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老化とガンの原因を理解する：環境が果たす役割

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Understanding the Causes of Aging and Cancer:

The Role of the Environment

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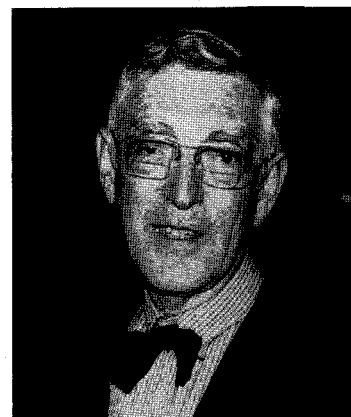
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●His 350 scientific publications have resulted in his being the 23rd most-cited scientist in all fields (1973-1984).

Understanding the Causes of Aging and Cancer: The Role of the Environment

Commemorative Lecture at the Conferring Ceremony on the 15th of
November, 1996, in Tokyo

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Abstract

Epidemiological studies have identified several factors that are likely to have a major effect on reducing rates of cancer: reduction of smoking, increased consumption of fruits and vegetables, and control of infections. Other factors include avoidance of intense sun exposure, increased physical activity, and reduced consumption of alcohol and possibly red meat. Risks of many types of cancer can already be reduced, and the potential for further reductions is great. In the United States cancer death rates for all cancers combined are decreasing, if lung cancer (90 percent of which is due to smoking), is excluded from the analysis. We review the research on causes of cancer and show why much cancer is preventable.

The idea that traces of synthetic chemicals, such as DDT, are major contributors to human cancer is not supported by the evidence, yet public concern and resource allocation for chemical pollution are very high, in part because standard risk assessment uses linear extrapolation from limited data in high-dose animal cancer tests. These tests are done at the maximum tolerated dose and are typically misinterpreted to mean that low doses of synthetic chemicals and industrial pollutants are relevant to human cancer. About half the chemicals tested, whether synthetic or natural, are carcinogenic to rodents at such high doses. Almost all chemicals in the human diet are natural. For example, 99.99 percent of the pesticides we eat are naturally present in plants to ward off insects and other predators. Half of the natural pesticides that have been tested at the maximum tolerated dose are rodent carcinogens. Cooking food produces large numbers of natural dietary chemicals. Roasted coffee, for example, contains more than a thousand chemicals: of twenty-seven tested, nineteen are rodent carcinogens.

Increasing evidence supports the idea that the high frequency of positive results in rodent bioassays is due to testing at the maximum tolerated dose, which frequently can cause chronic cell killing and consequent cell replacement -- a risk factor for cancer that can be limited to high doses. Because default risk assessments use linear extrapolation, which ignores effects of the high dose itself, low-dose risks are often exaggerated.

Cancer Trends

According to the National Cancer Institute's 1993 Surveillance, Epidemiology, and End-Results Program, SEER (1), cancer caused 23 percent of the person-years of premature loss of life and about 530,000 deaths in the U.S. in 1993. Four major cancers -- lung, colon-rectum, breast and prostate -- accounted for 55 percent of these deaths. Cancer death rates in the United States are decreasing, after adjusting for age and excluding lung cancer. The age-adjusted mortality rate for all cancers combined (excluding lung and bronchus) has declined 14 percent from 1950 to 1990. Smoking, in addition to causing 90 percent of lung cancer, contributes to cancers of the mouth, esophagus, pancreas, bladder, and possibly colon; if these were taken into account, the decline would be greater.

Peto and colleagues (2) have come to the same conclusion: "The common belief that there is an epidemic of death from cancer in developed countries is a myth, except for the effects of tobacco. In many countries cancer deaths from tobacco are going up, and in some they are at last coming down. But, if we take away the cancer deaths that are attributed to smoking then the cancer death rates that remain are, if anything, declining."

The number of people newly diagnosed with cancer (incidence rate) has been increasing for some types of cancer. In their comprehensive study on the causes of cancer, Doll and Peto (3) point out that incidence rates should not be taken in isolation, because reported incidence rates for a disease might reflect increases in registration of cases and improvements in diagnosis. For example, the rapid increase in age-adjusted prostate cancer incidence without any major increases in mortality is mostly due to increased screening and incidental detection during prostatectomy for benign prostatic hypertrophy (4). Devesa et al. (5) discuss incidence and mortality trends by site in detail.

Major Contributors to Risk of Cancer

Two critical factors in the formation of mutations are lesions in DNA, (produced when DNA is damaged) and cell division (which converts DNA lesions to mutations). Agents that increase either lesions or cell division in the cells that can give rise to tumors, increase mutations and as a consequence increase cancer incidence (see below) (4,6-8). Hormones stimulating cell division increase cancer incidence (e.g.,

estrogen in breast cancer and testosterone in prostate cancer); hormones may be a risk factor in about 20% of human cancer (4,6).

Oxidative Damage and the Degenerative Diseases of Aging. Aging and its degenerative diseases, such as cancer, appear to be due in good part to the accumulation of oxidative damage to DNA and other macromolecules (9). By-products of normal metabolism -- superoxide, hydrogen peroxide, and hydroxyl radical -- are the same oxidative mutagens produced by radiation (10). Oxidative lesions in DNA accumulate with age, so that by the time a rat is old (two years) it has about a million DNA lesions per cell, which is about twice that in a young rat (9). Mutations also accumulate with age. DNA is oxidized in normal metabolism because antioxidant defenses, though numerous, are not perfect. Endogenously-produced oxidants can damage proteins as well as DNA (11). In two human diseases associated with premature aging, Werner's syndrome and progeria, oxidized proteins accumulate at a much higher rate than normal (11).

Chronic inflammation from chronic infection results in release of oxidative mutagens from phagocytic cells and is a major contributor to cancer as discussed below.

Antioxidant defenses against oxidative damage include vitamins C and E and carotenoids. To the extent that the major external risk factors for cancer -- smoking, unbalanced diet, and chronic inflammation -- are diminished, cancer will appear at a later age, and the proportion of cancer that is caused by normal metabolic processes will increase.

Diet. Doll and Peto (3) and others (6) estimate that diet accounts for about one-third of cancer risk, and current research is slowly clarifying specific factors.

Cancer prevention by calorie or protein restriction. In rodents a calorie-restricted diet compared to *ad libitum* feeding markedly decreases tumor incidence and increases life span (12-14). Protein restriction appears to have a similar effect on rodents, although research is less extensive (15). An understanding of mechanisms for the marked effect of dietary restriction on aging and cancer is becoming clearer and may largely be due to reduced oxidative damage and reduced rates of cell division. 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 cancer among taller persons

(16,17). 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 (18).

Cancer prevention by dietary fruits and vegetables. Adequate consumption of fruits and vegetables is associated with a lowered risk of degenerative diseases such as cancer, cardiovascular disease, cataracts, and brain and immune dysfunction (9). Nearly 200 studies in the epidemiological literature have been reviewed, and they show a consistent association between inadequate consumption of fruits and vegetables and cancer (19-21). The quarter of the population with the lowest dietary intake of fruits and vegetables has roughly twice the cancer risk for most types of cancer (lung, larynx, oral cavity, esophagus, stomach, colon and rectum, bladder, pancreas, cervix, and ovary) compared with the quarter with the highest intake. For hormonally-related cancers, the protective effect of consuming fruits and vegetables is weaker and less consistent: for breast cancer the protective effect appears to be about 30 percent (16,19,22). Laboratory studies suggest that antioxidants such as vitamins C and E and carotenoids account for a good part of the beneficial effect of fruits and vegetables (9); however, epidemiologists have difficulty disentangling the effects of dietary intakes of the antioxidants from other important vitamins and ingredients in fruits and vegetables (23,24).

A wide array of compounds in fruits and vegetables in addition to antioxidants may contribute significantly to the reduction of cancer. Folic acid may be particularly important. Low folic acid intake in humans causes chromosome breaks (25,26), cognitive defects in adults, heart disease (25), and adenomas and cancers of the colon (27-29). Low folic intake in some rodent models causes chromosome breaks (30) and increased tumor incidence (31). Folic acid is essential for the synthesis of DNA. Maternal deficiency of folate is associated with neural tube birth defects (32). Folate deficiency causes massive incorporation of uracil into human DNA (4 million/cell) and chromosome breaks (25). The likely mechanism is the deficient methylation of dUMP to dTMP and subsequent incorporation of uracil into DNA by DNA polymerase. During repair of uracil in DNA, transient nicks are formed; two opposing nicks could lead to chromosome breaks. Both high DNA uracil levels and micronucleus frequency (a measure of chromosome breaks) are reversed by folate administration. The elevated DNA uracil and chromosome breaks could contribute to the increased risk of cancer and cognitive defects associated with folate deficiency in humans. Deficient intake of folic acid is common in U.S. diets. About 15 percent of

the U.S. population (33) has a folate level at which chromosome breaks are seen (25). A study of adolescents (34) and elderly (35) from urban, low-income, predominantly African-American households, found that about half had such levels.

Many other micronutrients in addition to folate and ascorbate, are likely to play a significant role in the prevention and repair of DNA damage, and thus to the maintenance of long term health. Deficiency of vitamin B12 traps folate as methylTHF and thus causes a functional folate deficiency, accumulation of homocysteine leading to heart disease (36), and misincorporation of uracil into DNA (37). 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. ascorbate) and many other micronutrients, and result in significant amounts of DNA damage and higher cancer rates (6,19,40). On the other hand, strict vegetarians are at increased risk of developing a B12 deficiency (36).

Other aspects of diet. Although epidemiologic studies most clearly support the benefits of fruits and vegetables in the prevention of cancer, strong international correlations suggest that animal (but not vegetable) fat and red meat may increase the incidence of cancers of the breast, colon, and prostate (41). However, large prospective studies have consistently shown either a weak association or a lack of association between fat intake and breast cancer (16). Consumption of animal fat and red meat have been correlated with risk of colon cancer internationally, but the relation with fat intake has not been supported in most case-control and cohort studies (42,43); the association with meat consumption appears more consistent (43-46). Consumption of animal fat and red meat has been associated with risk of prostate cancer (45,47). Mechanisms for these associations are not clear, but may include the effects of dietary fats on endogenous hormone levels (4), the local effects of bile acids on the colonic mucosa, the effects of carcinogens produced by cooking meat, and excessive iron intake from red meat. Excess iron absorption, particularly heme iron from meat, is a plausible, though unproven, contributor to the production of oxygen radicals (9). Some of the large geographical differences in colon cancer rates that have been attributed to dietary factors are probably due to differences in physical activity, which is inversely related to colon cancer risk in many studies (48-50). Dietary fiber, obtained only from foods of plant origin, may

contribute to lower risk of colon cancer (51). Plant foods also contain a wide variety of weak estrogens that may act as antiestrogens by competing with estrogenic hormones (20,24,52).

Alcoholic beverages cause inflammation and cirrhosis of the liver, and liver cancer (53). Alcohol is an important cause of oral and esophageal cancer and is also synergistic with smoking (53) and possibly contributes to colorectal cancer (29,54).

Cooking food is plausible as a contributor to cancer (55). Cooking forms a wide variety of chemicals. Four groups of chemicals that cause tumors in rodents have attracted attention because of mutagenicity, potency, or concentration: nitrosamines, heterocyclic amines, polycyclic hydrocarbons, and furfural and similar furans. Epidemiological studies on cooking are difficult and so far are inadequate to evaluate a carcinogenic effect in humans (56).

Tobacco. Smoking contributes to about one-third of cancer, about one-quarter of heart disease, and about 400,000 premature deaths per year in the United States (57). Tobacco is a known cause of cancer of the lung, bladder, mouth, pharynx, pancreas, stomach, larynx, esophagus (2), and possibly colon (58-60). Tobacco causes even more deaths by diseases other than cancer. The evidence for environmental tobacco smoke as a cause of cancer is much weaker. Studies have estimated that environmental tobacco smoke causes up to 3,000 additional cases of cancer (61,62), although this estimate has been disputed (63).

The carcinogenic mechanisms of tobacco smoking are not well understood. Smoke contains a wide variety of mutagens and rodent carcinogens, and smoking is 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 ascorbate than non-smokers to achieve the same level of ascorbate in blood, but they rarely do (64-66). Men with inadequate diets or who smoke may damage both their somatic DNA and the DNA of their sperm. When the level of dietary ascorbate is insufficient to keep seminal fluid ascorbate at an adequate level, the oxidative lesions in sperm DNA are increased 2.5 times (67). Inadequate concentration of ascorbate in plasma is more common among single males, the poor, and smokers (68). Paternal smoking may plausibly increase the risk of birth defects and childhood cancer in offspring (69).

Cancer from Inflammation Caused by Chronic Infection. White cells and other phagocytic cells of the immune system combat 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 (70,71) and thus contribute to the carcinogenic process. Antioxidants appear to inhibit some of the pathology of chronic inflammation (9).

Peroxynitrite, a powerful mutagenic oxidant and nitrating species is formed by the near diffusion-limited reaction of $\bullet\text{NO}$ and $\text{O}_2^{\bullet-}$ during activation of phagocytes. Chronic inflammation induced by phagocytes is a major contributor to cancer and other degenerative diseases. We examined how gamma-tocopherol (gT)—the principal form of vitamin E in the US diet—and alpha-tocopherol (aT)—the major form in supplements—protect against peroxynitrite-induced lipid oxidation (72). Lipid hydroperoxide formation in liposomes (but not isolated low density lipoprotein) exposed to peroxynitrite or the $\bullet\text{NO}$ and $\text{O}_2^{\bullet-}$ -generator SIN-1 was inhibited more effectively by gT than aT. However, gT was nitrated in both liposomes and human low density lipoprotein at the nucleophilic 5-position at yields of $\approx 50\%$ and $\approx 75\%$, respectively, and was not affected by the presence of aT. These results suggest that despite aT's action as an antioxidant, gT was required to effectively remove the peroxynitrite-derived nitrating species. We postulate that *in vivo* gT acts as a trap for membrane-soluble electrophilic nitrogen oxides and other electrophilic mutagens, forming stable carbon-centered adducts through its nucleophilic 5-position which is blocked in aT. Since large doses of dietary aT displaces gT in plasma and other tissues, the current wisdom of vitamin E supplementation with aT alone should be reconsidered.

We estimate that chronic infections contribute to about one-third of the world's cancer. Hepatitis B and C viruses are a major cause of chronic inflammation leading to liver cancer—one of the most common cancers in Asia and Africa (73-75). Hepatitis B and C viruses infect about 500 million people worldwide. Nearly half the world's liver cancer occurs in China (76). Vaccinating babies at birth is potentially an effective method to reduce liver cancer and is routinely done for hepatitis B in Taiwan. The mutagenic mold toxin, aflatoxin, which is found in moldy peanut and corn products, interacts with chronic hepatitis infection in liver cancer development (77-79).

Another major chronic infection is schistosomiasis, which is widespread in Egypt and Asia. In Egypt, the eggs of *Schistosoma haematobium*, deposited in the bladder, cause inflammation and bladder

cancer (80). In Asia, the eggs of *S. japonicum*, deposited in the colonic mucosa, cause inflammation, and there is limited epidemiological evidence for an association with colon cancer (80). *Opisthorchis viverrini*, a liver fluke, infects millions of people in Thailand and Malaysia. The flukes lodge in bile ducts and increase the risk of cholangiocarcinoma (80). *Chlonorchis sinensis* infects millions of people in China and increases the risk for biliary tract cancer (80). *Helicobacter pylori* bacteria, which infect the stomachs of more than one-third of the world's population, are a major cause of stomach cancer, ulcers, and gastritis (80). In the U.S. the infection is often asymptomatic, which suggests that inflammation may be at least partially suppressed, possibly by adequate levels of dietary antioxidants (81).

Human papilloma virus, a major risk factor for cervical cancer, does not appear to work through an inflammatory mechanism (82). It is spread by sexual contact, an effective way of transmitting viruses.

Chronic inflammation resulting from noninfectious sources can also lead to cancer. For example, asbestos exposure leading to chronic inflammation may be in good part the reason that asbestos is a significant risk factor for lung cancer (83,84).

Hormones. Henderson, Pike and colleagues have reviewed the extensive literature on hormones and cancer, which indicates that endogenous reproductive hormones play a large role in cancer, possibly contributing to as much as one-third of all cancer, including breast, prostate, ovary and endometrium (4). Hormones are likely to act by causing cell division (85).

Less Important Contributors to Risk of Cancer

We have discussed elsewhere some of the less important contributors to cancer, including hereditary factors, sun exposure, and medical interventions (6). Here we discuss occupation and pollution because the scientific basis for concern needs clarification.

Occupation. The International Agency for Research on Cancer of the World Health Organization evaluates potential cancer risks to humans from a range of chemical exposures (86). Half of the sixty chemicals and chemical mixtures the Agency has evaluated as having sufficient evidence of carcinogenicity in humans represent occupational exposures, which tend to be concentrated among small groups of people who have been chronically exposed at high levels. These include workplace exposures such as "rubber

industry" or "coke production," as well as exposure to specific aromatic amines, petrochemicals, and metals. How much cancer can be attributed to occupational exposure has been a controversial issue, but a few percent seems a reasonable estimate. Doll and Peto (3) have discussed difficulties in making such estimates, including the lack of accurate data on the history of exposure and current exposures, as well as confounding factors such as socioeconomic status and smoking. Lung cancer was by far the largest contributor to Doll and Peto's estimate of the proportion of cancers due to occupation. The preeminence of smoking as a cause of lung cancer confounds the interpretation of rates in terms of particular workplace exposures to substances such as asbestos; asbestos appears to multiply rather than just add to the effect of smoking. In contrast, asbestos alone is a known risk factor for mesothelioma. Doll and Peto (3) estimated that asbestos caused a high proportion of occupational cancers, but recent estimates for asbestos-related cancer are lower (87,88).

Exposures to substances in the workplace can be high in comparison with other chemical exposures in food, air, or water. Past occupational exposures have often been high and comparatively little quantitative extrapolation may be required for risk assessment from high-dose rodent tests to high-dose occupational exposures. Since occupational cancer is concentrated among small groups exposed at high levels, there is an opportunity to control or eliminate risks once they are identified. The Occupational Safety and Health Administration, however, unlike other federal agencies such as the Environmental Protection Agency, regulates few chemicals as potential human carcinogens. For seventy-five rodent carcinogens regulated by OSHA with permissible exposure limits, we recently ranked potential carcinogenic hazards on an index that compares the permitted dose-rate for workers with the carcinogenic dose for rodents (89). We found that for nine chemicals the permitted exposures were within a factor of ten of the rodent carcinogenic dose and for 17 they were between ten and a hundred times lower. These values are high in comparison with hypothetical risks regulated by other federal agencies. An additional 120 rodent carcinogens to which workers are exposed had no OSHA permissible exposure limit, which suggests the need for further regulatory attention and research on mechanism of carcinogenesis.

Pollution. Much of the public fears synthetic pollutants as major causes of cancer, but this fear is based on a misconception. Even assuming that the EPA's worst-case risk estimates for synthetic pollutants are true risks, the proportion of cancer that EPA could prevent by regulation would be tiny (90).

Epidemiological studies of pollutants, moreover, are difficult to conduct because of inadequacies in assessing low level exposures and failure to account for confounding factors like smoking, diet, and geographic mobility of the population. Since the focus of this chapter is cancer causation, we shall not discuss other issues in environmental protection.

Air Pollution. Indoor air is generally of greater concern than outside air because people spend 90 percent of their time indoors, and because the concentrations of pollutants indoors tend to be higher than outdoors. Radon is likely to be the most important carcinogenic air pollutant. It occurs naturally as a radioactive gas, generated as a decay product of the radium present in trace quantities in the earth's crust. Radon primarily enters houses in air that is drawn from the underlying soil. On the basis of epidemiological studies of high exposures to underground miners, researchers have estimated that radon causes as many as 15,000 lung cancers per year in the United States, mostly among smokers because of the synergistic effect with smoking (91-93). Epidemiological studies of radon exposures in homes (94,95) have failed to demonstrate convincingly an excessive risk. About 50,000 to 100,000 of the homes in the U.S. (0.1 percent) are estimated to have annual average radon levels approximately twenty times the national average, and inhabitants receive annual radiation doses that exceed the current occupational standard for underground miners. Efforts to identify houses with high levels of radon indicate that they occur most frequently in concentrated geographic areas (96). In areas with high levels of radon, individuals can perform a measurement in their homes for about \$20 and, if high levels are found, they can be reduced substantially--using available contractors--for perhaps \$1500 (92). With respect to outdoor air pollution, a recent large study has reported an association with lung cancer when sulfates are used as an index, but not when fine particles are used; the study did not control for diet (97).

Water Pollution. Water pollution as a risk factor for cancer appears small. Among potential hazards that have been of concern, the most important are radon (exposure is small compared to air) and arsenate. Natural arsenate is a known human carcinogen at high doses (98,99), and further research is needed to determine mechanisms of carcinogenesis and the dose response in humans. Chlorination of water, an important public health intervention, produces large numbers of chlorine-containing chemicals as by-products, some of which are rodent carcinogens. Evidence that chlorination of water increases cancer has been judged inadequate (100). A recent case-control interview study did not confirm earlier associations with bladder and colon cancer, but did find an association with rectal cancer (101).

Animal Cancer Tests and the Rachel Carson Fallacy

Neither toxicology nor epidemiology supports the idea that synthetic industrial chemicals are causing an epidemic of human cancer. 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 diet, which is a potentially large confounding factor. Moreover, the levels of synthetic pollutants are low and rarely seem plausible as a causal factor when compared to the background of natural chemicals that are rodent carcinogens (7).

Rachel Carson's fundamental misconception was: "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals, from the moment of conception until death" (102). She was wrong: The vast bulk of the chemicals to which humans are exposed are natural, and for every chemical some amount is dangerous. Carson thus lacked perspective about the wide variety of naturally occurring chemicals to which all people are exposed, and did not address the fact that, outside the workplace, exposures to synthetic pollutants are extremely low relative to the natural background.

Animal cancer tests are conducted on synthetic chemicals at the maximum tolerated dose of the chemical, and regulatory agencies use the results to predict human risk at low levels of exposure. Since the vast proportion of human exposures are to naturally-occurring chemicals, while the vast proportion of chemicals tested for carcinogenicity are synthetic, there is an imbalance in data and perception about chemicals and cancer.

The great bulk of chemicals ingested by humans is natural, by both weight and number. 99.99 percent of the pesticides in the diet are naturally present in plants to ward off insects and other predators (103). Half the natural pesticides tested--thirty-five of sixty-four--are rodent carcinogens (7,104,105). Reducing exposure to the .01 percent of pesticides that are synthetic, either individual chemicals or mixtures, will not appreciably reduce cancer rates. On the contrary, fruits and vegetables are important for reducing cancer; making them more expensive by reducing use of synthetic pesticides is likely to increase cancer. People with low incomes eat fewer fruits and vegetables (106) and spend a higher percentage of their income on food.

Humans also ingest large numbers of natural chemicals from cooking food. Of the more than one thousand chemicals identified in roasted coffee, over half of those tested--nineteen of twenty-seven--are rodent carcinogens (107). There are more natural "rodent carcinogens" by weight in a single cup of coffee than potentially carcinogenic synthetic pesticide residues in the average U. S. diet in a year, and there are still a thousand known chemicals in roasted coffee that have not been tested. That does not necessarily mean that coffee is dangerous, but that high-dose animal cancer tests and worst-case risk assessments build in enormous safety factors and should not be considered true risks at the low dose of most human exposures.

Because of their unusual lipophilicity and long environmental persistence, there has been particular concern for a small group of polychlorinated synthetic chemicals such as DDT and PCBs. There is no convincing epidemiological evidence (108), nor is there much toxicological plausibility (7), that the levels normally found in the environment are likely to contribute significantly to cancer. TCDD, which is produced naturally by burning when chloride ion is present, for example in forest and other fires, and as an industrial by-product, is an unusually potent rodent carcinogen, but seems unlikely to be a significant human carcinogen at the levels to which the general population is exposed.

The reason humans can eat the tremendous variety of "rodent carcinogens" in our diet is that, like other animals, we are extremely well protected by many general defense enzymes, most of which are inducible--that is, whenever a defense enzyme is in use, the body produces more of it (109). Defense enzymes are effective against both natural and synthetic chemicals, including potentially mutagenic, reactive chemicals. One does not expect, nor does one find, a general difference between synthetic and natural chemicals in their ability to cause cancer in high-dose rodent tests (7,107,110).

We have ranked possible carcinogenic hazards from known rodent carcinogens, by using an index that relates human exposure to carcinogenic potency in rodents (HERP) (7,107,111,112). Our ranking does not estimate risks because current science does not have the ability to do so. Instead, we put possible hazards of synthetic chemicals into perspective against the background of naturally occurring rodent carcinogens in typical portions and average exposures of common foods (107). The residues of synthetic pesticides or environmental pollutants rank low in comparison with the background of naturally occurring rodent carcinogens, despite the fact that such a comparison gives a minimal view of hypothetical background hazards because so few chemicals in the natural world have been tested for carcinogenicity in

rodents. Our results indicate that many ordinary foods would not pass the regulatory criteria used for synthetic chemicals. Our analysis does not necessarily indicate that coffee consumption, for example, is a significant risk factor for human cancer even though chemicals in coffee have HERP values that rank much higher in possible hazard than the HERP which converts to the default one-in-a-million worst-case risk estimate used by EPA (7). Adequate risk assessment from animal cancer tests requires more information about many aspects of toxicology, such as effects on cell division, induction of defense and repair systems, and species differences. EPA has recently given attention to these factors in its newly proposed cancer risk assessment guidelines (113).

Over half the chemicals, whether synthetic or natural, that have been tested at the MTD under standard testing procedures are classified as carcinogenic. The high positivity rate is consistent for synthetic chemicals, for natural chemicals, for natural pesticides, for chemicals in roasted coffee, and has not changed through the years of testing (107,114,115). Half the drugs in the *Physician's Desk Reference* that report animal cancer test results are carcinogenic (116). The Innes series of tests in 1969 of 119 synthetic chemicals, mainly all of the commonly-used pesticides of the time, is frequently cited as evidence that the proportion of carcinogens in the world of chemicals is low, as only 9 % were judged positive. Gold et al. (107,114) have pointed out that these tests were quite deficient in power compared to modern tests, and they have now reanalyzed Innes by asking whether any of the Innes-negative chemicals have been retested using current protocols. They found that 34 had been retested and 16 were judged carcinogenic, again about half (107).

What is the explanation for the high positivity rate in high dose animal cancer tests? When the testing protocol was developed in the 1960's, it was expected that chemical carcinogens would be rare and that they would be mutagens. Bias in picking more suspicious chemicals does not appear to be the sole explanation for the high positivity rate for numerous reasons (114,115,117). There is, however, an explanation that is supported by an increasing array of papers: 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 the high dose. This explanation is supported by a wide variety of evidence:

a) Endogenous oxidative damage to DNA is enormous, over a million oxidative lesions per rat cell (9). Thus, from first principles, the cell division rate must be a factor in converting such lesions to mutations, thereby increasing cancer. Therefore, raising the level of either DNA lesions or cell division in

the cells that can give rise to tumors will increase cancer. Just as DNA repair protects against lesions, p53 guards the cell cycle and protects against cell division if the lesion level gets too high; however, neither defense is perfect. Cell division is also a major factor in loss of heterozygosity through non-disjunction and other mechanisms (110,117,118).

b) Many studies on rodent carcinogenicity show a correlation between cell division at the MTD and cancer. Cunningham has analyzed 15 chemicals at the MTD, 8 mutagens and 7 non-mutagens, including several pairs of mutagenic isomers, one of which is a carcinogen and one of which is not (119-127). He has found a perfect correlation between cancer causation and cell division in the target tissue: when tested at the bioassay dose, the 9 chemicals causing cancer caused cell division in the target tissue and the 6 chemicals not causing cancer, did not. A similar result has been found in an analysis of Mirsalis (128), e.g. both dimethyl nitrosamine (DMN) and methyl methane sulfonate (MMS) methylate liver DNA and cause unscheduled DNA synthesis; however, DMN causes both cell division and liver tumors, while MMS does neither. The induction of cell division at high dose would explain why a high proportion of the known rodent carcinogens (42%) are not mutagenic, which is otherwise not satisfactorily explained. There is a large literature on rodent studies reviewed by Cohen (129,130) and by Ames et al. (117) showing that chronic cell division can induce cancer. Work on chloroform induction of mouse liver tumors by Butterworth and colleagues (131) also indicates the important role of increased cell division at bioassay doses. A large epidemiological literature reviewed by Preston-Martin et al. (85,132) shows that increased cell division by hormones and other agents can increase human cancer.

Thus it seems likely that a high proportion of the chemicals in the world may be "carcinogens" if tested in standard rodent bioassays at the MTD, but this will be primarily due to high-dose effects for non-mutagens, and for mutagens a synergistic effect of cell division at high doses with DNA damage. *Ad libitum* feeding in the standard bioassay, which also can increase cell division, may also contribute to the high positivity rate, as shown by a recent study at the National Toxicology Program (133). If tumor induction in bioassays is due to effects unique to high doses, then much more information on mechanism is required to understand the causes of human cancer. The default "risk assessment" virtually safe dose is simply a factor of 740,000 times below the MTD, as shown by Gaylor and Gold (134). If tests are conducted primarily on synthetic chemicals, and regulation is directed toward tiny traces of synthetic chemicals, as is now the case, resources will be diverted from more important issues. Thus the positivity

rate and the frequency of positive results that are unique to high doses, are key questions in getting an overview of the world of chemicals, both natural and synthetic.

Linear extrapolation from the maximum tolerated dose in rodents to low-level exposure in humans for synthetic chemicals, while ignoring the enormous background of natural chemicals, has led to exaggerated estimates of cancer risk and to an imbalance in the perception of hazard and the allocation of resources. If the costs were minor, the issue of putting hypothetical risks into perspective would not be so important, but the costs are great (135,136) and escalate as cleanliness approaches perfection. Most attempts to deal with pollutants do not adequately deal with trade-offs; instead, policy makers assume that upper-bound risk assessment to one in a million protects the public. Reports by the Office of Management and Budget (137) and the Harvard Center for Risk Analysis (138) compared costs of risk reduction among government agencies and concluded that the money spent to save a hypothetical life under EPA regulations is often orders of magnitude higher than that spent on regulations of other government agencies. The uncertainties in extrapolations to low dose assessments are great, and the true risk could be zero. Thus, the discrepancy between costs of EPA regulations and other agencies may be even greater, e.g. permitted worker exposure limits regulated by OSHA can be close to the carcinogenic dose-rate in rodent bioassays and little extrapolation is required. Many scholars have pointed out that expensive regulations intended to save lives may actually lead to increased deaths (139), in part because they divert resources from important health risks and in part because higher incomes are associated with lower mortality (140,141). Worst-case assumptions in risk assessment represent a policy decision, not a scientific one, and they confuse attempts to allocate money effectively for cancer prevention (142,143).

Discussion

Epidemiological evidence in humans is thus sufficient to identify several broad categories of cancer causation for which the evidence is strong and plausible. Since many of those risks are avoidable, it is possible to reduce rates of many types of cancer. One approach to estimating the population impact of adopting major lifestyle factors associated with low cancer risk is to compare cancer incidence and mortality rates of the general population to those of Seventh-Day Adventists--who generally do not smoke, drink heavily, or eat much meat but do eat a diet rich in fruits and vegetables (144,145). Seventh-Day Adventists experience substantially lower mortality rates of lung, bladder, and colon cancers. Total cancer

mortality is about half that of the general U.S. population. While this comparison has limitations--better use of medical services may contribute to reduced mortality, and imperfect compliance with recommendations may underestimate the impact of lifestyle--the results strongly suggest that a large portion of cancer deaths can be avoided by using knowledge at hand. Incidence rates rather than mortality rates provide a similar picture, although the differences are somewhat less. For breast cancer, the healthy behavior of Seventh-Day Adventists was not sufficient to have a major effect on risk.

Decreases in physical activity, and increases in smoking, obesity, and recreational sun exposure have contributed importantly to increases in some cancers in the modern industrial world, whereas improvements in hygiene have reduced other cancers related to infection. There is no good reason to believe that synthetic chemicals underlie the changes in incidence of some cancers. In the United States and other industrial countries, life expectancy has steadily increased and will increase even faster as smoking declines.

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