisms [61,62] and in expanding clones of mutated cells.

High doses can cause chronic wounding of tissues, cell death, and consequent chronic cell division of neighboring cells, which is a risk factor for cancer [53]. Tissues injured by high doses of chemicals have an inflammatory immune response involving activation of recruited and resident macrophages [63–69] (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 [57,62,70].

B. 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 [71–81]. They found a perfect correlation between cancer causation and cell division in the target tissue: The nine chemicals increasing cancer caused cell division in the target tissue and the six chemicals not increasing cancer did

not. A similar result has been found in the analyses of Mirsalis [82]; for example, 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, whereas 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 [83]. Chloroform at high doses induces liver cancer by chronic cell division [84]. Formaldehyde causes cancer at high doses, primarily through increases in cell division [60]. PhIP, a mutagenic heterocyclic amine from cooked protein, causes a significant increase in 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 [85]. Therefore, there was no correlation between adduct formation and these premalignant lesions, but there was between cell division and lesions. The importance of cell division for a variety of genotoxic and nongenotoxic agents has been demonstrated [86]. Extensive reviews on rodent studies [57,62,87–90] document that chronic cell division can induce cancer. There is also a large epidemiological literature reviewed by Preston-Martin and colleagues [91,92], showing that increased cell division by hormones and other agents can increase human cancer. At the low levels to which humans are usually exposed, such increased cell division does not occur. Therefore, the very low levels of chemicals to which humans are exposed through water pollution or synthetic pesticide residues are likely to pose no or minimal cancer risks.

C. Risk Assessment

In regulatory policy, the "virtually safe dose" (VSD), corresponding to a maximum, hypothetical cancer risk of one in a million, 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, as we pointed out in 1990 [62]:

> The high proportion of carcinogens among chemicals tested at the MTD emphasizes the importance of understanding cancer mechanisms in order to determine the relevance of rodent cancer test results for humans. A list of rodent carcinogens is not enough. The main rule in toxicology is that "the dose makes the poison": at some level, every chemical becomes toxic, but there are safe levels below that. However,

the precedent of radiation, which is both a mutagen and a carcinogen, gave credence to the idea that there could be effects of chemicals even at low doses. A scientific consensus evolved in the 1970s that we should treat carcinogens differently, that we should assume that even low doses might cause cancer, even though we lacked the methods for measuring carcinogenic effects at low levels. This idea evolved because it was expected that (*i*) only a small proportion of chemicals would have carcinogenic potential, (*ii*) testing at a high dose would not produce a carcinogenic effect unique to the high dose, and (*iii*) chemical carcinogenesis would be explained by the mutagenic potential of chemicals. However, it seems time to take account of new information suggesting that all three assumptions are wrong.

D. Synthetic Chemicals Should Be Viewed in the Context of Natural Chemicals

Gaining a broad perspective about the vast number of chemicals to which humans are exposed can be helpful when setting research and regulatory priorities [21,51,93,94]. Rodent bioassays provide little information about mechanisms of carcinogenesis and low-dose risk. The assumption that synthetic chemicals are hazardous has led to a bias in testing, such that synthetic chemicals account for 77% of the 559 chemicals tested chronically in both rats and mice (Table 3). The natural world of chemicals has never been tested systematically. One reasonable strategy is to use a rough index to *compare* and *rank* possible carcinogenic hazards from a wide variety of chemical exposures at levels that humans typically receive, and then to focus on those that rank highest [21,94,95]. The Human Exposure/Rodent Potency (HERP) ranking, including a table of 74 human exposures to rodent carcinogens, is presented in the article by Gold et al. in this issue. Overall, our analyses have shown that HERP values for some historically high exposures in the workplace and some pharmaceuticals rank high, and that there is an enormous background of naturally occurring rodent carcinogens in typical portions of common foods that cast doubt on the relative importance of low-dose exposures to residues of synthetic chemicals such as pesticides [21,94,96]. A committee of the National Research Council/National Academy of Sciences recently reached similar conclusions about natural versus synthetic chemicals in the diet and called for further research on natural chemicals [97].

The possible carcinogenic hazards from synthetic pesticides (at average exposures) are minimal compared to the background of nature's pesticides,

although neither may be a hazard at the low doses consumed (see article by Gold et al. in this issue). This analysis also indicates that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. Our results call for a reevaluation of the utility of animal cancer tests in protecting the public against minor hypothetical risks.

It is often assumed that because natural chemicals are part of human evolutionary history, whereas synthetic chemicals are recent, the mechanisms that have evolved in animals to cope with the toxicity of natural chemicals will fail to protect against synthetic chemicals. This assumption is flawed for several reasons [51,53]:

1. Humans have many natural defenses that make us well buffered against normal exposures to toxins [51], and these are usually general, rather than tailored for each specific chemical. Thus, they work against both natural and synthetic chemicals. Examples of general defenses include the continuous shedding of cells exposed to toxins—the surface layers of the mouth, esophagus, stomach, intestine, colon, skin, and lungs are discarded every few days; DNA repairs enzymes, which repair DNA that was damaged from many different sources; and detoxification enzymes of the liver and other organs which generally target classes of toxins rather than individual toxins. That defenses are usually general, rather than specific for each chemical, makes good evolutionary sense. The reason that predators of plants evolved general defenses is presumably to be prepared to counter a diverse and ever-changing array of plant toxins in an evolving world; if a herbivore had defenses against only a set of specific toxins, it would be at a great disadvantage in obtaining new food when favored foods became scarce or evolved new toxins.
2. Various natural toxins, which have been present throughout vertebrate evolutionary history, nevertheless cause cancer in vertebrates [51,54]. Mold toxins, such as aflatoxin, have been shown to cause cancer in rodents and other species, including humans (Table 3). Many of the common elements are carcinogenic to humans at high doses (e.g., salts of cadmium, beryllium, nickel, chromium, and arsenic) despite their presence throughout evolution. Furthermore, epidemiological studies from various parts of the world show that certain natural chemicals in food may be carcinogenic risks to humans; for example, the chewing of betel nuts with tobacco has been correlated with oral cancer worldwide.
3. Humans have not had time to evolve a "toxic harmony" with all of their dietary plants. The human diet has changed dramatically in the

last few thousand years. Indeed, very few of the plants that humans eat today (e.g., coffee, cocoa, tea, potatoes, tomatoes, corn, avocados, mangoes, olives, and kiwi fruit) would have been present in a hunter-gatherer's diet. Natural selection works far too slowly for humans to have evolved specific resistance to the food toxins in these newly introduced plants.

4. DDT is often viewed as the typically dangerous synthetic pesticide because it concentrates in the tissues and persists for years, being slowly released into the bloodstream. DDT, the first synthetic pesticide, eradicated malaria from many parts of the world, including the United States. It was effective against many vectors of disease such as mosquitoes, tsetse flies, lice, ticks, and fleas. DDT was also lethal to many crop pests, and significantly increased the supply and lowered the cost of food, making nutritious foods more accessible to poor people. It was also remarkably nontoxic to humans. A 1970 National Academy of Sciences report concluded: "In little more than two decades DDT has prevented 500 million deaths due to malaria, that would other wise have been inevitable" [98]. There is no convincing epidemiological evidence, nor is there much toxicological plausibility, that the levels normally found in the environment are likely to be a significant contributor to cancer. DDT was unusual with respect to bioconcentration, and because of its chlorine substituents, it takes longer to degrade in nature than most chemicals; however, these are properties of relatively few synthetic chemicals. In addition, many thousands of chlorinated chemicals are produced in nature, and natural pesticides also can bioconcentrate if they are fat soluble. Potatoes, for example, naturally contain the fat-soluble neurotoxins solanine and chaconine, which can be detected in the bloodstream of all potato eaters. High levels of these potato neurotoxins have been shown to cause birth defects in rodents [51].
5. Because no plot of land is immune to attack by insects, plants need chemical defenses—either natural or synthetic—in order to survive pest attack. Thus, there is a trade-off between naturally occurring pesticides and synthetic pesticides. One consequence of disproportionate concern about synthetic pesticide residues is that some plant breeders develop plants to be more insect resistant by making them higher in natural toxins. A recent case illustrates the potential hazards of this approach to pest control: When a major grower introduced a new variety of highly insect-resistant celery into commerce, people who handled the celery developed rashes when they were subsequently exposed to sunlight. Some detective work found that

the pest-resistant celery contained 6200 parts per billion (ppb) of carcinogenic (and mutagenic) psoralens instead of the 800 ppb present in common celery [51].

E. Are Pesticides and Other Synthetic Chemicals Disrupting Human Hormones?

Hormonal factors are important in cancer (see above). A recent book [99] holds that traces of synthetic chemicals, such as pesticides with weak hormonal activity, may contribute to cancer and reduce sperm counts. This view ignores the fact that the usual diet contains natural chemicals that have estrogenic activity millions of times higher than that due to traces of synthetic estrogenic chemicals [100,101] and that life-style factors can markedly change the levels of endogenous hormones (see above). The low levels of human exposure to residues of industrial chemicals are toxicologically implausible as a significant cause of cancer or reproductive abnormalities, especially when compared to the natural background [100–102]. In addition, even if sperm counts really were declining, which is not at all clear [103], there are many more likely causes, such as smoking and diet (see above).

V. DOES REGULATION OF LOW HYPOTHETICAL RISKS ADVANCE PUBLIC HEALTH?

The world is not risk-free, and resources are limited; therefore, society must set priorities based on which risks are most important in order to save the most lives. The EPA estimates that total U.S. expenditures on environmental regulation costs $140 billion per year. It has been argued that, overall, these regulations harm public health [104–107], because "wealthier is not only healthier but highly risk reducing." One estimate indicates "that for every 1% increase in income, mortality is reduced by 0.05%" [105,108]. In addition, the median toxin control program costs 58 times more per life-year saved than the median injury prevention program and 146 times more than the median medical program [109]. It has been estimated that the United States could prevent 60,000 deaths a year by redirecting resources to more cost-effective programs [110]. The discrepancy is likely to be greater because cancer risk estimates used for toxin-control programs are worst-case, hypothetical estimates, and the true risks at low dose are often likely to be zero [21,53,54] (see above).

Regulatory efforts to reduce low-level human exposures to synthetic chemicals are expensive because they aim to eliminate minuscule concentrations that now can be measured with improved techniques. These efforts are distractions from the major task of improving public health through increasing knowledge, public understanding of how life-style influences health, and effectiveness in incentives and spending to maximize health. Basic biomedical research is the basis for improved public health and longevity, yet its cost is less than 10% the cost to society of EPA regulations.

Rules on air and water pollution are necessary (e.g., it was a public health advance to phase lead out of gasoline) and, clearly, cancer prevention is not the only reason for regulations. As we pointed out in 1990 [111]: "What is chiefly needed is to take seriously the control of the major hazards that have been reliably identified, without diverting attention from these major causes by a succession of highly publicized scares about factors that may well be of little or no importance as causes of human diseases."

VI. SUMMARY

1. The major causes of cancer are as follows:
   (a) Smoking: about a third of U.S. cancer (90% of lung cancer).
   (b) Dietary imbalances, e.g., lack of dietary fruits and vegetables: The quarter of the population eating the least fruits and vegetables has double the cancer rate for most types of cancer compared to the quarter eating the most; micronutrients may account for much of the protective effect of fruits and vegetables. Excess calories may also contribute to cancer.
   (c) Chronic infections: mostly in developing countries.
   (d) Hormonal factors influenced by life-style.
2. There is no epidemic of cancer, except for lung cancer due to smoking. Cancer mortality rates have declined 16% since 1950 (excluding lung cancer and adjusted for the increased life span of the population).
3. Regulatory policy that is focused on traces of synthetic chemicals is based on misconceptions about animal cancer tests. Recent research contradicts these ideas:
   (a) Rodent carcinogens are not rare. Half of all chemicals tested in standard high-dose animal cancer tests, whether occurring naturally or produced synthetically, are "carcinogens."
   (b) There are high-dose effects in these rodent cancer tests that are not relevant to low-dose human exposures and which can explain the high proportion of carcinogens.

(c) Though 99.9% of the chemicals humans ingest are natural, the focus of regulatory policy is on synthetic chemicals.
- Over 1000 chemicals have been described in coffee: 27 have been tested and 19 are rodent carcinogens.
- Plants that we eat contain thousands of natural pesticides which protect plants from insects and other predators: 64 have been tested and 35 are rodent carcinogens.

4. There is no convincing evidence that synthetic chemical pollutants are important for human cancer. Regulations that try to eliminate minuscule levels of synthetic chemicals are enormously expensive: EPA estimates that total expenditures on environmental regulations cost $140 billion/year. It has been estimated by others that the United States spends 100 times more to prevent one hypothetical, highly uncertain death from a synthetic chemical than it spends to save a life by medical intervention. Attempting to reduce tiny hypothetical risks also has costs; for example, if reducing synthetic pesticides makes fruits and vegetables more expensive, thereby decreasing consumption, then cancer will be increased.
5. Improved health will come from knowledge due to biomedical research and from life-style changes by individuals. Little money is spent on biomedical research or on educating the public about life-style hazards, compared to the cost of regulations.

ACKNOWLEDGMENT

This article has been adapted in part from Refs. 6, 50, and 51.

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