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May 31, 1989

S. R. Holm, Jr., CAPT, CEC, USN
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Santa Ana, CA 92709-5001

Dear Captain Holm:

Enclosed are the articles I promised you by Dr. Bruce Ames. He appears to be the only sane voice in the toxics wilderness. Should you ever get the opportunity to hear him speak, you will probably find the experience very enlightening.

Cordially,

James A. Goodrich
Director of Basin Management

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enclosures (7)

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Dietary Carcinogens and Anticarcinogens

Oxygen radicals and degenerative diseases

Bruce N. Ames

Summary. The human diet contains a great variety of natural mutagens and carcinogens, as well as many natural antimutagens and anticarcinogens. Many of these mutagens and carcinogens may act through the generation of oxygen radicals. Oxygen radicals may also play a major role as endogenous initiators of degenerative processes, such as DNA damage and mutation (and promotion), that may be related to cancer, heart disease, and aging. Dietary intake of natural antioxidants could be an important aspect of the body's defense mechanism against these agents. Many antioxidants are being identified as anticarcinogens. Characterizing and optimizing such defense systems may be an important part of a strategy of minimizing cancer and other age-related diseases.

Comparison of data from different countries reveals wide differences in the rates of many types of cancer. This leads to hope that each major type of cancer may be largely avoidable, as is the case for cancers due to tobacco, which constitute 30 percent of the cancer deaths in the United States and the United Kingdom (*1*). Despite numerous suggestions to the contrary, there is no convincing evidence of any generalized increase in U.S. (or U.K.) cancer rates other than what could plausibly be ascribed to the delayed effects of previous increases in tobacco usage (*1–3*). Thus, whether or not any recent changes in life-style or pollution in industrialized countries will substantially affect future cancer risks, some important determinants of current risks remain to be discovered among long-established aspects of our way of life. Epidemiologic studies have indicated that dietary practices are the most promising area to explore (*1, 4*). These studies suggest that a general increase in consumption of fiber-rich cereals, vegetables, and fruits and decrease in consumption of fat-rich products and excessive alcohol would be prudent (*1, 4*). There is still a lack of definitive evidence about the dietary components that are critical for humans and about their mechanisms of action. Laboratory studies of natural foodstuffs and cooked food are beginning to uncover an extraordinary variety of mutagens and possible carcinogens and anticarcinogens. In this article I discuss dietary mutagens and carcinogens and anticarcinogens that seem of importance and speculate on relevant biochemical mechanisms, particularly the role of oxygen radicals and their inhibitors in the fat-cancer relationship, promotion, anticarcinogenesis, and aging.

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Natural Mutagens and Carcinogens in Food

Plant material. Plants in nature synthesize toxic chemicals in large amounts, apparently as a primary defense against the hordes of bacterial, fungal, and insect and other animal predators (*5–40*). Plants in the human diet are no exception. The variety of these toxic chemicals is so great that organic chemists have been characterizing them for over 100 years, and new plant chemicals are still being discovered (*12, 24, 25*). However, toxicological studies have been completed for only a very small percentage of them. Recent widespread use of short-term tests for detecting mutagens (*41, 42*) and the increased number of animal cancer tests on plant substances (*6*) have contributed to the identification of many natural mutagens, teratogens, and carcinogens in the human diet (*5–40*). Sixteen examples are discussed below.

1) *Safrole, estragole, methyleugenol,* and related compounds are present in many edible plants (*5*). Safrole, estragole, and methyleugenol are carcinogens in rodents, and several of their metabolites are mutagens (*5*). Oil of sassafras, which had been used in "natural" sarsaparilla root beer, is about 75 percent safrole. Black pepper contains small amounts of safrole and large amounts (close to 10 percent by weight) of the closely related compound *piperine* (*26*). Extracts of black pepper cause tumors in mice at a variety of sites at a dose of extract equivalent to 4 mg of dried pepper per day (about 160 mg/kg per day) for 3 months; an estimate of the average human intake of black pepper is over 140 mg per day (about 2 mg/kg per day) for life (*26*).

2) Most *hydrazines* that have been tested are carcinogens and mutagens, and large amounts of carcinogenic hydrazines are present in edible mushrooms. The widely eaten false morel (*Gyromitra esculenta*) contains 11 hydrazines, three of which are known carcinogens (*28*). One of these, *N*-methyl-*N*-formylhydrazine, is present at a concentration of 50 mg per 100 g and causes lung tumors in mice at the extremely low dietary level of 20 μg per mouse per day (*28*). The most common commercial mushroom, *Agaricus bisporus*, contains about 300 mg of *agaritine*, the δ-glutamyl derivative of the mutagen 4-hydroxymethylphenylhydrazine, per 100 g of mushrooms, as well as smaller amounts of the closely related carcinogen *N*-acetyl - 4 - hydroxymethylphenylhydrazine (*28*). Some agaritine is metabolized by the mushroom to a diazonium derivative which is a very potent carcinogen (a single dose of 400 ng/g gave 30 percent of mice stomach tumors) and which is also present in the mushroom in smaller amounts (*28*). Many hydrazine carcinogens may act by producing oxygen radicals (*43*).

3) Linear *furocoumarins* such as *psoralen derivatives* are potent light-activated carcinogens and mutagens and are widespread in plants of the Umbelliferae family, such as celery, parsnips, figs, and parsley (for instance, 4 mg per 100 g of parsnip) (*17, 19, 44*). The level in celery (about 100 μg per 100 g) can increase about 100-fold if the celery is stressed or diseased (*19*). Celery pickers and handlers commonly develop skin

rashes on their arms when exposed to diseased celery (*19*). Oil of bergamot, a citrus oil, is very rich in a psoralen and was used in the leading suntan lotion in France (*17*). Psoralens, when activated by sunlight, damage DNA and induce tanning more rapidly than the ultraviolet component of sunlight, which is also a carcinogen (*17*). Psoralens (plus light) are also effective in producing oxygen radicals (*18*).

4) The potato glycoalkaloids *solanine* and *chaconine* are strong cholinesterase inhibitors and possible teratogens and are present at about 15 mg per 200 g of potato (*12, 13*). When potatoes are diseased, bruised, or exposed to light, these and other (*24*) glycoalkaloids reach levels that can be lethal to humans (*12*). Plants typically respond to damage by making more (and often different) toxic chemicals as a defense against insects and fungi (*19, 24, 25*). The different cultivars of potatoes vary in the concentration of these toxic glycoalkaloids (the concentration is a major determinant of insect and disease resistance); one cultivar bred for insect resistance had to be withdrawn from use because of its toxicity to humans (> 40 mg of glycoalkaloids in a 200-g potato is considered to be a toxic level) (*12*).

5) *Quercetin* and several similar flavonoids are mutagens in a number of short-term test systems. Flavonoids are extremely widespread (daily levels close to 1 g) in the human diet (*8, 16, 20, 21*). There is evidence for the carcinogenicity of quercetin in two strains of rats (*8*), although it was negative in other experiments (*21*).

6) *Quinones* and their phenol precursors (*9, 14, 16, 23, 45*) are widespread in the human diet. Quinones are quite toxic as they can act as electrophiles or accept a single electron to yield the semiquinone radical, which can either react directly with DNA (*14, 46*) or participate in a redox cycle of superoxide radical generation by transferring the electron to O_2 (*47*). The superoxide radical and its metabolic product H_2O_2 can, in turn, lead to the oxidation of fat in cellular membranes by a lipid peroxidation chain reaction, thus generating mutagens and carcinogens, as discussed below. A number of quinones and dietary phenols have been shown to be mutagens (*7, 9, 16, 23, 44*). Mutagenic anthraquinone derivatives are found in plants such as rhubarb and in mold toxins (*7, 16, 48*). Many dietary phenols can spontaneously autoxidize to quinones, generating hydrogen peroxide at the same time [examples are catechol derivatives such as the caffeic acid component of chlorogenic acid (*9*), which is present at about 250 mg per cup of coffee]. The amounts of these phenols in human urine (and in the diet) are appreciable (*45*). Catechol, for example, is excreted in urine at about 10 mg per day and appears to be mainly derived from metabolism of plant substances (*45*). Catechol is a potent promoter of carcinogenesis (*45*), an inducer of DNA damage, a likely active metabolite of the carcinogen benzene (*46*), and a toxic agent in cigarette smoke (*45*). Catecholamine induction of cardiomyopathy is thought to occur through generation of oxygen radicals (*49*).

7) *Theobromine*, a relative of caffeine, has been shown to be genotoxic in a variety of tests, to potentiate (as does caffeine) DNA damage by various carcinogens in human cells, and to cause testicular atrophy and spermatogenic cell abnormalities in rats (*27*). Cocoa powder is about 2 percent theobromine, and therefore humans may consume hundreds of milligrams of theobromine a day from chocolate. Theobromine is also present in tea.

8) *Pyrrolizidine* alkaloids are carcinogenic, mutagenic, and teratogenic and are present in thousands of plant species (often at > 1 percent by weight), some of which are ingested by humans, particularly in herbs and herbal teas and occasionally in honey (*7, 29*). Pyrrolizidine alkaloid poisonings in humans (as well as in other mammals) cause lung and liver lesions and are commonly misdiagnosed (*29*).

9) The broad (fava) bean (*Vicia faba*), a common food of the Mediterranean region, contains the toxins *vicine* and *convicine* at a level of about 2 percent of the dry weight (*30*). Pythagoras forbade his followers to eat the beans, presumably because he was one of the millions of Mediterranean people with a deficiency of glucose-6-phosphate dehydrogenase. This deficiency results in a low glutathione concentration in blood cells, which causes increased resistance to the malarial parasite, probably accounting for the widespread occurrence of the mutant gene in malarial regions. However, the low glutathione concentration also results in a marked sensitivity to agents that cause oxidative damage, such as the fava bean toxins and a variety of drugs and viruses. Sensitive individuals who ingest fava beans develop a severe hemolytic anemia caused by the enzymatic hydrolysis of vicine to its aglycone, *divicine*, which forms a quinone that generates oxygen radicals (*30*).

10) *Allyl isothiocyanate*, a major flavor ingredient in oil of mustard and horseradish, is one of the main toxins of the mustard seed and has been shown to cause chromosome aberrations in hamster cells at low concentration (*50*) and to be a carcinogen in rats (*31*).

11) *Gossypol* is a major toxin in cottonseed and accounts for about 1 percent of its dry weight (*32*). Gossypol causes pathological changes in rat and human testes, abnormal sperm, and male sterility (*32, 33*). Genetic damage has been observed in embryos sired by gossypol-treated male rats: dominant lethal mutations in embryos were measured after males were taken off gossypol treatment and allowed to mate (*33*). Gossypol appears to be a carcinogen as well: it has been reported to be a potent initiator and also a promoter of carcinogenesis in skin painting studies with mice (*34*). Crude, unrefined cottonseed oil contains considerable amounts of gossypol (100 to 750 mg per 100 ml). Thus human consumption may be appreciable in countries, such as Egypt, where fairly crude cottonseed oil is commonly used in cooking. Gossypol is being tested as a male contraceptive in over 10,000 people in China (at an oral dose of about 10 mg per person per day), as it is inexpensive and causes sterility during use (*33*). Gossypol's mode of action as a spermicide may be through the production of oxygen radicals (*35*).

Plant breeders have developed "glandless cotton," a new strain with low levels of gossypol, but seeds from this strain are much more susceptible to attack by the fungus *Aspergillus flavus*, which produces the potent carcinogen aflatoxin (*36*).

12) *Sterculic acid* and *malvalic acid* are widespread in the human diet. They are toxic cyclopropenoid fatty acids present in cottonseed oil and other oils from seeds of plants in the family Malvaceal (for instance, cotton, kapok, okra, and durian) (*51*). Another possible source of human exposure is consumption of fish, poultry, eggs, and milk from animals fed on cottonseed (*51*). Cyclopropenoid fatty acids are carcinogens in trout, markedly potentiate the carcinogenicity of aflatoxin in trout, cause atherosclerosis in rabbits, are mitogenic in rats, and have a variety of toxic effects in farm animals (*51*). The toxicity of these fatty acids could be due to their ease of oxidation to form peroxides and radicals (*51*).

13) Leguminous plants such as lupine contain very potent teratogens (*22*). When cows and goats forage on these plants, their offspring may have severe teratogenic abnormalities; an example is

the characteristic "crooked calf" abnormality due to the ingestion of *anagyrine* from lupine (*22*). In addition, significant amounts of these teratogens are transferred to the animals' milk, so that drinking the milk during pregnancy is a serious teratogenic hazard (*22*). In one rural California family, a baby boy, a litter of puppies, and goat kids all had "crooked" bone birth-defect abnormalities. The pregnant mother and the dog had both been drinking milk obtained from the family goats, which had been foraging on lupine (the main forage in winter) (*22*). It was at first mistakenly thought that the birth defects were caused by spraying of 2,4-D.

14) *Sesquiterpene lactones* are widespread in many plants (*37*), although because they are bitter they are not eaten in large amounts. Some have been shown to be mutagenic (*37*). They are a major toxin in the white sap of *Lactuca virosa* (poison lettuce), which has been used as a folk remedy. Plant breeders are now transferring genes from this species to commercial lettuce to increase insect resistance (*38*).

15) The *phorbol esters* present in the Euphorbiacea, some of which are used as folk remedies or herb teas, are potent promoters of carcinogenesis and may have been a cause of nasopharyngeal cancer in China and esophageal cancer in Curaçao (*39*).

16) Alfalfa sprouts contain *canavanine*, a highly toxic arginine analog that is incorporated into protein in place of arginine. Canavanine, which occurs in alfalfa sprouts at about 1.5 percent of their dry weight (*40*), appears to be the active agent in causing the severe lupus erythematosus–like syndrome seen when monkeys are fed alfalfa sprouts (*40*). Lupus in man is characterized by a defect in the immune system which is associated with autoimmunity, antinuclear antibodies, chromosome breaks, and various types of pathology (*40*). The chromosome breaks appear to be due to oxygen radicals as they are prevented by superoxide dismutase (*52*). The canavanine–alfalfa sprout pathology could be due in part to the production of oxygen radicals during phagocytization of antibody complexes with canavanine-containing protein.

The 16 examples above, plus coffee (discussed below), illustrate that the human dietary intake of "nature's pesticides" is likely to be several grams per day—probably at least 10,000 times higher than the dietary intake of man-made pesticides (*53*).

Levels of plant toxins that confer insect and fungal resistance are being increased or decreased by plant breeders (*38*). There are health costs for the use of these natural pesticides, just as there are for man-made pesticides (*41, 54*), and these must be balanced against the costs of producing food. However, little information is available about the toxicology of most of the natural plant toxins in our diet, despite the large doses we are exposed to. Many, if not most, of these plant toxins may be "new" to humans in the sense that the human diet has changed drastically with historic times. By comparison, our knowledge of the toxicological effects of new man-made pesticides is extensive, and general exposure is exceedingly low (*53*).

Plants also contain a variety of anticarcinogens (*55*), which are discussed below.

Alcohol. Alcohol has long been associated with cancer of the mouth, esophagus, pharynx, larynx, and, to a lesser extent, liver (*1, 56*), and it appears to be an important human teratogen, causing a variety of physical and mental defects in babies of mothers who drink (*57*). Alcohol drinking causes abnormalities in mice (*57a*) and is a synergist for chromosome damage in humans (*58*). Alcohol metabolism generates acetaldehyde, which is a mutagen and teratogen (*59*), a cocarcinogen, and possibly a carcinogen (*60*), and also radicals that produce lipid hydroperoxides (*61*) and other mutagens and carcinogens (*62*; see below). In some epidemiologic studies on alcohol (*56*), it has been suggested that dietary green vegetables are a modifying factor in the reduction of cancer risk.

Mold carcinogens. A variety of mold carcinogens and mutagens are present in mold-contaminated food such as corn, grain, nuts, peanut butter, bread, cheese, fruit, and apple juice (*15, 63*). Some of these, such as sterigmatocystin and aflatoxin, are among the most potent carcinogens and mutagens known (*15, 63*). Dietary glutathione has been reported to counteract aflatoxin carcinogenicity.

Nitrite, nitrate, and nitrosamines. A number of human cancers, such as stomach and esophageal cancer, may be related to nitrosamines and other nitroso compounds formed from nitrate and nitrite in the diet (*64, 65*). Beets, celery, lettuce, spinach, radishes, and rhubarb all contain about 200 mg of nitrate per 100-g portion (*65*). Anticarcinogens in the diet may be important in this context as well (*66*).

Fat and cancer: possible oxidative mechanisms. Epidemiologic studies of cancer in humans suggest, but do not prove, that high fat intake is associated with colon and breast cancer (*1, 4, 67*). A number of animal studies have shown that high dietary fat is a promoter and a presumptive carcinogen (*4, 67, 68*). Colon and breast cancer and lung cancer (which is almost entirely due to cigarette smoking) account for about half of all U.S. cancer deaths. In addition to the cyclopropenoid fatty acids already discussed, two other plausible mechanisms involving oxidative processes could account for the relation (*69*) between high fat and both cancer and heart disease.

1) *Rancid fat*. Fat accounts for over 40 percent of the calories in the U.S. diet (*67*), and the amount of ingested oxidized fat may be appreciable (*70, 71*). Unsaturated fatty acids and cholesterol in fat are easily oxidized, particularly during cooking (*70, 71*). The lipid peroxidation chain reaction (rancidity) yields a variety (*71–73*) of mutagens, promoters, and carcinogens such as fatty acid hydroperoxides (*62*), cholesterol hydroperoxide (*74*), endoperoxides, cholesterol and fatty acid epoxides (*74–77*), enals and other aldehydes (*44, 59, 78*), and alkoxy and hydroperoxy radicals (*44, 72*). Thus the colon and digestive tract are exposed to a variety of fat-derived carcinogens. Human breast fluid can contain enormous levels (up to 780 μM) (*75*) of cholesterol epoxide (an oxidation product of cholesterol), which could originate from either ingested oxidized fat or oxidative processes in body lipids. Rodent feeding studies with oxidized fat (*79*) have not yielded definitive results.

2) *Peroxisomes* oxidize an appreciable percentage of dietary fatty acids, and removal of each two-carbon unit generates one molecule of hydrogen peroxide (a mutagen, promoter, and carcinogen) (*80, 81*). Some hydrogen peroxide escapes the catalase in the peroxisome (*80, 82, 83*), thus contributing to the supply of oxygen radicals, which also come from other metabolic sources (*72, 83–85*). Hydroperoxides generate oxygen radicals in the presence of iron-containing compounds in the cell (*72*). Oxygen radicals, in turn, can damage DNA and can start the rancidity chain reaction which leads to the production of the mutagens and carcinogens listed above (*72*). Drugs such as clofibrate, which cause lowering of serum lipids and proliferation of peroxisomes in rodents, result in age pigment (lipofuscin) accumulation (a sign of lipid peroxidation in tissues) and liver tumors in animals (*80*). Some fatty acids, such as $C_{22:1}$ and certain *trans* fatty acids, appear to cause peroxisomal proliferation because they are poorly oxidized in mitochondria and are preferentially oxidized in the peroxisomes, although they may be selective for heart or

liver (*86*). There has been controversy about the role of *trans* fatty acids in cancer and heart disease, and recent evidence suggests that *trans* fatty acids might not be a risk factor for atherosclerosis in experimental animals (*87*). Americans consume about 12 g of *trans* fatty acids a day (*87*) and a similar amount of unnatural *cis* isomers [which need further study (*88*)], mainly from hydrogenated vegetable fats. Dietary $C_{22:1}$ fatty acids are also obtained from rapeseed oil and fish oils (*86*). Thus oxidation of certain fatty acids might generate grams of hydrogen peroxide per day within the peroxisome (*86*). Another source of fat toxicity could be perturbations in the mitochondrial or peroxisomal membranes caused by abnormal fatty acids, yielding an increased flux of superoxide and hydrogen peroxide. Mitochondrial structure is altered when rats are fed some abnormal fatty acids from partially hydrogenated fish oil (*89*). Dietary $C_{22:1}$ fatty acids and clofibrate also induce ornithine decarboxylase (*86*), a common attribute of promoters.

A recent National Academy of Sciences committee report suggests that a reduction of fat consumption in the American diet would be prudent (*4*), although other scientists argue that, until we know more about the mechanism of the fat-cancer relation and about which types of fat are dangerous, it is premature to recommend dietary changes (*90*).

Cooked Food as a Source of Ingested Burnt and Browned Material

Work of Sugimura and others has indicated that the burnt and browned material from heating protein during cooking is highly mutagenic (*21, 91*). Several chemicals isolated on the basis of their mutagenicity from heated protein or pyrolyzed amino acids were found to be carcinogenic when fed to rodents (*21*). In addition, the browning reaction products from the caramelization of sugars or the reaction of amino acids and sugars during cooking (for instance, the brown material on bread crusts and toasted bread) contain a large variety of DNA-damaging agents and presumptive carcinogens (*23, 38, 92*). The amount of burnt and browned material in the human diet may be several grams per day. By comparison about 500 mg of burnt material is inhaled each day by a smoker using two packs of cigarettes (at 20 mg of tar per cigarette) a day. Smokers have more easily detectable levels of mutagens in their urine than nonsmokers (*93*), but so do people who have consumed a meal of fried pork or bacon (*94*). In the evaluation of risk from burnt material it may be useful (in addition to carrying out epidemiologic studies) to compare the activity of cigarette tar to that of the burnt material from cooked food (or polluted air) in short-term tests and animal carcinogenicity tests involving relevant routes of exposure. Route of exposure and composition of the burnt material are critical variables. The risk from inhaled cigarette smoke can be one reference standard: an average life shortening of about 8 years for a two-pack-a-day smoker. The amount of burnt material inhaled from severely polluted city air, on the other hand, is relatively small: it would be necessary to breathe smoggy Los Angeles air (111 $\mu g/m^3$ total particulates; 31 $\mu g/m^3$ soluble organic matter) for 1 to 2 weeks to equal the soluble organic matter of the particulates or the mutagenicity from one cigarette (20 mg of tar) (*95*). Epidemiologic studies have not shown significant risks from city air pollution alone (*1, 96*). Air in the houses of smokers is considerably more polluted than city air outside (*97*).

Coffee, which contains a considerable amount of burnt material, including the mutagenic pyrolysis product methylglyoxal, is mutagenic (*21, 98*). However, one cup of coffee also contains about 250 mg of the natural mutagen chlorogenic acid (*9*) [which is also an antinitrosating agent (*66*)], highly toxic atractylosides (*10*), the glutathione transferase inducers kahweal palmitate and cafestol palmitate (*11*), and about 100 mg of caffeine [which inhibits a DNA-repair system and can increase tumor yield (*99*) and cause birth defects at high levels in several experimental species (*100*)]. There is preliminary, but not conclusive, epidemiologic evidence that heavy coffee drinking is associated with cancer of the ovary, bladder, pancreas, and large bowel (*101*).

Cooking also accelerates the rancidity reaction of cooking oils and fat in meat (*70, 71*), thus increasing consumption of mutagens and carcinogens.

Anticarcinogens

We have many defense mechanisms to protect ourselves against mutagens and carcinogens, including continuous shedding of the surface layer of our skin, stomach, cornea, intestines, and colon (*102*). Understanding these mechanisms should be a major goal of cancer, heart, and aging research. Among the most important defenses may be those against oxygen radicals and lipid peroxidation if, as discussed here, these agents are major contributors to DNA damage (*103*). Major sources of endogenous oxygen radicals are hydrogen peroxide (*83*) and superoxide (*72, 104*) generated as side products of metabolism, and the oxygen radical burst from phagocytosis after viral or bacterial infection or the inflammatory reaction (*105*). A variety of environmental agents could also contribute to the oxygen radical load, as discussed here and in recent reviews (*72, 106*). Many enzymes protect cells from oxidative damage; examples are superoxide dismutase (*104*), glutathione peroxidase (*107*), DT-diaphorase (*108*), and the glutathione transferases (*109*). In addition, a variety of small molecules in our diet are required for antioxidative mechanisms and appear to be anticarcinogens; some of these are discussed below.

1) *Vitamin E* (tocopherol) is the major radical trap in lipid membranes (*72*) and has been used clinically in a variety of oxidation-related diseases (*110*). Vitamin E ameliorates both the cardiac damage and carcinogenicity of the quinones adriamycin and daunomycin, which are mutagenic, carcinogenic, cause cardiac damage, and appear to be toxic because of free radical generation (*111*). Protective effects of tocopherols against radiation-induced DNA damage and mutation and dimethylhydrazine-induced carcinogenesis have also been observed (*112*). Vitamin E markedly increases the endurance of rats during heavy exercise, which causes extensive oxygen radical damage to tissues (*113*).

2) β-*Carotene* is another antioxidant in the diet that could be important in protecting body fat and lipid membranes against oxidation. Carotenoids are free-radical traps and remarkably efficient quenchers of singlet oxygen (*114*). Singlet oxygen is a very reactive form of oxygen which is mutagenic and particularly effective at causing lipid peroxidation (*114*). It can be generated by pigment-mediated transfer of the energy of light to oxygen, or by lipid peroxidation, although the latter is somewhat controversial. β-Carotene and similar polyprenes are present in carrots and in all food that contains chlorophyll, and they appear to be the plants' main defense against singlet oxygen generated as a byproduct from the interaction of light an chlorophyll (*115*). Carotenoids ha been shown to be anticarcinogens in r and mice (*116*). Carotenoids (in gr and yellow vegetables) may be an cinogens in humans (*1, 56, 117*). protective effects in smokers m related to the high level of oxi both cigarette smoke and tar (Carotenoids have been used m

the treatment for some genetic diseases, such as porphyrias, where a marked photosensitivity is presumably due to singlet oxygen formation (*119*).

3) *Selenium* is another important dietary anticarcinogen. Dietary selenium (usually selenite) significantly inhibits the induction of skin, liver, colon, and mammary tumors in experimental animals by a number of different carcinogens, as well as the induction of mammary tumors by viruses (*120*). It also inhibits transformation of mouse mammary cells (*121*). Low selenium concentrations may be a risk factor in human cancer (*122*). A particular type of heart disease in young people in the Keshan area of China has been traced to a selenium deficiency, and low selenium has been associated with cardiovascular death in Finland (*123*). Selenium is in the active site of glutathione peroxidase, an enzyme essential for destroying lipid hydroperoxides and endogenous hydrogen peroxide and thus helping to prevent oxygen radical–induced lipid peroxidation (*107*), although not all of the effects of selenium may be accounted for by this enzyme (*120*). Several heavy-metal toxins, such as Cd^{2+} (a known carcinogen) and Hg^{2+}, lower glutathione peroxidase activity by interacting with selenium (*107*). Selenite (and vitamin E) has been shown to counter the oxidative toxicity of mercuric salts (*124*).

4) *Glutathione* is present in food and is one of the major antioxidants and antimutagens in the soluble fraction of cells. The glutathione transferases (some of which have peroxidase activity) are major defenses against oxidative and alkylating carcinogens (*109*). The concentration of glutathione may be influenced by dietary sulfur amino acids (*125, 126*). *N*-Acetylcysteine, a source of cysteine, raises glutathione concentrations and reduces the oxidative cardiotoxicity of adriamycin and the skin reaction to radiation (*127*). Glutathione concentrations are raised even more efficiently by L-2-oxothiazolidine-4-carboxylate, which is an effective antagonist of acetaminophen-caused liver damage (*126*). Acetaminophen is thought to be toxic through radical and quinone oxidizing metabolites (*128*). Dietary glutathione may be an effective anticarcinogen against aflatoxin (*129*).

5) Dietary *ascorbic acid* is also important as an antioxidant. It was shown to be anticarcinogenic in rodents treated with ultraviolet radiation, benzo[*a*]pyrene, and nitrite (forming nitroso carcinogens) (*64, 65, 130*), and it may be inversely associated with human uterine cervical dysplasia (although this is not proof of a cause-effect relationship) (*131*). It was recently hypothesized that ascorbic acid may have been supplemented and perhaps partially replaced in humans by uric acid during primate evolution (*132*).

6) *Uric acid* is a strong antioxidant present in high concentrations in the blood of humans (*132*). The concentration of uric acid in the blood can be increased by dietary purines; however, too much causes gout. Uric acid is also present in high concentrations in human saliva (*132*) and may play a role in defense there as well, in conjunction with lactoperoxidase. A low uric acid level in blood may possibly be a risk factor in cigarette-caused lung cancer in humans (*133*).

7) Edible plants and a variety of substances in them, such as phenols, have been reported to inhibit (cabbage) or to enhance (beets) carcinogenesis (*11, 55, 134*) or mutagenesis (*23, 66, 92, 135*) in experimental animals. Some of these substances appear to inhibit by inducing cytochrome P-450 and other metabolic enzymes [(*134*); see also (*11*)], although on balance it is not completely clear whether it is generally helpful or harmful for humans to ingest these inducing substances.

The hypothesis that as much as 80 percent of cancer could be due to environmental factors was based on geographic differences in cancer rates and studies of migrants (*136*). These differences in cancer rates were thought to be mainly due to life-style factors, such as smoking and dietary carcinogens and promoters (*136*), but they also may be due in good part [see also (*1*)] to less than optimum amounts of anticarcinogens and protective factors in the diet.

The optimum levels of dietary antioxidants, which may vary among individuals, remain to be determined; however, at least for selenium (*120*), it is important to emphasize the possibility of deleterious side effects at high doses.

Oxygen Radicals and Degenerative Diseases Associated with Aging

Aging. A plausible theory of aging holds that the major cause is damage to DNA (*102, 137*) and other macromolecules and that a major source of this damage is oxygen radicals and lipid peroxidation (*43, 84, 103, 138–141*). Cancer and other degenerative diseases, such as heart disease (*102*), are likely to be due in good part to this same fundamental destructive process. Age pigment (lipofuscin) accumulates aging in all mammalian species and has been associated with lipid peroxidation (*73, 84, 138, 139*). The fluorescent products in age pigment are thought to be formed by malondialdehyde (a mutagen and carcinogen and a major end product of rancidity) cross-linking protein and lipids (*138*). Metabolic rate is directly correlated with the rate of lipofuscin formation (and inversely correlated with longevity) (*139*).

Cancer increases with about the fourth power of age, both in short-lived species such as rats and mice (about 30 percent of rodents have cancer by the end of their 2- to 3-year life-span) and in long-lived species such as humans (about 30 percent of people have cancer by the end of their 85-year life-span) (*142*). Thus, the marked increase in life-span that has occurred in 60 million years of primate evolution has been accompanied by a marked decrease in age-specific cancer rates; that is, in contrast to rodents, 30 percent of humans do not have cancer by the age of 3 (*142*). One important factor in longevity appears to be basal metabolic rate (*139, 141*), which is much lower in man than in rodents and could markedly affect the level of endogenous oxygen radicals.

Animals have many antioxidant defenses against oxygen radicals. Increased levels of these antioxidants, as well as new antioxidants, may also be a factor in the evolution of man from short-lived prosimians (*143*). It has been suggested that an increase in superoxide dismutase is correlated (after the basal metabolic rate is taken into account) with increased longevity during primate evolution, although this has been disputed (*141*). Ames *et al.* proposed (*132*) that as uric acid was an antioxidant and was present in much higher concentrations in the blood of humans than in other mammals, it may have been one of the innovations enabling the marked increase in life span and consequent marked decrease in age-specific cancer rates which occurred during primate evolution. The ability to synthesize ascorbic acid may have been lost at about the same time in primate evolution as uric acid levels began to increase (*144*).

Cancer and promotion. Both DNA-damaging agents (initiating mutagens) (*21, 41, 42*) and promoters (*145*) appear to play an important role in carcinogenesis (*21, 146*). It has been postulated that certain promoters of carcinogenesis act by generation of oxygen radicals and resultant lipid peroxidation (*73, 146–149*). Lipid peroxidation cross-links proteins (*43, 150*) and affects all aspects of cell organization (*72*), including membrane and surface structure, and the mi-

otic apparatus. A common property of promoters may be their ability to produce oxygen radicals. Some examples are fat and hydrogen peroxide (which may be among the most important promoters) (*67, 68, 81*), TCDD (*151*), lead and cadmium (*152*), phorbol esters (*147, 149, 153*), wounding of tissues (*154*), asbestos (*155*), peroxides (*156*), catechol (*45*) (see quinones above), mezerein and teleocidin B (*147*), phenobarbital (*157*), and radiation (*72, 158*). Inflammatory reactions involve the production of oxygen radicals by phagocytes (*105*), and this could be the basis of promotion for asbestos (*155*) or wounding (*154*). Some of the antioxidant anticarcinogens (discussed above) are also antipromoters (*73, 121, 146, 159, 160*), and phorbol ester–induced chromosome damage (*149*) or promotion of transformation (*159*) is suppressed by superoxide dismutase, as would be expected if promoters were working through oxidative mechanisms. Many "complete" carcinogens cause the production of oxygen radicals (*73, 161*); examples are nitroso compounds, hydrazines, quinones, polycyclic hydrocarbons (through quinones), cadmium and lead salts, nitro compounds, and radiation. A good part of the toxic effects of ionizing radiation damage to DNA and cells is thought to be due to generation of oxygen radicals (*103, 162*), although only a tiny part of the oxygen radical load in humans is likely to be from this source.

Recent studies give some clues as to how promoters might act. Promoters disrupt the mitotic apparatus, causing hemizygosity and expression of recessive genes (*163*). Phorbol esters generate oxygen radicals, which cause chromosome breaks (*164*) and increase gene copy number (*165*). Promoters also cause formation of the peroxide hormones of the prostaglandin and leukotriene family by oxidation of arachidonic acid and other C_{20} polyenoic fatty acids, and inhibitors of this process appear to be antipromoters (*160*). These hormones are intimately involved in cell division, differentiation, and tumor growth (*166*) and could have arisen in evolution as signal molecules warning the cell of oxidative damage. Effects on the cell membrane have also been suggested as the important factor in promotion, causing inhibition of intercellular communication (*167*) or protein kinase activation (*167a*).

Heart disease. It has been postulated that atherosclerotic lesions, which are derived from single cells, are similar to benign tumors and are of somatic mutational origin (*102, 168*). Fat appears to be one major risk factor for heart disease as well as for colon and breast cancer (*69*). In agreement with this, a strong correlation has been observed between the frequency of atherosclerotic lesions and adenomatous polyps of the colon (*69*). Thus, the same oxidative processes involving fat may contribute to both diseases. Oxidized forms of cholesterol have been implicated in heart disease (*169*), and atherosclerotic-like lesions have been produced by injecting rabbits with lipid hydroperoxide or oxidized cholesterol (*169*). The anticarcinogens discussed above could be anti–heart disease agents as well. As pointed out in the preceding section, vitamin E ameliorates both the cardiac damage and carcinogenicity of the free-radical-generating quinones adriamycin and daunomycin; *N*-acetylcysteine reduces the cardiotoxicity of adriamycin; and selenium is an antirisk factor for one type of heart disease.

Other diseases. The brain uses 20 percent of the oxygen consumed by man and contains an appreciable amount of unsaturated fat. Lipid peroxidation (with consequent age pigment) is known to occur readily in the brain (*72*), and possible consequences could be senile dementia or other brain abnormalities (*84*). Several inherited progressive diseases of the central nervous system, such as Batten's disease, are associated with lipofuscin accumulation and may be due to a lipid peroxidation caused by a high concentration of unbound iron (*170*). Mental retardation is one consequence of an inherited defective DNA repair system (XP complementation group D) for depurinated sites in DNA (*171*).

Senile cataracts have been associated with light-induced oxidative damage (*172*). The retina and an associated layer of cells, the pigment epithelium, are extremely sensitive to degeneration in vitamin E and selenium deficiency (*173*). The pigment epithelium accumulates massive amounts of lipofuscin in aging and dietary antioxidant deficiency (*173*). The eye is well known to be particularly rich in antioxidants.

The testes are quite prone to lipid peroxidation and to the accumulation of age pigment. A number of agents, such as gossypol, which cause genetic birth defects (dominant lethals) may be active by this mechanism. The various agents known to cause cancer by oxidative mechanisms are prospective mutagenic agents for the germ line. Thus, vitamin E, which was discovered 60 years ago as a fertility factor (*72*), and other antioxidants such as selenium (*174*), may help both to engender and to protect the next generation.

Risks

There are large numbers of mutagens and carcinogens in every meal, all perfectly natural and traditional [see also (*21, 23*)]. Nature is not benign. It should be emphasized that no human diet can be entirely free of mutagens and carcinogens and that the foods mentioned are only representative examples. To identify a substance, whether natural or manmade, as a mutagen or a carcinogen, is just a first step. Beyond this, it is necessary to consider the risks for alternative courses of action and to quantitate the approximate magnitude of the risk, although the quantification of risk poses a major challenge. Carcinogens differ in their potency in rodents by more than a millionfold (*175*), and the levels of particular carcinogens to which humans are exposed can vary more than a billionfold. Extrapolation of risk from rodents to humans is difficult for many reasons, including the longevity difference, antioxidant factors, and the probable multicausal nature of most human cancer.

Tobacco smoking is, without doubt, a major and well-understood risk, causing about 30 percent of cancer deaths and 25 percent of fatal heart attacks (as well as other degenerative diseases) in the United States (*1*). These percentages may increase even more in the near future as the health effects of the large increase in women smokers become apparent (*1*). Diet, which provides both carcinogens and anticarcinogens, is extremely likely to be another major risk factor. Excessive alcohol consumption is another risk, although it does not seem to be of the same general importance as smoking and diet. Certain other high-dose exposures might also turn out to be important for particular groups of people—for instance, certain drugs, where consumption can reach hundreds of milligrams per day; particular cosmetics; and certain occupational exposures (*2*), where workers inhale dusts or solvents at high concentration. We must also be prudent about environmental pollution (*41, 54*). Despite all of these risks, it should be emphasized that the overall trend in life expectancy in the United States is continuing steadily upward (*176*).

The understanding of cancer and degenerative disease mechanisms is being aided by the rapid progress of science and technology, and this should help to dispel confusion about how important health risks can be identified among the vast number of minor risks. We have many methods of attacking the problem of environmental carcinogens (and anticarcinogens), including human epidemi-

ology (*1*), short-term tests (*41, 42, 177*), and animal cancer tests (*175*). Powerful new methods are being developed [for instance, see (*58, 177*)] for measuring DNA damage or other pertinent factors with great sensitivity in individuals. These methods, which are often noninvasive as they can be done on blood or urine (even after storage), can be combined with epidemiology to determine whether particular factors are predictive of disease. Thus, more powerful tools will be available for optimizing antioxidants and other dietary anti-risk factors, for identifying human genetic variants at high risk, and for identifying significant health risks.

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RESEARCH ARTICLE

Imaging Dopamine Receptors in the Human Brain by Positron Tomography

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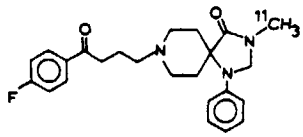
Abstract. *Neurotransmitter receptors may be involved in a number of neuropsychiatric disease states. The ligand 3-*N*-[^{11}C]methylspiperone, which preferentially binds to dopamine receptors in vivo, was used to image the receptors by positron emission tomography scanning in baboons and in humans. This technique holds promise for noninvasive clinical studies of dopamine receptors in humans.*

One of the most intriguing problems in biomedical research today is that of relating manifestations of neuropsychiatric diseases to chemical processes in different parts of the brain. The neurotransmitter dopamine appears to be associated with abnormalities related to disorders such as Parkinson's disease and schizophrenia. The highest density of dopamine neurons occurs in the nigrostriatal dopamine pathway which degenerates in Parkinson's disease (*1*). Neuroleptic drugs elicit extrapyramidal parkinsonian side effects by blocking dopamine receptors in the corpus striatum and also exert antischizophrenic action by blocking dopamine receptors, perhaps in limbic areas (*2*). Numbers of dopamine receptors are increased by chronic neuroleptic treatment (*3*) and are also increased in some schizophrenics, perhaps as a result of neuroleptic therapy (*4*).

The development of positron emission tomography (PET) and appropriate radioactive tracers labeled with positron-emitting radionuclides has now made it possible to relate regional biochemistry within the human brain to measurements of behavior in normal subjects and to elucidate abnormalities in patients with Alzheimer's disease (*5*), Huntington's disease (*6*), depression (*7*), and multiple infarct dementia (*8*). The technique consists of intravenous injection of a substance such as ^{18}F-labeled deoxyglucose, [^{11}C]carboxyhemoglobin, ionic rubidium-82, ^{68}Ga-labeled EDTA, and other radiopharmaceuticals, and subsequent imaging of the distribution of the radioactive label in the brain by means of the tomographic method, based on detection of the annihilation radiation produced during positron emission (*9*).

The butyrophenone neuroleptic drug spiperone has been useful in binding studies for measuring dopamine receptors both in vitro (*10*) and in vivo (*11*). We now report initial results obtained with 3-*N*-[^{11}C]methylspiperone (^{11}C-NMSP), a spiperone derivative, in PET



scanning studies to visualize the distribution of dopamine receptors in the brains of baboons and a human being. All studies were performed with a NeuroECAT scanner (Ortec, Inc., Oak Ridge, Tennessee), which has a spatial resolution of approximately 8 mm (full width at half maximum) in the plane of the slice. The distance between slices is 3 cm.

The newly developed tracer ^{11}C-NMSP was synthesized by *N*-alkylation of spiperone with [^{11}C]methyl iodide; the iodide was produced from $^{11}CO_2$, which in turn had been produced with an in-hospital cyclotron (model RNP-16, Scanditronix Cyclotron, Sweden). Carbon-11 is a positron-emitting isotope with a physical half-life of 20 minutes. The entire synthesis was accomplished with material ready for injection within 55 minutes after the end of the cyclotron

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Cancer Scares Over Trivia

Natural Carcinogens in Food Outweigh Traces in Our Water

By BRUCE N. AMES

The following commentary was adapted from testimony before the California Senate Committee on Toxics and Public Safety Management.

The carcinogens currently being found in California water supplies, such as in Silicon Valley, are present in extraordinarily tiny amounts that, except in rare cases, are trivial relative to the background level of carcinogens in nature. Therefore, I am convinced that such water pollution is irrelevant as a cause of human cancer.

The fallacy in our approach to such pollution is the belief that carcinogens are rare and that they are mostly man-made chemicals. Quite the contrary is the case; every meal has many natural carcinogens. My estimate is that more than 99.99% of the carcinogens we ingest are from natural or traditional sources such as cigarettes, alcohol and chemicals formed by cooking food.

Man-made toxic chemicals in food and water are almost always present in the parts per billion (ppb) range. One part per billion, (one person in all of China) is an extraordinarily small amount. The carcinogens in some common beverages occur in much higher concentrations.

Coffee contains the natural carcinogens hydrogen peroxide and methylglyoxal, each at about 4,000 ppb. Tap water contains the carcinogen chloroform at 83 ppb (U.S. average) due to chlorination. Cola drinks contain the carcinogen formaldehyde at 7,900 ppb. Even human blood averages about 3,000 ppb in formaldehyde from normal metabolism. Beer contains the carcinogens formaldehyde (700 ppb), and alcohol (50 million ppb, or 5%). Alcohol consumption is a known cause of 3% of human cancer in this country, and pure ethyl alcohol is a carcinogen in rats.

Milk contains a high percentage of fat. High fat consumption has been linked to human colon and breast cancer (though calcium from milk may be an important anti-carcinogen). Fruit juices may have carcinogenic mold toxins.

The primary way we identify carcinogens is by testing chemicals at enormous doses in animals. The potency of carcinogens varies more than a million-fold. For example, aflatoxin, a mold carcinogen that is present in small amounts in peanut butter (2 ppb U.S. average), or in corn products such as tortillas, requires about a million times smaller dose to cause the same incidence of cancer in test animals as trichloroethylene, which was the main contaminant in Silicon Valley wells. Calculating a possible hazard to humans from a cancer test on rats must take into account a chemical's potency as well as the daily human dose. My colleagues and I have done such a study and these are some examples of our findings.

The level of identified carcinogens in contaminated well water only rarely involves a possible hazard more than that of ordinary chlorinated tap water. Of 35 private wells shut down in Silicon Valley because of their supposed carcinogenic hazard found in an Environmental Protection Agency study, only two were of greater possible hazard than ordinary chlorinated tap water, and the most polluted well (2,800 ppb trichloroethylene) is still at least 1,000 times *less* of a possible hazard than an equal volume of cola, beer or wine. This is because trichloroethylene is an extremely weak carcinogen. It is comparable to saccharin and only 10 times more potent than alcohol, which is present at about 50 million ppb in a beer. Given that we drink only about one or two quarts of tap water per day, the trace amounts of man-made pollution typically found are an insignificant hazard.

Man-made pesticide residues in our food are about 100 ppb on the average; most of these residues are noncarcinogenic. DDT and its metabolite DDE, however, are carcinogens in animals. The possible DDT-DDE hazard of the average U.S. daily intake equals that of the chloroform in one glass of tap water and is insignificant compared to natural carcinogens in our diet. Even an occasional highly DDT-DDE or PCB-contaminated fish (100 times the average level) would contribute a possible hazard that is comparable to the average peanut butter sandwich and is very small compared to other common minimal risks, such as a glass of beer.

Our diet contains natural pesticides in amounts at least 10,000 times greater than residues of man-made pesticides. Natural pesticides are toxic chemicals, which are present in all plants, usually making up 5% to 10% of a plant's weight. There is an enormous variety of them, though only a few are present in each plant species. The function of these chemicals is to protect the plants against fungi, insects and animal predators. Thus a major aspect of evolution of plants is chemical warfare. There has been relatively little research in the toxicology or carcinogenicity of these compounds, and so very few of the large number present in the human diet have been tested in animals.

A fair percentage of those few that have been tested have turned out to be carcinogens in rats or mice. They include estragole (in basil), safrole (in herbs), symphitine (in comfrey tea), psoralens (in parsley and celery), hydrazines (in mushrooms), and allyl isothiocyanate (in mustard). The possible carcinogenic hazard of nature's pesticides completely overshadows the traces of man-made pesticide residues found in the daily diet. Plants also contain anti-carcinogens and valuable nutrients, so I believe that even these possible hazards seem too small to worry about, particularly in view of the difficulties of predicting risks to humans from tests in rats.

All calculations of human risk based on rat and mouse cancer tests, both from natural and man-made carcinogens, are hypothetical. Thus they should be viewed with a great deal of skepticism, unlike known human carcinogens, such as smoking and alcohol. Smoking causes 400,000 deaths from cancer, heart disease and other maladies every year; alcoholic beverages cause 100,000 deaths each year in the U.S.

There also are many new reasons for being skeptical of uncritical low-dose extrapolation of risk to humans from animal data obtained by feeding enormous doses of carcinogens, which are too complicated to explain here. This is reinforced by the studies of cancer epidemiologists who are making considerable progress in understanding the smoking, dietary, hormonal, viral and occupational contributions to human cancer, but who are finding remarkably little solid evidence for any significant contribution from pollution.

Since we now know that carcinogens are common, not rare (more than half the chemicals tested in rodents were judged carcinogens), we must ignore the trivia if we are to deal effectively with the important causes of cancer. We might possibly eliminate every trace of man-made carcinogens from our water or food supply, but it would cost an enormous amount, be of minimal relevance to the causes of human cancer and distract health workers from real, more important cancer risks.

What we do need are some sensible regulations about pollution. We should also remember that life expectancy increases every year. Age-adjusted death rates for stomach, uterus and liver cancer have been decreasing for years; other major cancers, such as colon, breast and prostate have not increased significantly; only lung cancer—which is almost always due to smoking—has increased dramatically.

Bruce N. Ames is chairman of the biochemistry Department at UC Berkeley, a member of the National Academy of Sciences and a former member of the board of directors of the National Cancer Institute. He does no consulting for the chemical, drug or food industries, or for law firms.

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DEPARTMENT OF BIOCHEMISTRY BERKELEY, CALIFORNIA 94720

November 11, 1985

Testimony of
Professor Bruce N. Ames, Chairman
Department of Biochemistry
University of California
Berkeley, California 94720

Professor Ames was formerly on the Board of Directors of the National Cancer Institute (National Cancer Advisory Board). He is a member of the National Academy of Sciences. He was the recipient of the most prestigious award for cancer reseach, the General Motors Cancer Research Foundation Prize (1983), and of the highest award in environmental achievement, the Tyler Prize (1985). He does no consulting for the chemical, drug, or food industry, or for law firms.

The Honorable Art Torres
Chairman, Senate Committee on
Toxics and Public Safety Management
State Capitol, Room 4062
Sacramento, California 95814

Dear Senator Torres:

The carcinogens and toxic chemicals being found in California water supplies are present in extraordinarily tiny amounts and, except in rare cases, are present in trivial amounts relative to the background level of carcinogens in Nature. I am convinced that water pollution is irrelevant to the causes of human cancer.

The main current fallacy consists in thinking that carcinogens are rare and that they are mostly man-made chemicals. My own estimate is that over 99.99% of the carcinogens Californians ingest are natural (e.g., natural toxic chemicals in plants, mold carcinogens) or traditional (e.g., cooking food, smoking cigarettes, alcohol).

Every meal is full of carcinogens and when one compares the level of carcinogens in contaminated water (or pesticide residues in food) to the level of natural carcinogens, it is clear that water pollution (or pesticide residues) represents a trivial risk. Every common drink contains carcinogens. I list a few sources and

Nature's pesticides. We are ingesting natural pesticides in our diet in amounts at least 10,000 times more than man-made pesticide residues. Natural pesticides are natural toxic chemicals, which are present in all plants, usually making up 5-10% of a plant's weight. They have an enormous variety of chemical structures, though only a few are present in each plant species. Their function is protection against fungi, insects and animal predators. A major aspect of evolution of plants is chemical warfare. There has been relatively little interest in the toxicology or carcinogenicity of these compounds until quite recently, and very few of the large number present in the human diet have been tested in animal cancer bioassays, and only some of these tests are adequate for estimating their potency. Some of those tested are carcinogens. They include estragole (in basil), safrole (in herbs), symphitine (in comfrey tea), psoralens (in parsley and celery), hydrazines (in mushrooms), and allyl isothiocyanate (in mustard). Calculations on the carcinogenic risk of these compounds show that they completely overshadow the traces of man-made pollutants found in the daily diet, e.g., 5 basil leaves are 100 times more hazardous than the worst well in Silicon Valley (at least 5 basil leaves would be ingested in a portion of "pasta al pesto"). Thousands more of Nature's pesticides are present in the human diet and because many mutagens are being discovered among them, many are potential carcinogens.

Skepticism about extrapolating risks from rodents. All risk calculations based on rat and mouse cancer tests, both from natural and man-made carcinogens, are hypothetical: thus, they should be taken with a great dose of skepticism, unlike known human carcinogens such as radioactive radon gas coming out of the ground into California houses or smoking (400,000 real deaths per year in the U.S.). There are many new reasons for skepticism of low-dose extrapolation of risk to humans from rodent data, and for suspicions about linear dose-response extrapolations, which I won't discuss here. I will just mention one qualitative point. Of the carcinogens tested in both rats and mice in our database on potency, 42% of the chemicals were positive in the mouse and negative in the rat, or vice versa. Thus, even two closely related short-lived creatures, the rat and the mouse, don't predict very well for each other whether a substance is a carcinogen.

We might possibly eliminate every trace of man-made carcinogen from our water supply, but it will cost an enormous amount of California's wealth (wealth is related to health) and be irrelevant to causes of human cancer and also might cause new risks to arise that are worse and distract health workers from real, more important risks. Thus, one can either chase after parts per billion of every man-made carcinogen that turns up or have some sensible regulation about pollution. As one of the world's most eminent epidemiologists has said:

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CALIFORNIA Q & A

One day in 1964, Bruce Ames, chairman of the biochemistry department at Berkeley, happened to read the list of ingredients on a potato chip package. A geneticist as well as a biochemist, he began to think about the new chemicals entering the environment, and he wondered if a simple test could be developed to screen them for mutagenicity—the ability to damage the DNA in our cells. This led to the development of the Ames test, now the most widely used test for identifying probable carcinogenic, or cancer-causing, substances.

To demonstrate the relationship between mutations and cancer, Ames used his test to show that most known carcinogens were mutagens. Next, concerned primarily with man-made chemicals, he set out to identify mutagens in the environment; this work produced many findings, including the mutagenicity of hair dyes and the flame retardants in children's sleepwear. Lately, he has turned his interest toward naturally occurring substances, and in a recent review in Science *magazine he discussed mutagens and carcinogens that have been identified in a variety of foods: broiled steak, dark toast, coffee, mushrooms, celery, parsley, cottonseed oil, peanut butter, black pepper, comfrey herb tea, mustard, and cheeses.*

As an international expert on diet and cancer, Ames is deluged with offers for speaking engagements throughout the world; he also gets his share of letters from individuals seeking dietary advice. A soft-spoken man with a sense of humor, he says of his fame: "I guess everyone's interested in cancer, and everyone's interested in diet. If I had sex in there, I'd be busy all the time."

The Ames test uses special strains of the bacterium Salmonella typhimurium *that are unable to make histidine, an amino acid found in all proteins, and therefore require this nutrient for growth. If the bacteria are exposed to a mutagenic substance, some of them regain the ability to make histidine. These mutants form visible colonies on a histidine-free petri plate. Stronger mutagens cause more mutations to occur and, consequently, more colonies to appear.*

Ames says, "During the course of this work on mutagenesis, I became convinced that one essential aspect of carcinogens is their ability to damage DNA. We kept lists of popular carcinogens and kept working to make improvements in the test which could detect them as mutagens. One key development was the addition of a rat liver homogenate to our petri plates. With this and other improvements, we were able to determine that more than 80 percent of carcinogens are mutagens."

Born in New York City in 1928, Ames grew up in a home where science was familiar and learning encouraged. His father was chairman of a high school chemistry department, later Supervisor in Science for the New York City Schools, and finally Assistant Superintendent of Schools.

Ames can't remember a time when he wasn't interested in science. In his childhood, he says, "I was always interested in chemistry and biology. I used to read the books my father left lying around, and in the summer I collected frogs and snakes."

After graduating from the Bronx High School of Science in 1946, he attended Cornell University, where he received his B.A. in 1950 with a major in chemistry and minor in biology. In 1953, he received his Ph.D. in biochemistry from the California Institute of Technology, then spent 15 years as a biochemist at the National Institutes of Health. He joined the Department of Biochemistry at Berkeley as a full professor in 1968.

In 1960, he married Dr. Giovanna Ferro-Luzzi, who also is a biochemist on the faculty at Berkeley. They have two children: their daughter is a senior at the Massachusetts Institute of Technology, and their son plans to begin studies at the University of Wisconsin this fall.

Ames's numerous awards and honors include the Eli Lilly Award of the American Chemical Society, the Environmental Mutagen Society Award, the Lewis Rosenstiel Award, the John Scott Medal, and election to the National Academy of Sciences and the American Academy of Arts and Sciences. Most recently, he received the 1983 General Motors Cancer Research Foundation Award for Cancer Research.

In February, he gave the first of this year's two Faculty Research Lectures. Being asked to deliver such a lecture represents the highest honor a professor can receive from his or her colleagues. This interview, which took place the week before the lecture, includes discussion of many of the issues he addressed there.

Q: What causes cancer?

A: Probably a lot of things. Some of it may be built into us as part of our normal metabolism and may be related to the same processes that cause aging. Cancer can also be triggered by substances in the environment, such as man-made chemicals and natural substances in our food.

Q: What percentage of cancer do you think is caused by natural substances in food, and what percentage is caused by man-made chemicals and pollution?

A: I think very little is caused by man-made chemicals and pollution. A little bit might be occupational—things like asbestos. Back in the old days, people were wading around in certain chemicals in factories, and a high percentage of these workers in a few factories got cancer, so people got the idea that man-made chemicals cause cancer. But now chemical companies are a lot cleaner than they used to be. There are still probably some cases where a worker might be getting enough of something to cause cancer, but I think the most reliable estimates state that occupation is causing only a few percent of cancer deaths. And I don't think pollution is causing very much cancer at all.

Doll and Peto, two of the leading epidemiologists in the world, did a major study and concluded that tobacco causes 30 percent of cancer, alcohol 3 percent, and obesity, occupation, and pollution a few percent each, with diet likely to account for even more cancer than tobacco. Of course, this doesn't mean that we should neglect occupational hazards and pollution. It's just that these are relatively minor things overall. The one big thing we really know about is tobacco, and I think all the hints from both epidemiology and experimental work are that natural substances in the diet are another major source of carcinogens.

Q: What do you think of the theory that each case of cancer can have more than one cause?

A: It's probably correct. For example, normally, to give liver cancer to a rat, you need a dose of a carcinogenic substance close to the toxic level; but if you damage the liver by taking a piece of it out or exposing the rat to alcohol, a much lower dose is necessary. Tissue damage—which can be due to such factors as hepatitis virus, alcohol, or smoking—probably often acts in combination with mutations to cause cancer. Also, it's been shown that the effects of two or more carcinogens can be more than additive: asbestos plus smoking is worse than you'd expect by looking at asbestos alone or smoking alone.

Q: Have any of the mutagenic substances that you've identified in foods actually been shown to be carcinogenic as well?

A: Yes. For example, Sugimura in Japan was watching his wife cook some little fish on a hibachi one day. He'd been using our test system to look at various things, and he had the idea of scraping the surface of the fish and testing it. Well, it was extremely mutagenic. Then he starting heating up carbohydrates and proteins, and he found that when you heat up protein, you get all sorts of mutagens. Using our test as a bioassay, he isolated a dozen mutagens from heated protein, then tested one after another in animal cancer tests. So far, he's tested eight, and all eight are carcinogenic. So it's clear that when you cook your food you're making mutagens and carcinogens too. Sugimura also has shown that the main mutagen in coffee is a carcinogen.

Q: Do you think such dietary carcinogens could be sufficient to cause cancer in the absence of other factors?

A: I suspect not at a low dose, but maybe at a high dose where you're also damaging the tissue. In animal experiments, high enough doses are given to cause tissue damage as well as mutagenesis.

Q: Do you think the carcinogens in cooked food play a significant role in human cancer?

A: We don't really know; it's hard to do epidemiology on cooking food, because everybody cooks their food. We do know that we're getting at least the same amount of, if not more, burnt material from eating our food as we do from smoking. However, this material may be less dangerous in our digestive systems than in our lungs.

Q: Do you think we should eat raw food whenever possible?

A: Not really, but I don't think I should give dietary advice. This is all so sensitive that I think it's better for advice to come from national committees rather than individual scientists.

Q: What other dietary carcinogens should such committees consider?

A: Fat might be the next most serious thing after smoking, because we know that high fat is associated with colon and breast cancer. However, we don't really know the mechanism for it yet. Bob Bruce, a researcher in Canada, has a theory I find attractive. He finds that if he gives high fat to rats and mice, there's a lot of damage to the epithelial cells in their intestines; the fatty acids strip away the protective lining of the digestive system. He also finds, though, that enough dietary calcium completely overcomes this. The idea is that perhaps the fatty acids are stripping away the calcium that holds the cells together and are forming an insoluble fatty acid-calcium soap.

Bruce's idea is that calcium is the key factor, and that if we supplement our flour with calcium or lower our fat intake, we'll get away from a lot of colon cancer. Some epidemiology studies support this view; I don't know whether it's right or not. But if it is, it's a relatively simple answer, and it has nothing to do with traditional carcinogens. It's with our protective systems.

Q: How do traditional carcinogens work?

A: DNA is the genetic material in the nuclei of our cells. It's a double-stranded molecule; when it replicates, each strand determines its complement. Occasionally, when you copy, there's a mistake, and that's a mutation. It's as if you were copying a tape and there was an error.

You can increase the mutation rate by agents such as radiation, hydrogen peroxide, or various chemicals. Direct mutagens directly hit the DNA. Indirect mutagens can work by other mechanisms, for example by increasing the concentration of oxygen radicals, which damage DNA, fat, and other cellular molecules.

Q: How do anticarcinogens work?

A: Vitamin E, for example, stops fat from going rancid. Every cell has a layer of membrane around it which contains fat that can go rancid if it isn't protected. Rancid just means oxidized. It's similar to what happens when you paint your house: when linseed oil ~~fatty acid~~ in the paint, is exposed to oxygen, it starts cross-linking—it all solidifies. Rancidity generates a variety of peroxides and other carcinogenic and mutagenic oxidizing agents. Vitamin E, which is one of nature's antioxidants, will stop this process in your cells.

Q: What other substances are anticarcinogenic?

A: In a number of epidemiology studies, green and yellow vegetables seem to be anticarcinogenic. Fewer smokers who eat green and yellow vegetables get can-

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Lucille Day has three degrees from Berkeley: a B.A. in biological sciences (1971), an M.A. in zoology (1973), and a Ph.D. in science and mathematics education (1979). She is co-author of *How to Encourage Girls in Math and Science: Strategies for Parents and Educators* (Prentice-Hall, 1982), and has published a volume of poetry, *Self-Portrait with Hand Microscope*.

(Continued from page 9)

My real concern with dietary pesticides is with natural pesticides. As it turns out, every plant in nature is making toxic chemicals to protect itself from insects, and these chemicals can comprise as much as 5 percent of the plant. The amount of nature's pesticides we are ingesting is at least 10,000 times the level of man-made pesticides: the variety of these natural chemicals we're eating is incredible, and many are now being shown to be both mutagenic and carcinogenic. Yet people are deathly afraid of traces of man-made chemicals. I think concerns are a little out of whack.

Q: Haven't humans and other animals evolved to protect themselves against pesticides in plants?

A: We have a lot of defenses. For example, our digestive system has a protective lining; as new cells are produced, the old ones, which have been exposed to mutagens, are sloughed off. Also, our liver defends us against foreign chemicals, and cells throughout our bodies have antioxidants and enzymes that protect us against oxidative damage. We have layers and layers of defenses that work against both natural and man-made chemicals. But none of these defenses are perfect: there are always little bits of harmful chemicals getting by.

Q: How far do you think we are from having a cure for cancer?

A: Cancer is many different diseases, so we probably won't have one general cure, but people are making progress. However, my hopes are with prevention. I'm very optimistic because life expectancy gets longer every year: whatever we're doing, we're doing something right. Some people are afraid of the modern world and modern technology, but wealth, industrialization, and new knowledge are associated with a longer life span. I think one could make the argument that America is less polluted (with pollutants that matter) than it was a generation ago.

There are compelling arguments for thinking that prevention will be as important as cure. For example, Japan has a very high rate of stomach cancer—one of the highest in the world—whereas the U.S. has one of the lowest stomach cancer rates, but a very high rate for colon and breast cancer. Epidemiologists who have studied what happens to Japanese immigrants in the United States have found that their children become like Americans: they have high colon and breast cancer rates, but low stomach cancer rates.

Presumably, something in the Japanese diet is causing stomach cancer, and something in the American diet is causing colon and breast cancer. There also might be differences in consumption of anti-carcinogens. When we determine what these carcinogens and anti-carcinogens are, we can eat less or more of them and get less of all three kinds of cancer. For example, lowering fat, increasing calcium, and increasing fiber may be the important factors for preventing colon cancer.

As we learn more about basic biology, there's going to be an enormous impact on aging and cancer and heart disease. Just as scientists advise you now not to eat too much saturated fat because it's associated with heart disease, we'll be able to make definitive statements about food and cancer. Since the indications are that diet is causing even more cancer than smoking, eventually we should be able to eliminate a lot of cancer by controlling our diet.

Q: What's the current process by which a substance is legally declared a carcinogen?

A: If it causes cancer in rats and mice, it's called a carcinogen. If it's a mutagen, it's just a prospective carcinogen: our *Salmonella* test isn't enough to ban something.

Q: How much do you think the government should be involved in setting policy concerning food?

A: I'm not sure we want the government to ban mustard, celery, and mushrooms because there are carcinogens in mustard, celery, and mushrooms. But I think information is good: the main thing is to provide information that puts things in perspective.

There are so many carcinogens around—every meal is full of them—that before we start banning something, we want to really think about the alternatives. Are they going to be worse? Are we talking about significant amounts?

I wouldn't want to give up mustard, celery, and mushrooms unless there were reason to think the risk of these foods was appreciable relative to other risks. It turns out that everything you do has some risk. Every time you drive your car, there's a certain risk you'll get into an accident. Sunshine carries risk: it's a carcinogen. But you don't want to put up an umbrella every time you go outside.

Q: Do you think there should be any changes in government policy concerning carcinogens and cancer research?

A: I think we need to concentrate on the major things we know about, such as cigarettes, while doing research to identify other important risk factors. The government is putting a billion dollars a year into EPA (as much as for all the cancer research in the country). I find it really strange that Congress directs the EPA to chase after really tiny doses of carcinogens when we have almost 400,000 premature deaths a year from cigarettes—and tobacco farmers are subsidized.

I think we need to continue our support for basic research to understand cancer, and I think we need to look more at natural things. A single mushroom or cup of coffee has more carcinogens than all of the man-made pollution you're likely to get in a day. But very little of the government's testing program is concerned with natural substances. Furthermore, even though comfrey herb tea has long been known to be full of carcinogens, no one has told the public about it.

Q: When will we know more definitively what to eat and what not to eat?

A: It might be a while. In the meantime, committees have advised us not to eat too much fat, because it's associated with heart disease, colon cancer, and breast cancer. Also, eat a good balanced diet, eat some green vegetables, and avoid smoking and drinking too much alcohol. I also want to tell people not to worry—life expectancy is increasing, new knowledge is coming in very quickly, and scientists are learning more about how to prevent cancer. ■

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Dear Senator Torres:

The carcinogens and toxic chemicals being found in California water supplies are present in extraordinarily tiny amounts and, except in rare cases, are present in trivial amounts relative to the background level of carcinogens in Nature. I am convinced that water pollution is irrelevant to the causes of human cancer.

The main current fallacy consists in thinking that carcinogens are rare and that they are mostly man-made chemicals. My own estimate is that over 99.99% of the carcinogens Californians ingest are natural (e.g., natural toxic chemicals in plants, mold carcinogens) or traditional (e.g., cooking food, smoking cigarettes, alcohol).

Every meal is full of carcinogens and when one compares the level of carcinogens in contaminated water (or pesticide residues in food) to the level of natural carcinogens, it is clear that water pollution (or pesticide residues) represents a trivial risk. Every common drink contains carcinogens. I list a few sources and

levels of natural carcinogens below, and I compare them to the Silicon Valley's contaminated wells as an example.

a) Coffee contains about 1,000 micrograms of hydrogen peroxide (a known carcinogen) per cup (4,000 ppb; ppb = parts per billion) as well as about 1,000 micrograms (4,000 ppb) of methylglyoxal, which has recently been shown to be a carcinogen. b) Tap water contains the carcinogen chloroform at 83 micrograms per liter (83 ppb U.S. average), which is generated from chlorinating the water. c) Cola contains the carcinogen formaldehyde at 2,800 micrograms per 12 ounces (7,900 ppb). d) Beer contains nitrosamines, formaldehyde (700 ppb), and alcohol (50 million ppb), all known carcinogens. Ethyl alcohol is a known human carcinogen (3% of U.S. cancer) as well as a carcinogen in rats. e) Milk contains a high percentage of fat, and high fat has been implicated in human breast and colon cancer and rodent cancer (though milk is an important source of calcium, which may be important as an anticarcinogen); and f) organic fruit juices may have various amounts of carcinogenic mold toxins. We are just completing a study where we compare risks for humans due to intake of carcinogens. In this study we adjust for the potency of each carcinogen from rodent data. This adjustment is necessary because the potency of carcinogens varies over a million-fold, e.g., aflatoxin, a mold carcinogen, present in small amounts in peanut butter (2 ppb U.S. average) or corn products such as tortillas, is about a million times more potent as a carcinogen than trichloroethylene, which often contaminates well water.

I give some comparisons below.

Contaminated water. The level of carcinogens in contaminated well water (e.g., Silicon Valley or Woburn) only rarely involves a risk above the risk of ordinary tap water. Of 35 wells shut down in Silicon Valley because of their supposed carcinogenic hazard in an EPA study, only two were of greater risk than ordinary tap water (well water usually lacks the chloroform present in chlorinated tap water), and the most polluted well (2,800 ppb trichloroethylene) is at least 1,000 times less hazardous than an equal volume of cola, beer, or wine. Given that the consumption of tap water is only about 1 or 2 liters per day, it seems unlikely that man-made water pollution is causing more than a minimal hazard. This is in contrast to inhalation, particularly in the workplace, where breathing in 10,000 liters of air containing a carcinogen in a work day can result in appreciable doses and thus could represent a significant hazard.

Pesticide residues. Man-made pesticide residues present in our food amount to about 150 micrograms/day on the average; most of these residues are composed of non-carcinogenic compounds. The most significant man-made pesticide carcinogenic residue in food is likely to be DDE, a metabolite of DDT. The risk of the DDE in the average U.S. daily intake is equivalent to the risk due to chloroform in 1 glass of tap water and, thus, it is insignificant compared to the risk due to the high level of natural carcinogens in our diet. Even an occasional highly DDE- or PCB-contaminated fish (e.g., 100 times the average level) would contribute a risk that is small compared to other very common minor risks such as a glass of beer or a peanut butter sandwich.

Nature's pesticides. We are ingesting natural pesticides in our diet in amounts at least 10,000 times more than man-made pesticide residues. Natural pesticides are natural toxic chemicals, which are present in all plants, usually making up 5-10% of a plant's weight. They have an enormous variety of chemical structures, though only a few are present in each plant species. Their function is protection against fungi, insects and animal predators. A major aspect of evolution of plants is chemical warfare. There has been relatively little interest in the toxicology or carcinogenicity of these compounds until quite recently, and very few of the large number present in the human diet have been tested in animal cancer bioassays, and only some of these tests are adequate for estimating their potency. Some of those tested are carcinogens. They include estragole (in basil), safrole (in herbs), symphitine (in comfrey tea), psoralens (in parsley and celery), hydrazines (in mushrooms), and allyl isothiocyanate (in mustard). Calculations on the carcinogenic risk of these compounds show that they completely overshadow the traces of man-made pollutants found in the daily diet, e.g., 5 basil leaves are 100 times more hazardous than the worst well in Silicon Valley (at least 5 basil leaves would be ingested in a portion of "pasta al pesto"). Thousands more of Nature's pesticides are present in the human diet and because many mutagens are being discovered among them, many are potential carcinogens.

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Exposure to Radiation and Chemicals, A. D. Woodhead, C. J. Shellabarger, V. Pond, and A. Hollaender, eds. (Plenum Press, New York, 1985), pp. 3-16.]

Yours truly,

Bruce N. Ames

Bruce N. Ames
Professor and Chairman

BNA/ssk

Enclosure:
Cal Monthly article

cc: Assemblyman Bill Jones

[I am sending a copy to Assemblyman Bill Jones because he sent me a copy of his bill. Unfortunately, I cannot appear to testify concerning it, but I support the idea of reasonable standards.]

CALIFORNIA Q&A

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Ames says, "During the course of this work on mutagenesis, I became convinced that one essential aspect of carcinogens is their ability to damage DNA. We kept lists of popular carcinogens and kept working to make improvements in the test which could detect them as mutagens. One key development was the addition of a rat liver homogenate to our petri plates. With this and other improvements, we were able to determine that more than 80 percent of carcinogens are mutagens."

Born in New York City in 1928, Ames grew up in a home where science was familiar and learning encouraged. His father was chairman of a high school chemistry department, later Supervisor in Science for the New York City Schools, and finally Assistant Superintendent of Schools.

Ames can't remember a time when he wasn't interested in science. In his childhood, he says, "I was always interested in chemistry and biology. I used to read the books my father left lying around, and in the summer I collected frogs and snakes."

After graduating from the Bronx High School of Science in 1946, he attended Cornell University, where he received his B.A. in 1950 with a major in chemistry and minor in biology. In 1953, he received his Ph.D. in biochemistry from the California Institute of Technology, then spent 15 years as a biochemist at the National Institutes of Health. He joined the Department of Biochemistry at Berkeley as a full professor in 1968.

In 1960, he married Dr. Giovanna Ferro-Luzzi, who also is a biochemist on the faculty at Berkeley. They have two children: their daughter is a senior at the Massachusetts Institute of Technology; and their son plans to begin studies at the University of Wisconsin this fall.

Ames's numerous awards and honors include the Eli Lilly Award of the American Chemical Society, the Environmental Mutagen Society Award, the Lewis Rosenstiel Award, the John Scott Medal, and election to the National Academy of Sciences and the American Academy of Arts and Sciences. Most recently, he received the 1983 General Motors Cancer Research Foundation Award for Cancer Research.

In February, he gave the first of this year's two Faculty Research Lectures. Being asked to deliver such a lecture represents the highest honor a professor can receive from his or her colleagues. This interview, which took place the week before the lecture, includes discussion of many of the issues he addressed there.

Q: What causes cancer?

A: Probably a lot of things. Some of it may be built into us as part of our normal metabolism and may be related to the same processes that cause aging. Cancer can also be triggered by substances in the environment, such as man-made chemicals and natural substances in our food.

Q: What percentage of cancer do you think is caused by natural substances in food, and what percentage is caused by man-made chemicals and pollution?

A: I think very little is caused by man-made chemicals and pollution. A little bit might be occupational—things like asbestos. Back in the old days, people were wading around in certain chemicals in factories, and a high percentage of these workers in a few factories got cancer, so people got the idea that man-made chemicals cause cancer. But now chemical companies are a lot cleaner than they used to be. There are still probably some cases where a worker might be getting enough of something to cause cancer, but I think the most reliable estimates state that occupation is causing only a few percent of cancer deaths. And I don't think pollution is causing very much cancer at all.

Doll and Peto, two of the leading epidemiologists in the world, did a major study and concluded that tobacco causes 30 percent of cancer, alcohol 3 percent, and obesity, occupation, and pollution a few percent each, with diet likely to account for even more cancer than tobacco. Of course, this doesn't mean that we should neglect occupational hazards and pollution. It's just that these are relatively minor things overall. The one big thing we really know about is tobacco, and I think all the hints from both epidemiology and experimental work are that natural substances in the diet are another major source of carcinogens.

Q: What do you think of the theory that each case of cancer can have more than one cause?

A: It's probably correct. For example, normally, to give liver cancer to a rat, you need a dose of a carcinogenic substance close to the toxic level; but if you damage the liver by taking a piece of it out or exposing the rat to alcohol, a much lower dose is necessary. Tissue damage—which can be due to such factors as hepatitis virus, alcohol, or smoking—probably often acts in combination with mutations to cause cancer. Also, it's been shown that the effects of two or more carcinogens can be more than additive: asbestos plus smoking is worse than you'd expect by looking at asbestos alone or smoking alone.

Q: Have any of the mutagenic substances that you've identified in foods actually been shown to be carcinogenic as well?

A: Yes. For example, Sugimura in Japan was watching his wife cook some little fish on a hibachi one day. He'd been using our test system to look at various things, and he had the idea of scraping the surface of the fish and testing it. Well, it was extremely mutagenic. Then he starting heating up carboyhdrates and proteins, and he found that when you heat up protein, you get all sorts of mutagens. Using our test as a bioassay, he isolated a dozen mutagens from heated protein, then tested one after another in animal cancer tests. So far, he's tested eight, and all eight are carcinogenic. So it's clear that when you cook your food you're making mutagens and carcinogens too. Sugimura also has shown that the main mutagen in coffee is a carcinogen.

Q: Do you think such dietary carcinogens could be sufficient to cause cancer in the absence of other factors?

A: I suspect not at a low dose, but maybe at a high dose where you're also damaging the tissue. In animal experiments, high enough doses are given to cause tissue damage as well as mutagenesis.

Q: Do you think the carcinogens in cooked food play a significant role in human cancer?

A: We don't really know: it's hard to do epidemiology on cooking food, because everybody cooks their food. We do know that we're getting at least the same amount of, if not more, burnt material from eating our food as we do from smoking. However, this material may be less dangerous in our digestive systems than in our lungs.

Q: Do you think we should eat raw food whenever possible?

A: Not really, but I don't think I should give dietary advice. This is all so sensitive that I think it's better for advice to come from national committees rather than individual scientists.

Q: What other dietary carcinogens should such committees consider?

A: Fat might be the next most serious thing after smoking, because we know that high fat is associated with colon and breast cancer. However, we don't really know the mechanism for it yet. Bob Bruce, a researcher in Canada, has a theory I find attractive. He finds that if he gives high fat to rats and mice, there's a lot of damage to the epithelial cells in their intestines: the fatty acids strip away the protective lining of the digestive system. He also finds, though, that enough dietary calcium completely overcomes this. The idea is that perhaps the fatty acids are stripping away the calcium that holds the cells together and are forming an insoluble fatty acid-calcium soap.

Bruce's idea is that calcium is the key factor, and that if we supplement our flour with calcium or lower our fat intake, we'll get away from a lot of colon cancer. Some epidemiology studies support this view; I don't know whether it's right or not. But if it is, it's a relatively simple answer, and it has nothing to do with traditional carcinogens. It's with our protective systems.

Q: How do traditional carcinogens work?

A: DNA is the genetic material in the nuclei of our cells. It's a double-stranded molecule; when it replicates, each strand determines its complement. Occasionally, when you copy, there's a mistake, and that's a mutation. It's as if you were copying a tape and there was an error.

You can increase the mutation rate by agents such as radiation, hydrogen peroxide, or various chemicals. Direct mutagens directly hit the DNA. Indirect mutagens can work by other mechanisms, for example by increasing the concentration of oxygen radicals, which damage DNA, fat, and other cellular molecules.

Q: How do anticarcinogens work?

A: Vitamin E, for example, stops fat from going rancid. Every cell has a layer of membrane around it which contains fat that can go rancid if it isn't protected. Rancid just means oxidized. It's similar to what happens when you paint your house: when linseed oil ~~a fatty acid~~ in the paint, is exposed to oxygen, it starts cross-linking—it all solidifies. Rancidity generates a variety of peroxides and other carcinogenic and mutagenic oxidizing agents. Vitamin E, which is one of nature's antioxidants, will stop this process in your cells.

Q: What other substances are anticarcinogenic?

A: In a number of epidemiology studies, green and yellow vegetables seem to be anticarcinogenic. Fewer smokers who eat green and yellow vegetables get can-

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Lucille Day has three degrees from Berkeley: a B.A. in biological sciences (1971), an M.A. in zoology (1973), and a Ph.D. in science and mathematics education (1979). She is co-author of *How to Encourage Girls in Math and Science: Strategies for Parents and Educators* (Prentice-Hall, 1982), and has published a volume of poetry, *Self-Portrait with Hand Microscope.*

A CONVERSATION WITH BRUCE AMES

By Lucille Day

cer than smokers who don't. Several studies suggest that the protection comes from beta-carotene, an antioxidant that gives the orange color to carrots and is present in all plants.

It might turn out to be more useful to optimize protective factors in our diet than to try to eliminate every carcinogen. If vitamin E protects against the whole set of mutagens that work through oxidative mechanisms, then we might want to optimize vitamin E. We might also want to optimize selenium, beta-carotene, vitamin C, and other antioxidants that are part of our normal protective systems, as well as other dietary ingredients, such as calcium.

Q: How is aging related to cancer?

A: Cancer rates go up very sharply with age. For example, rats get cancer very sharply with age: 30 percent of rats on ordinary lab feed have cancer by the end of their two-year life span. People also get cancer very sharply with age. So cancer, like heart disease, can be seen as a degenerative disease that comes with old age. Yet a rat is living only two years, while we're living 80 years.

So why don't our cells become tumor cells by age two? It might have something to do with metabolic rate: a rat is breathing in oxygen very rapidly, whereas humans have a relatively low metabolic rate. A lot of DNA damage appears to come from normal metabolism. People worry about radiation, but the damage produced by oxygen radicals resulting from normal metabolism is the same kind of damage as that produced by radiation. In a sense, just living is like getting irradiated. We have recently found that a rat is getting this oxidative DNA damage at 15 times the rate of a person.

One interesting thing we're all getting excited about now is that people have shown there's an easy way to get rats and mice to live longer. Researchers have tried almost everything, and only one thing works: if you starve the animals a bit, they live a whole year, or even two years, longer. So just cutting down on calories can double the life span. In addition, these animals have fewer tumors of all kinds.

Q: Do they show less DNA damage than rats that don't live as long?

A: We've just developed an assay that we can use to measure thymine glycol and thymidine glycol, oxidatively-damaged DNA products excreted in the urine. The test can be used on people as well as animals, and it will enable us to study caloric intake in individuals and see how it affects oxidative damage. We can also look at other variations between people—things like smoking, exercising, and not getting enough antioxidants—and determine which ones are related to DNA damage.

Q: Could the assay also be used to identify people at high risk for getting cancer?

A: That's another hope. I think eventually there will be a biochemical epidemiology that will enable scientists to correlate specific chemicals in the body with cancer and other diseases.

Q: What else are you doing currently?

A: We recently did a big project that was just published: a data base on the potency of carcinogens. We did calculations to determine how effective various chemicals are as carcinogens. I think the public gets very scared when someone says there's a carcinogen in their drinking water; they don't know how to interpret that. In fact, every meal is chock full of carcinogens, and one wants to know whether some new carcinogen is present in significant amounts. This study of relative risk will give people some feeling for this kind of thing.

For example, aflatoxin, a mold toxin found in tiny amounts in peanut butter, is a super carcinogen: you need very low doses per kilogram to get cancer. In contrast, trichloroethylene (TCE), which is in the well water in Silicon Valley, is very weak, you need enormous doses. Another way of saying this is that, at a given dose, aflatoxin increases the probability of rats getting cancer more than TCE does. It's important to compare risks, which are based on both dose and potency of chemicals, in order to put potential dangers in perspective.

Q: How do you establish the risk levels?

A: The calculations I am currently doing are based on the information from animal cancer tests in our data base. I do these calculations on carcinogens that people are exposed to, but the relative risk is based on rats. I took as a standard a liter of average U.S. chlorinated tap water, which contains traces of the carcinogen chloroform.

Most contaminated well water in Silicon Valley is probably safer than tap water, because it doesn't have chloroform in it, which is a more potent carcinogen than TCE. The risk associated with drinking water from the worst well in Silicon Valley is similar to the risk from drinking ordinary water.

But these are really pretty minor risks. The risk of the average peanut butter sandwich is 20 times the risk of a liter of tap water, and I think that peanut butter is even too tiny a risk to worry about. The risk of comfrey herb tea, which contains potent carcinogens called pyrrolizidine alkaloids, is much higher. Comfrey tablets are worse yet: I calculated the risk from some comfrey tablets I bought at a local health food store, and the risk was thousands of times that of chlorinated tap water.

Q: Are extrapolations from rats to humans always reliable?

A: No. Some chemicals cause cancer in rats but not in mice. Others cause cancer in mice but not in rats, or in rats and mice but not in people. A single phenobarbital pill comes out 10,000 times higher on my rodent risk scale than a liter of water, yet studies of humans taking phenobarbital haven't shown any detectable cancer risk at all. Metabolism sometimes differs from one species to another, so knowing how one species reacts does not always enable us to say how another one will.

Another problem is that when we find cancer as a result of giving a high dose of something to a rat, we don't really know that we'll find proportional cancer rates at the lower doses people are actually exposed to. In fact, a low dose might be much less dangerous proportionally than a high dose because of the factor of cell toxicity.

Q: What about the risk of pesticides in our food?

A: I think the risk associated with man-made pesticides in food is pretty minor. Our daily risk from eating residues of ethylene dibromide (EDB) fumigant in grain is less than the risk of drinking a glass of water. Since workers can get enormous doses, of course their risk is greater. However, Dow Chemical studied EDB workers who had been getting daily doses for decades that were hundreds of thousands of times higher than our daily exposure in grain, and they didn't see any increase in cancer. Nevertheless, I think we need to keep a really sharp eye on the chemicals being inhaled by factory workers, because exposure levels can be so high.

A number of years ago I was so concerned about the levels of EDB that factory workers were getting that I testified for tightening up the levels for California workers. California was the first state to enact a standard tighter than the national one—in fact, 100 times more stringent.

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My real concern with dietary pesticides is with natural pesticides. As it turns out, every plant in nature is making toxic chemicals to protect itself from insects, and these chemicals can comprise as much as 5 percent of the plant. The amount of nature's pesticides we are ingesting is at least 10,000 times the level of man-made pesticides: the variety of these natural chemicals we're eating is incredible, and many are now being shown to be both mutagenic and carcinogenic. Yet people are deathly afraid of traces of man-made chemicals. I think concerns are a little out of whack.

Q: Haven't humans and other animals evolved to protect themselves against pesticides in plants?

A: We have a lot of defenses. For example, our digestive system has a protective lining; as new cells are produced, the old ones, which have been exposed to mutagens, are sloughed off. Also, our liver defends us against foreign chemicals, and cells throughout our bodies have antioxidants and enzymes that protect us against oxidative damage. We have layers and layers of defenses that work against both natural and man-made chemicals. But none of these defenses are perfect: there are always little bits of harmful chemicals getting by.

Q: How far do you think we are from having a cure for cancer?

A: Cancer is many different diseases, so we probably won't have one general cure, but people are making progress. However, my hopes are with prevention. I'm very optimistic because life expectancy gets longer every year: whatever we're doing, we're doing something right. Some people are afraid of the modern world and modern technology, but wealth, industrialization, and new knowledge are associated with a longer life span. I think one could make the argument that America is less polluted (with pollutants that matter) than it was a generation ago.

There are compelling arguments for thinking that prevention will be as important as cure. For example, [illegible] very high rate of stomach cancer—one of the highest in the world—whereas the U.S. has one of the lowest stomach cancer rates, but a very high rate for colon and breast cancer. Epidemiologists who have studied what happens to Japanese immigrants in the United States have found that their children become like Americans: they have high colon and breast cancer rates, but low stomach cancer rates.

Presumably, something in the Japanese diet is causing stomach cancer, and something in the American diet is causing colon and breast cancer. There also might be differences in consumption of anti-carcinogens. When we determine what these carcinogens and anti-carcinogens are, we can eat less or more of them and get less of all three kinds of cancer. For example, lowering fat, increasing calcium, and increasing fiber may be the important factors for preventing colon cancer.

As we learn more about basic biology, there's going to be an enormous impact on aging and cancer and heart disease. Just as scientists advise you now not to eat too much saturated fat because it's associated with heart disease, we'll be able to make definitive statements about food and cancer. Since the indications are that diet is causing even more cancer than smoking, eventually we should be able to eliminate a lot of cancer by controlling our diet.

Q: What's the current process by which a substance is legally declared a carcinogen?

A: If it causes cancer in rats and mice, it's called a carcinogen. If it's a mutagen, it's just a prospective carcinogen: our *Salmonella* test isn't enough to ban something.

Q: How much do you think the government should be involved in setting policy concerning food?

A: I'm not sure we want the government to ban mustard, celery, and mushrooms because there are carcinogens in mustard, celery, and mushrooms. But I think information is good: the main thing is to provide information that puts things in perspective.

There are so many carcinogens around—every meal is full of them—that before we start banning something, we want to really think about the alternatives. Are they going to be worse? Are we talking about significant amounts?

I wouldn't want to give up mustard, celery, and mushrooms unless there were reason to think the risk of these foods was appreciable relative to other risks. It turns out that everything you do has some risk. Every time you drive your car, there's a certain risk you'll get into an accident. Sunshine carries risk: it's a carcinogen. But you don't want to put up an umbrella every time you go outside.

Q: Do you think there should be any changes in government policy concerning carcinogens and cancer research?

A: I think we need to concentrate on the major things we know about, such as cigarettes, while doing research to identify other important risk factors. The government is putting a billion dollars a year into EPA (as much as for all the cancer research in the country). I find it really strange that Congress directs the EPA to chase after really tiny doses of carcinogens when we have almost 400,000 premature deaths a year from cigarettes—and tobacco farmers are subsidized.

I think we need to continue our support for basic research to understand cancer, and I think we need to look more at natural things. A single mushroom or cup of coffee has more carcinogens than all of the man-made pollution you're likely to get in a day. But very little of the government's testing program is concerned with natural substances. Furthermore, even though comfrey herb tea has long been known to be full of carcinogens, no one has told the public about it.

Q: When will we know more definitively what to eat and what not to eat?

A: It might be a while. In the meantime, committees have advised us not to eat too much fat, because it's associated with heart disease, colon cancer, and breast cancer. Also, eat a good balanced diet, eat some green vegetables, and avoid smoking and drinking too much alcohol. I also want to tell people not to worry—life expectancy is increasing, new knowledge is coming in very quickly, and scientists are learning more about how to prevent cancer. ■

justice of Nevada. This is impressive to be sure, but not one of the high-prestige clerkships that automatically mark the recipients as future leaders of the bar. She went to work in the public defender's office in Santa Clara County, where she did well enough to be chosen to teach part-time at Stanford Law School. In 1974, she quit both jobs and was about to open a private practice. It was then Jerry Brown made all the difference in her career.

They had met casually at International House in Berkeley, where they both lived as students. A dozen years later, while in between jobs, she volunteered to work for Brown, who was then running for governor.

Far from the inner circle of Brown's political organization, she was in charge of running his campaign in San Mateo, a county that he unexpectedly won. (She drove him a couple of times; she recalls that he liked her inexpensive car and found the idea of a woman driver "amusing." In many profiles, she has been portrayed as the future governor's "chauffeur," a decided exaggeration.)

After the election, she reluctantly postponed starting her private law practice to serve on Brown's transition team. She eventually screened candidates for jobs in the new administration. "I told him exactly what I thought," she recalls, and he welcomed her candor. She was amply rewarded.

First, in 1975, she became Brown's choice for secretary of the Agriculture and Services Agency, a cabinet position that had usually gone to a farmer. She was an aggressive administrator and soon became embroiled in controversy. Among other things, she helped to write the Agricultural Labor Relations Act, a piece of progressive legislation that embittered agribusiness.

Then, in 1977, Brown nominated her to the post of chief justice. He cited her years of "writing legislation and carrying out its intent." This, he said, gave her "that real-world kind of experience that will be valuable in making the judgments a Supreme Court justice must make."

It was an astonishing appointment. Other women with more impressive credentials had been considered, but not picked. Bird was young for an appellate post, had limited government background and lacked judicial experience.

At her swearing in, as Governor Brown administered the oath of office, she flubbed her lines, and it has not been easy for her since. Perhaps because she was perceived as Brown's candidate, perhaps because she was young, perhaps because she was a woman, perhaps because she was an outsider, Bird was never popular with the voters. Never has she been free from attack or

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SHOULD TAP WATER BE FOR DRINKING?

Check one:

☐ ***I'm for clean drinking water. Stop contaminating it.***

☐ ***I'm for clean drinking water. Don't stop contaminating it.***

BY CARL POPE

A SACRAMENTO TEENAGER reaches for a glass of tap water on a hot summer's day, sips, grimaces and throws the water back into the sink. Then he reaches for a bottle of mineral water. He is part of a growing revolution that may replace the tax rebellion as the centerpiece of California politics—a rebellion for safe drinking water.

Public opinion polls now show that for many Californians, drinking water safety is a leading public safety concern. California leads the nation in its reliance on bottled water—17 percent of the state and 30 percent of the residents of Los Angeles pay to have special water supplies brought into their homes to avoid the need to drink what comes out of their taps.

So far, the problem of toxic contamination of drinking water has been one of the two dominant themes of the governor's race, and it is rapidly emerging as a focus of the U.S. Senate race as well. Alan Cranston, in challenging his Republican opponent, Ed Zschau, to support Proposition 65, the Safe Drinking Water and Toxic Enforcement Act, said, "The people of California are entitled to be able to turn on their kitchen tap water with confidence that they and their children can drink it without being poisoned. Yet six million Californians are presently drinking contaminated water. This is a disgrace." And Richie Ross, political strategist for the Assembly Democrats, believes "the issue of drinking water safety is twice as important in determining which candidate a voter supports as the candidate's stand on Rose Bird."

Two decades ago, a tap water rebellion in California would have been unthinkable. This was the state of the hydrologic revolution, the state that made the desert bloom, of William Mulholland and the California Water Project. California's aqueducts and dams were second only to its freeways as symbols of the state's technological wizardry. In many ways, all of California shared the city of Modesto's motto: "Water, Wealth, Contentment, Health." But rebellions, as Thomas Jefferson noted in the Declaration of Independence, require just two conditions: "a long train of abuses" long ignored. Evidence suggests that both conditions exist in today's California, and that the stage may well be set for a new kind of revolution.

Our Sacramento teenager won't drink the water because of an abuse that occurs only a few miles away. For most of its length, the snowmelt that feeds the Sacramento River runs cold and clean. But just north of the city of Sacramento, a good deal of the river is diverted by rice farmers across their fields, where it picks up a broad variety of fertilizers, herbicides and pesticides before flowing back into the river proper. One of these herbicides, Bolero, is used in quantities sufficient to give drinking water in the area a distinctly bad taste.

The Sacramento River is just part of the state's complex system for delivering drinking water to cities like San Francisco, San Jose, Los Angeles and San Diego, none of which could survive on their own local water sources. Contamination by Bolero is not the last abuse visited on the river as it winds its way south.

The water that is rejected at the Sacramento tap flows into the city's sewers, where it mixes with household waste and industrial effluent containing a variety of heavy metals and solvents. Some of these, but only some, are removed by the sewage treatment plant. The remainder, dissolved in the effluent, pour down into the delta where the Sacramento is joined by the San Joaquin River. Down the San Joaquin

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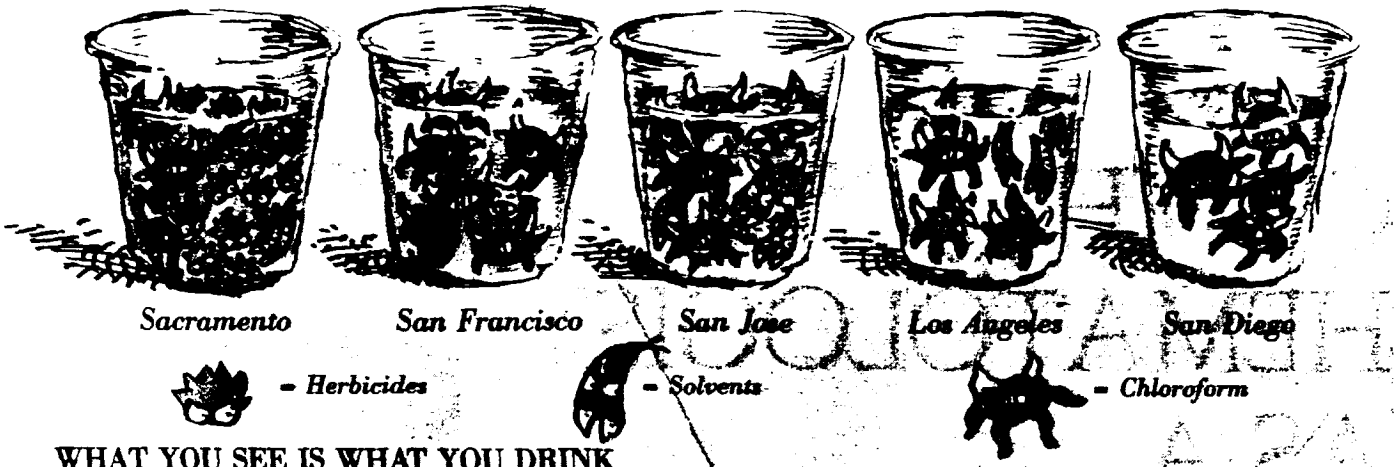
Sierra Club political director Carl Pope is the author of Hazardous Waste in America *and a coauthor of Proposition 65.*



WHAT YOU SEE IS WHAT YOU DRINK

Chloroform causes cancer and poses risks to the liver, thyroid and immune system. It is the most common of four compounds called trihalomethanes, which form when natural organic matter in the water reacts with chlorine. Chloroform can be found in Sacramento tap water at a level of 30 to 40 parts per billion (ppb), in San Francisco tap water at 66 ppb, in San Jose tap water at 50 to 70 ppb, in Los Angeles tap water at 35 ppb and in San Diego tap water at 15 to 60 ppb. Thus, the drinking water in California's major cities meets the U.S. safety standard of less than 100 ppb but exceeds the less than 30 ppb recommended by the World Health Organization.

The herbicides Ordram and Bolero are used by rice farmers in Sacramento. Ordram, which causes sterility in male mice, can be found in the water at a level of 10 to 15 ppb, below the allowable 20 ppb. Bolero is present at 4 ppb, also below its standard of 10 ppb, and gives the water a metallic taste.

Solvents like trichloroethylene (TCE), perchloroethylene (PCE) and 1,1,1-trichloroethane (TCA) are degreasers used primarily by aircraft and electronics industries. TCE and PCE are suspected carcinogens; they are present in Los Angeles tap water at levels of 4 ppb and 2 ppb respectively, below the allowable 5 ppb and 4 ppb. TCA and Freon-113, a dry-cleaning solvent, are present in San Jose water at levels of 2 ppb and 4 ppb. No standard has been established for Freon, and the standard for TCA (200 ppb) was set prior to completion of studies.

Source: Citizens for a Better Environment

come toxaphene, mercury, chlordane, PCBs, arsenic, cadmium, copper, chromium, lead and selenium, all of which are on the Environmental Protection Agency (EPA) list of priority pollutants—a mix making this one of the most heavily polluted rivers in the state. Most of this pollution comes from surface and subsurface agricultural drainage; the remainder from mining, timber and other industrial activities. The delta itself adds more pesticides and herbicides from agricultural operations, heavy metals from energy facilities and organics from gasoline storage and transfer facilities. Then, as the water makes its way to San Jose, Los Angeles and San Diego in the California aqueduct, it continues to pick up pesticide residues from spraying operations on farmlands along the aqueduct itself.

Some of these chemicals are volatile and thus evaporate as the water flows southward. The herbicide Ordram, for example, is not detectable by the time the water reaches Southern California customers. But others, particularly the metals like mercury (a highly potent neurotoxin), lead (a carcinogen and neurotoxin) and cadmium (which causes cancer, heart disease and high blood pressure)—highly toxic even in tiny quantities—remain.

Underground sources of drinking water are no better protected. A recent Department of Health Services study found that 18 percent of the state's drinking water wells were contaminated with toxic chemicals—6 percent of them at concentrations above the safety levels set by state and federal agencies. Just 3 percent have been closed. The study shocked even Lloyd Connelly, the Sacramento assemblyman who requested it: "These results do not paint a very comforting view," he says. "We knew we had problems but I didn't think they were this bad." Contamination of underground wells originates in several industrial and agricultural practices.

In Silicon Valley, leaking underground storage tanks containing toxic solvents used by the electronics industry are one source of major contamination, but so are truck drivers who clean out their hoses before delivering solvents to the tanks by squirting them on the ground. According to Ted Smith, head of the Silicon Valley Toxics Coalition, "The tragedy is that an industry which prides itself on being so precise and careful in so many ways was so insensitive and sloppy when it came to protecting the environment."

In the San Fernando Valley, no one has been able to pinpoint the exact sources of industrial solvents, principally trichloroethylene (TCE), which have caused more wells to be shut down in Los Angeles County than in any other county in the state.

In the Central Valley, 2,000 wells are contaminated, particularly with the now banned pesticide DBCP, which fell under government scrutiny when workers producing it became sterile as a result. (Not all observers agreed with the decision to ban DBCP. A leader of the National Peach Council suggested that use of the chemical continue but that only those too old to have children or those whose religion prohibits the use of artificial birth control be employed in its production and application.)

In many cases, current concentrations in most water supplies are below the levels defined by state agencies as requiring action. How reliable those levels may be over time, as yet untested, remains to be seen. Although chlorinated solvents and pesticides can be absorbed readily through the skin, bathing is rarely, if ever, taken into consideration when levels are set. Since volatiles evaporate quickly, one fifteen-minute shower can provide as much chemical to the body as drinking eight glasses of water. Infants—presumably those who need the most protection from the state—are especially vulnerable.

In any case, with every passing year, the number of contaminated wells increases. Moreover, none of these organic chemicals and heavy metals belong in drinking water. They would not have been found by a modern analytic chemist checking the Sacramento and San Joaquin rivers or San Fernando Valley groundwater in 1848. Many Californians are already carrying excessive levels of many of these chemicals, and even relatively low concentrations of a toxin like lead in drinking water can result in hundreds of

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J.T. STEINY

terious-looking, with great projections of aluminum-covered rock and beehive-like holes carved in the mountainsides, remnants of the bauxite mining that went on there in the Middle Ages. According to legend, one of the Biblical Maji founded a community here 2,000 years ago. The story goes that the Maji's descendants used to throw people off the very cliff where Mary Frances felt threatened. Mary Frances says she knew nothing of the legend at the time, only that she was in a very evil place. "It was too much, too strong; I had to hang on." She says she clung to a large crucifix at the edge of the plateau to prevent herself from going over.

Such spells could get a woman in serious trouble a few hundred years ago, but it is safe to admit to them today. When you are 78 and a famous writer, you can admit to just about anything, even to being an "old soul" attuned to spirits of the past. Mary Frances uses the phrase in explaining why she has always felt more at home in Europe's ancient hills: "I'm an old soul, you know," she says. "I need to be in older countries to be more fully me."

The casually uttered words do not escape Jeanne, ever on the alert for literary references. "Do you mean that in the E.M. Forster sense?" she says. In *A Passage to India*, Forster describes an old soul as one who enjoys a residue of wisdom gained from numerous past lives. Shirley MacLaine, the actress, subscribes to a belief in old souls, and has made a best-seller out of it. Mary Frances hasn't read Shirley MacLaine, and isn't sure whether Forster's concept applies to herself. She thinks "spirit" is a better word than soul, and that it takes a couple of thousand years to be an old one. She feels drawn to them as she is to old countries—all three of her husbands were old spirits, she says, Dillwyn being the oldest. As for herself, "I've been here a thousand times before."

Whatever you make of it, her belief is consonant with some aspects of her extraordinary life: her affection for Europe, for extremely worldly men, for the sophisticated pleasures of the palate, her sanguine outlook in the face of difficulty, the disinclination to worry, the ability to not take things too seriously. After all, if you've been around before, there's no reason to think you won't be around again.

A foreshadowing of her current spiritual disposition appears toward the end of *The Gastronomical Me*. The author and Dillwyn, whom she calls Chexbres, are seated in the dining car of the train from Vevey to Milan. It is the summer of 1939, and they have returned to Europe to dispose of their property there, knowing that war is imminent and that Dillwyn is incurably ill. "We were two

(continued on page 93)

Water

(continued from page 67)

thousands of children suffering neurological damage.

Thus, after spending billions of dollars on the world's most elaborate network of surface and subsurface plumbing, still more billions on sewers and sewage treatment plants and millions on a complex structure of environmental laws and regulations, California finds itself accused of being unable to guarantee the safety of its tap water. How did all this effort and investment produce enough public anxiety and anger to fuel a tap water rebellion?

By issuing permits.

Historically, most societies have treated the poisoning of wells as a crime; in dry climates, like ours, it is said that such criminals were executed. In modern California, however, we rely on government to protect our water. Instead of demanding that those who use dangerous chemicals keep them out of drinking water, instead of holding them accountable for any contamination, we have asked that they play by rules set up by various agencies. Compliance with rules, as embodied in "permits," rather than protection of water has become the standard to which industry is held. And as the word suggests, the "permits" often amount to a legal sanction to release toxic chemicals into drinking water.

Each of the chemical releases cited in our Sacramento River example was approved and licensed by the state of California, from the rice farmer's release of Bolero directly into the waters of the Sacramento to the industrial and agricultural effluent that pours into the delta from the San Joaquin. Every year, millions of pounds of chemicals that can cause cancer, birth defects or sterility even in trace amounts are released directly or indirectly into our drinking water—with the approval, sanction and authority of state and federal agencies.

For the most part, these laws articulate the goal of protecting the environment, the public health and the state's water supplies. The Porter-Cologne Water Quality Control Act, for example, calls for the prevention of "anything that is injurious to health: in the waters of the state." The federal Clean Air and Clean Water acts call for rigorous control of pollution from toxics. In practice, though, these statutes have done far too little to protect our drinking water from contamination.

Each statute requires that the bureaucracy write a specific rule for each chemical, or plant, or facility. In some cases the rules never get written; in other cases they are written but are tied up indefinitely in legal challenges. A third source of weakness is the rules and permits that specifically allow for degradation of water supplies.

Take, for example, ethylene dibromide (EDB). In 1977 the EPA discovered that EDB caused cancer. After the chemical was found in both wells and grain products as a result of its use as a pesticide to fumigate grain, the EPA in 1983 banned most uses of EDB as a pesticide. Even then, however, an exception was made: EDB could still be used to treat winter citrus crops for export to Japan. This allows for the possibility of further contamination of wells by the pesticide. And workers loading ships are exposed to an enormous cancer risk from the fumes.

Worse, the EPA did nothing to regulate the principal use of EDB—as a gasoline additive. While only relatively small amounts of the chemical are now likely to reach groundwater from use as a pesticide, every one of the thousands of underground gasoline storage tanks in the state is now a potential contamination source of EDB.

Overall, our toxics regulatory programs are more loophole than safety net. Massive lobbying, floods of campaign contributions and relentless litigation by the oil and chemical companies keep these loopholes open, and keep the flood of toxic chemicals flowing through the state's economy. The legislature, the governor and the bureaucracy are simply incapable of saying no to the pleadings of these ample pocketbooks.

When Mendocino and Trinity counties moved to protect their streams from contamination by aerial spraying of phenoxy herbicides, then-attorney general Deukmejian intervened and charged that such local regulation of pesticides was illegal. When he lost, and the state Supreme Court ruled that counties did have the power to protect their waters, it took the legislature less than two months to pass a bill explicitly stripping them of that right.

The public may not perceive exactly how such special-interest loopholes are enacted. But the continued failure of the present system to provide protection against toxics has thoroughly disenchanted most Californians. Seventy-three percent of those polled by the University of Southern California last year said they "don't trust government to protect [them] and [their] family against toxic chemicals."

And just as repeated failures by the legislature to respond to the public demand for property tax relief spawned Proposition 13 as the climactic battle of the tax revolt, a new statewide ballot proposition has emerged as a result of this public mood. Proposition 65 is shaping up to become the main battle-

ground of the tap water rebellion.

At the heart of this initiative is a concept that seems to strike terror into the hearts of many of the state's oil and chemical companies. Instead of telling business to "follow government rules," the voters would hold industry directly accountable for their use of those chemicals that can cause cancer or birth defects. Proposition 65 requires the governor to publish a list of chemicals on which there is a scientific consensus: these chemicals cause cancer, birth defects or sterility.

After a grace period, businesses using chemicals on the list must meet two standards: they must keep any significant quantity of these chemicals from reaching a source of drinking water; and they must make a reasonable effort to warn anyone they expose to a significant level of such a chemical.

The state is allowed to define safe levels for these chemicals, so that trivial releases do not trigger these requirements. State agencies may also publish guidelines to define for businesses how they should go about warning people who are exposed. In some situations, say, consumer products containing a carcinogen, a label may be needed. At gas stations, posting of signs could warn customers of the hazardous fumes they are being exposed to. But the basic responsibility would remain on the businesses—whether or not state agencies wrote regulations.

These two requirements would apply across the board, whether the chemical in question was a pesticide or a fuel additive and whether it was released by a power plant or a chemical factory. They would for the first time place a consistent safety net between the public and chemicals that cause cancer and birth defects. And, in a further step to empower ordinary citizens, the initiative allows for direct citizen enforcement if law enforcement officials do not act against a violator within 60 days of being informed.

While cracking down on legal releases of chemicals that cause cancer and birth defects, the initiative also toughens existing penalties for illegal uses. Violators of the provisions requiring exposure warnings and prohibiting releases into drinking water could be fined up to $2,500 a day. Fines for criminal dumping would double from $50,000 to $100,000 a day; if serious injury was incurred by any victims, the fines could go as high as $250,000 a day and the possible jail term would increase from three to six years. Twenty-five percent of all fines would go to the district attorney (or to whichever individual or party brought the suit), 25 percent to police or health agencies involved and the remaining 50 percent would be deposited in the state Superfund (toxic waste dump cleanup fund).

Also, an antisecrecy provision would make it a crime for certain government employees to intentionally conceal their knowledge of an illegal discharge of hazardous waste; they must notify the board of supervisors and local health officer within 72 hours.

Even with all these provisions, there are a number of problems relating to drinking water quality that the measure does not address. David Roe of the Environmental Defense Fund, one of the authors of the initiative, admits, "Of course, this doesn't solve all the problems. It deals with a narrow range of the problem. But we think it cuts deep, and sets a precedent for going after the rest of it." Roe identifies three major areas untouched by the initiative. First, it is designed to prevent future contamination of drinking water—it does not deal with the expensive, muddy problem of cleaning up already contaminated sources. Second, the initiative does not solve the problem of chemicals that have not yet been tested—the so-called "data gap." Finally, Roe points out, there are medical problems other than cancer and birth defects caused by toxics.

Opponents of the initiative, organized by the California Chamber of Commerce and the oil industry, as well as some environmentalists, see other loopholes. They complain about the exemptions for government— the military in particular is a major source of groundwater contamination—and small businesses, as well as the fact that Proposition 65 does not directly regulate municipal landfills or water companies.

Roe replies that with the exception of the military exemption, an unfortunate legal necessity, the other objections raised are "relatively minor." He says that legitimate small businesses with less than ten employees simply do not generate a large volume of toxic chemicals that might threaten drinking water. Should such a small business be involved in illegal dumping, however, it would *not* be exempt from criminal penalties. Roe also asserts that although the initiative does not specifically deal with landfills and water companies, it does deal with the heart of the problem by going after those businesses that discharge toxic chemicals into the facilities and aquifers operated by governing agencies.

Advocates of the toxics initiative, including such major statewide organizations as the Sierra Club, Consumers Union, California League of Conservation Voters and the Northern California Public Health Association, say that passage of the proposition will send a clear signal to the chemical industry that the tap water rebellion is serious—and the future contamination of drinking water must stop. Memos drafted by lawyers for some of the key corporations opposing the measure echo this notion. One lawyer warned a major oil company that "whatever its direct impact, the initiative sets an important precedent for this state and others. . . . a dangerous precedent which may rapidly be followed elsewhere. . . ."

If it passes.

Both sides expect this to be one of the most hotly contested issues on the fall ballot. In addition to the environmental and public health organizations that initially designed the measure, Proposition 65 has received support from the California District Attorneys Association, which thinks it will provide prosecutors with new tools against toxic dumpers; from organized labor, which believes the initiative's warning requirements are more effective than those in existing law; and from a panoply of elected officials, including Mayor Dianne Feinstein and state Senator Art Torres.

In addition to the Chamber of Commerce, the California Farm Bureau and the oil and chemical companies, early opposition to Proposition 65 has come from the Assembly Republican caucus, particularly caucus leader Pat Nolan, who has expressed the belief that the initiative is "an arrow pointed at Governor Deukmejian's heart."

The coalition against the initiative has hired the consulting firm of Russo Watts & Rollins, which in previous years did work for a number of successful candidates and propositions, including the governor. A skilled and effective campaign team, Russo Watts & Rollins begins far behind in the polls, with the knowledge that its principal financial backers have very low public credibility on the toxics issue.

Their campaign strategy, says Tom Epstein, who heads the "Yes! Get Tough on Toxics" campaign for Proposition 65, is likely to be the classic strategy of a well-funded campaign trying to defeat a popular idea: confusion. "Their ballot argument," Epstein says, "is a classic. They present four main points, which are not consistent with each other. They'll probably have a TV spot to go with each point, and hope to confuse enough people to defeat us." Epstein says the four main points apparently identified by Russo Watts & Rollins are the exemptions incorporated into the initiative, the effect on agriculture, the provision allowing citizens to sue and the argument that the state already has enough laws on toxics.

Epstein believes that as long as spending for the "No" side does not get "too tremendous," he is confident the voters will support Proposition 65. "We just have to make sure that everyone in the state knows what the initiative is, and what it does. No amount of confusing 30-second spots will convince the voters once they really understand it." ■

San Francisco Chronicle 9/5/86 ★★★★

EPA Estimates 730 Deaths a Year

Warning on Radioactive Drinking Wate

Washington

Naturally occurring radioactivity in drinking water poses a serious health threat across the country and requires stricter regulation, the Environmental Protection Agency said yesterday.

Radon, radium and uranium in drinking water supplies are causing as many as 730 cancer deaths a year, agency officials reported at a press conference. They noted, however, that there are readily available means of reducing radioactivity in drinking water to safe levels.

The agency said it plans to propose rules a year from now to expand and strengthen its current regulations governing permissible amounts of radioactivity in drinking water. Current rules cover radium and many other radioactive materials, not radon or uranium. Agency officials said they need more information and time for public comment before they devise new rules.

Radioactive contamination of drinking water is found virtually everywhere in the country, the agency said. It said there are high concentrations in New England, where there is considerable radon in the water; in the North Central and Appalachian states, which also have high levels of radon, and in the Rocky Mountains, where high levels of uranium are frequently found.

Michael Cook, director of the agency's Office of Drinking Water, said the problem is found largely in small water systems that draw from underground water tables.

The agency said that radon — a gas emitted from decaying uranium that produces solid particles that can cause lung cancer — is the biggest problem. It estimated that from 30 to 600 cancer cases a year were caused by radon in drinking water. This compares with 5000 to 20,000 cases of lung cancer caused each year by radon in the soil.

Nevertheless, Joseph A. Cotruvo, director of the criteria and standards division of the Office of Drinking Water, said radon in water is still a much more serious public health threat than some of the more widely publicized risks presented by pesticides and other toxic chemicals.

Radium isotopes 226 and 228 are each estimated by the agency to cause from three to 60 cases of bone cancer a year. Uranium is said to cause from one to 10 cases a year.

The agency noted that the individual risk of getting cancer from radioactive contamination of drinking water depends on the concentration of the radioactivity. For example, there are 20 states in which the levels reach 1000 picocuries of radiation per liter of water. A picocurie is one-trillionth of a curie, a standard measurement of radioactivity.

At that level, a person who is exposed to the water over 70 years has a 1 in 10,000 chance of developing cancer. At an exposure level of 10,000 picocuries, the cancer risk is 1 in 1000.

The agency estimates 300,000 people in the United are exposed to radon in wa levels that exceed a 1-in-100 time risk of cancer.

Cook said that probably drinking water in the United contains some level of radioac but added that concentrati this contamination reach d ous levels only in some areas.

By announcing the ris said, the agency is seeking to tize the public to the health lems that exist."

New Yor

Leukemia Cases

Accord Reached In Pollution Suit

New York

W. R. Grace and Co. agreed yesterday to pay more than $8 million in an out-of-court settlement in a major environmental trial in Woburn, Mass.

The case involved allegations that chemical pollution of the town's drinking water had caused six deaths from leukemia and other illnesses.

Although details of the settlement were kept secret, a knowledgeable source told the Los Angeles Times that the agreement provides for payments by the New York-based chemical manufacturer of $1 million each to the eight families who filed the suit, and additional money to other affected families in the blue-collar Boston suburb.

The settlement ends a 4-year-old case that legal experts had watched closely as a precedent for dozens of similar suits nationwide involving attempts to prove links between industrial pollution by companies and specific cases of illness and death.

In this case, the suit charged that contamination of two Woburn municipal wells with two toxic chemicals caused the leukemia deaths of at least five children and one adult since 1978, and cardiac and neurological problems for 25 other people.

Before announcing the settlement yesterday morning, U.S. District Judge Walter J. Skinner told the six jurors that he had decided to void their previous ruling against W. R. Grace, issued July 27 after a five-month trial, and order a new trial on the company's liability. The settlement precludes another trial.

The families said they decided to accept the settlement primarily because they were tired of the lengthy trial and dreaded testifying.

"There was a lot of fear going through the second phase (of the trial) of having to bring up a lot of the emotional part of what we've been through, what I've been through with my son, and having to get on the stand and go through all that is just torture thinking about it," said Donna Robbins, who said one of her two sons died of leukemia at age nine.

Kathryn Gamache, whose husband, Roland, died of leukemia seven months ago, said she was glad the case was over. "Money was never an important factor, but for them to settle out of court proves to me that they're guilty, they know they're guilty, and they're willing to pay for it," she said.

W. R. Grace spokesman Fred Bona said the company did not admit any liability in the settlement.

"We continue to maintain and are now more convinced than ever that we did not pollute the wells and we were in no way responsible for the tragic events . . . in the Woburn community," Bona said, reading from a statement here. He said the company decided to settle because of "our concern for the additional strain on the families, litigation costs, complexity of the case and the length of the trial."

Lawyers involved in the negotiations said the judge told them Wednesday of his sealed decision to order a new trial and that the decision had pushed both sides to compromise.

BY ASSOCIATED PRESS

Donna Robbins and her son Robby hugged after a court settlement involving the leukemia death of Robbins' other son

In the July ruling, the jurors found that Grace had negligently "substantially contributed" to the contamination of two municipal drinking wells in Woburn with trichloroethylene and tetrachloroethylene. The jury cleared another defendant, Beatrice Cos. of Chicago, of any liability.

The two cleaning solvents were used to make food packaging equipment at Grace's plant in Woburn, a city of 35,000 about 12 miles north of Boston. The U.S. Environmental Protection Agency classifies both chemicals as "probable" causes of cancer in humans.

Source: ACWA News 8/25/86

Guest Column

The Public Gives Water Utilities High Marks

(Editor's Notes: The American Water Works Association Research Foundation (AWWARF) commissioned a public attitudes survey on drinking water issues in the fall of 1985. The following article by John B. Mannion is a very brief overview of the conclusions that emerged from the study and is being reprinted for the benefit of ACWA's member agencies and the California water community. The article, "The Public Gives Water Utilities High Marks," appeared in the June issue of *Journal AWWA* along with a companion article titled, "Public Attitudes Toward Water Utilities," by James F. Manwaring, Stanley M. Zdep, and Ida M. Sayre. Mannion is deputy executive director of the AWWA Research Foundation.)

Water utilities enjoy better standing among their customers than one might assume from reading newspapers. Nevertheless, utilities face a significant challenge in the matter of public education, especially among young people. These are among the conclusions that emerge from a study of the 63 tables that constitute the raw data behind the AWWA Research Foundation's "Report on Public Attitudes Toward Drinking Water Issues."

The most notable oddity in the survey results is that two apparently contradictory attitudes exist side-by-side among some consumers. On one hand, people give good ratings to local water quality, the performance of their water utility, and other factors that indicate favorable opinions of utilities and their service. On the other hand, there is unmistakable fear among respondents concerning harmful contaminants in drinking water. How can this be?

In the survey responses related to contamination, the positive data are striking. For example, 19 of 20 respondents were unaware of local water contamination during the past two years. Some 71 percent of those aware of contamination believed the utility was doing something about the problem. Only 24 percent of those who rated their water average, below average, or not safe believed it contained harmful contaminants, and almost half of them were thinking of chlorine and fluoride, which are actually beneficial. Consumers named their local utility, more often than any other organization, as the most accurate source of information about drinking water. Across the United States, 87 percent of consumers were sufficiently confident of their water to rate it excellent, above average, or average—very positive responses indeed.

These consumers are the same people who are turning to bottled water in surprising numbers (15.4 percent) and paying about 800 to 1000 times as much for it as for tap water. Some 72 percent of all respondents said they are concerned about encountering a substance in water that over their lifetime would be responsible for their death. About one in 100,000 of us will be killed by lightning during a 70-year lifetime, but throughout all regions of the country, people are more concerned about death by drinking water contaminants. Willingness to pay for increased water treatment and protection and for more research are also indicators of concern. Almost 30 percent of those who were aware of a recent local contamination incident reported that they found out about it by their own observation (21.6 percent said the water utility told them).

Can this concern and confidence be reconciled? Strictly speaking, the survey does not provide an unequivocal explanation. A few reviewers have speculated, and it is no more than speculation, that the questions about concern and risk might easily have been interpreted as conjectural rather than interrogatory; i.e., hypothetical, not inquiring about facts. Not being mind readers, all that can be said with any certainty is that the two attitudes coexist in the minds of some consumers. There are genuinely positive opinions about local water and water utilities, and there is a minority among consumers that is sincerely concerned. This concern may be unfocused or misplaced, but it is real.

A message for managers and owners

One of the clearer messages of the survey concerns the need for utility programs of public information and education. Misunderstanding and concern seem to occur throughout the various subgroups in the population, without much regard for geographic region, education level, sex, income category, and so on. Age apparently affects some attitudes but not consistently so.

Respondents rated the overall performance of utility personnel very highly, with 23.3 percent saying it was very good, 50 percent saying good. It is instructive to examine the top rating by age group. This rating was obtained among 10.8 percent of the 18- to 25-year-old group; 18.3 percent of the 26- to 45-year-old group; 31.8 percent of the 46- to 65-year-old group; and 33.6 percent of those aged 65 or older. Similarly, almost 76 percent of all respondents said they could name their water utility; only 50 percent of those in the 18- to 25-year-old group said so. These responses indicate that younger people are in particular need of more accurate information about their water and water suppliers.

Though age may be something of a factor in some issues, the overriding conclusion is that a substantial minority of the public—one fourth to one third of them, perhaps more—is apprehensive about the issue of drinking water and health. In that group are many who are uninformed or misinformed. At the same time, may of them and many respondents in general profess confidence in the local water utility—a solid base to build upon. People say they are ready to support improved treatment costs and research, and they believe the utility is the most accurate source of information in these matters.

The industry should be encouraged by the results of this study and moved to mount a more vigorous program of public communication. Where treatment changes or other measures to improve water quality are indicated, utilities might take some comfort from this survey. The message is that water utilities are well thought of, and a concerned public stands ready to follow their leadership.

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Positions Open

Superintendent of Treatment Plants to be responsible for the operation and maintenance of reclamation facilities; a grade V wastewater certificate is preferred; a grade IV may be considered, depending on qualifications; salary is dependent on qualifications, plus benefits; a minimum of seven years of progressive experience in the operation of a comparable wastewater treatment facility, five years of which must have been in a supervisory capacity; resumes and applications accepted until the position is filled; for applications, call (714) 582-3204; send application and resume to the Santa Margarita Water District, P.O. Box 2279, Mission Viejo 92690.

General Manager; excellent benefit package, salary negotiable; district provides water supply, treatment distribution and sewage collection and treatment systems for a small Northern California community (Lake California); candidate must possess strong business

2nd place. San Juan Suburban Water District; 3rd place. Monterey County Flood Control and Water Conservation District.

Group 7 (46-79 employees)—1st place. Walnut Valley Water District; 2nd place. Casitas Municipal Water District; 3rd place. Rancho California Water District.

Group 8 (80 and over employees)—1st place. Moulton Niguel Water District; 2nd place. Padre Dam Municipal Water District; 3rd place. Sweetwater Authority.

Ames: Don't Scare The Public About Unimportant Toxic Risks

"The poison makes the dose—every chemical is toxic in some sense," Professor Bruce N. Ames, chairman of the Department of Biochemistry, University of California at Berkeley, told the over 500 conferees attending the May 8 luncheon at ACWA's 1986 Spring Conference in Monterey.

Ames, recipient of two of the country's most prestigious awards for cancer research, declared water pollution irrelevant to the causes of human cancer.

"The carcinogens and toxic chemicals being found in California water supplies are present in extraordinarily tiny amounts and, except in rare cases, are present in trivial amounts relative to the background level of carcinogens found in nature," he said. "I am convinced that water pollution and man-made pesticide residues are irrelevant to the causes of human cancer.

"I am convinced that water pollution and man-made pesticide residues are irrelevant to the causes of human cancer."

"The main current fallacy consists in thinking that carcinogens are rare and that they are mostly man-made chemicals. My own estimate is that over 99.99 percent of the carcinogens Californians ingest are natural (natural toxic chemicals in plants and molds) or traditional (cooking food, cigarettes, alcohol).

"Every meal has many carcinogens, and when one compares the level of carcinogens in contaminated water (or pesticide residues in food) to the level of natural carcinogens, it is clear that water pollution (or pesticide residues) represents a trivial exposure.

"The whole world is full of carcinogens. So what is important and what is trivia?

"Water pollution and pesticide residues are almost always present in the parts per billion range. One part per billion (or, one person in all of China) is an extraordinarily small amount.

"The level of carcinogens in contaminated well water (such as in Silicon Valley) only rarely involves a possible hazard more than that of ordinary tap water. Of 35 wells shut down in Silicon Valley because an EPA study showed a supposed carcinogenic hazard, only two were of greater possible hazard than ordinary tap water (well water usually lacks the chloroform present in chlorinated tap water), and the most polluted well (2,800 ppb trichloroethylene) poses at least 1,000 times less of a possible hazard than an equal volume of cola, beer or wine.

Bruce N. Ames
Luncheon Speaker

. . . and the most polluted well (2,800 ppb trichloroethylene) poses at least 1,000 times less of a possible hazard than an equal volume of cola, beer or wine."

"Given that the consumption of tap water is only about one or two liters per day, it seems unlikely that man-made water pollution is causing more than a minimal hazard.

"The man-made carcinogenic residue of most interest in food is likely to be DDE . . . and is insignificant compared with natural carcinogens in our diet. Even an occasional highly DDE- or PCB-contaminated fish (100 times the average level) would contribute a risk that is small compared to other very common minimal risks such as a glass of beer or a peanut butter sandwich.

We are ingesting natural pesticides in our diet in amounts at least 10,000 times more than man-made pesticide residues."

"On the other hand, we are ingesting natural pesticides in our diet in amounts at least 10,000 times more than man-made pesticide residues. Natural pesticides are natural toxic chemicals, which are present in all plants, usually making up five percent to 10 percent of a plant's weight . . . Calculations on the possible carcinogenic hazard of plant compounds show that they completely overshadow the traces of man-made pollutants found in the daily diet.

"We do not live in a risk-free world."

"We do not live in a risk-free world. We might possibly eliminate every trace of man-made carcinogen from our water or food supply, but it will cost an enormous amount and be irrelevant to causes of human cancer. My advice? 'Don't scare the public about unimportant risks.' "

Ag Panel Focuses On Perspectives In Water Politics

By Melissa Blanton
M.B. Communications

One of the highlights of the ACWA Spring Conference was a panel discussion on "Perspective/Trends in Agricultural Water Politics," sponsored by the Agricultural Water Committee. Moderated by Committee Chairman Daniel Nelson, manager of the Broadview Water District, the panel expressed provocative and sometimes divergent views of the changes that have occurred over the past six decades.

William R. Gianelli, consulting civil engineer and recipient of ACWA's 1985 Water Leader of the Year award, presented an historic overview, touching upon the development of major federal, state and local projects.

A major turning point in the political clout of agriculture occurred when the California Legislature was reapportioned 20 years ago. The abandonment of the system whereby the Senate was selected on an areawide, rather than a population, basis has made issues more partisan, preventing the traditional

statesmanlike approach to problem solving.

Planning and Conservation League Director Gerald H. Meral discussed some of the reasons for the transitional stage of the past few years during which a new public and political response to agricultural projects has evolved. Support for major projects began phasing out in the 1960s, signalling the end to an era.

Over time, the reasons for the changing perspective have included social, environmental and economic considerations. In addition, the politics of the Central Valley itself has changed. There are still areas in which irrigated agriculture can make some gains, including water transfers, mitigation of problems such as those experienced at Kesterson and resolution of problems in the Delta.

Constraints faced by public agencies were outlined by James Ganulin, general counsel, Westlands Water District. Among them are economic, environmental, legal, institutional, political and technical concerns. Westlands activities at Kesterson provide a case study of how these problems affect water agencies. There is some potential in having the water community and the environmental community meet in a spirit of cooperation and consensus. Negotiation solves more problems than litigation.

In a wrap-up to the discussion, consulting civil engineer B. J. Miller gave his thoughts on three factors affecting the southern part of the San Joaquin Valley. These are, in order of descending immediacy: subsurface drainage, water marketing and overdraft.

The common thread in the failure to reach consensus in these areas is the failure of the people debating the issues to reach agreement on what "reality" is. Until this happens, we'll be stuck with the problems, Miller said.

The panel discussion was followed by a lively question-and-answer session, which ended only because the clock ran out.

Getting together during an ACWA Conference break are (from left) Jamie Hartshorn Damer, Rita Schmidt Sudman and Nancy Long, all with the Water Education Foundation.

A glimpse of some of the nearly 1,500 people attending the ACWA 1986 Spring Conference in Monterey.

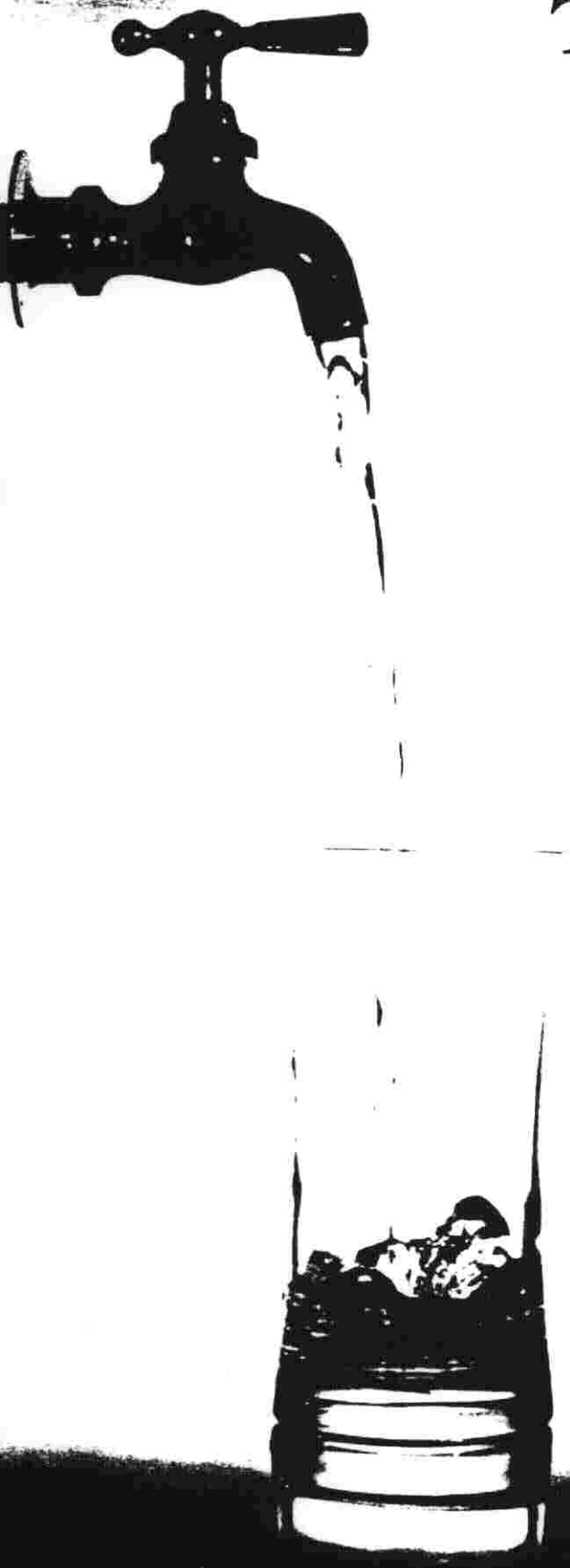
Brenda Mabry, human relations and communications consultant, gives advice on helping employees increase their "people skills" by learning communication and human relation skills.

Assemblyman Jim Costa explains Prop. 44—the Water Conservation and Water Quality Bond Law of 1986—during the Legislative Issues program.

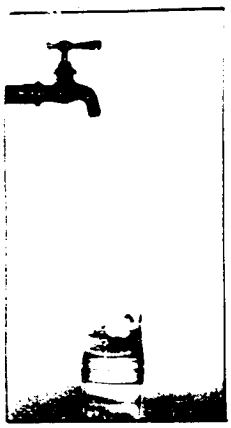
Lowell Weeks of Coachella, expresses his thanks to ACWA President Rex Pursell for being named as an Honorary Life Member of the Association.

Clara County

TAP WATER IS SAF



Santa Clara Valley Water District



WHY BUY BOTTLED WATER?

Personal taste, not a concern over safety of tap water quality, should be the main reason to buy bottled water or a water filter. This brochure will demonstrate that bottled water is typically no better or worse than tap water. The difference is in the taste and cost—tap water costs less than 1¢ for 10 gallons, and bottled water 50¢ to $7.00 for one gallon. Taste is a personal matter. Try keeping tap water in the refrigerator. See if you can taste the difference between it and refrigerated bottled water.

HOW DO I KNOW TAP WATER IS SAFE?

WELL WATER

All municipal tap water in our county must meet strict tests for quality and safety. About half the water used in our valley is well water. It is pumped from deep in the ground, free of bacteria and other natural contamination. Only a very small percentage of municipal wells have ever been contaminated by toxic chemicals in Santa Clara County. Any chemicals that are found in working wells are heavily diluted in water before being sent to consumers. Or, the wells are closed. All well water delivered by major municipal suppliers in our county meets state and federal drinking water standards. Tests of well water are made regularly to guarantee the water is safe.

IMPORTED WATER

The other half of the tap water in our valley is treated surface water, imported from hundreds of miles through rivers and aqueducts. When chlorine is used to kill waterborne diseases and bacteria, compounds called trihalomethanes (THMs) are produced. Federal standards require that THMs be produced at levels less than 100 parts per billion averaged over a year. Local tap water contains annual averages of about 60 parts per billion, which is well within safe drinking water standards. The Water District is studying ways to significantly reduce THMs.

CAN ACCURATE TESTS OF MY HOME WATER QUALITY BE MADE AT MY HOME?

It's highly doubtful. There are cases of sales people adding a liquid chemical to tap water samples and turning it cloudy or changing its color. Consumers are told that these tests can detect solvents, metals, pesticides, and toxic chemicals. They cannot. Highly accurate analytical instruments used in state certified laboratories provide the only dependable test results.

WHY AREN'T TAP WATER ICE CUBES CLEAR?

Most tap water in our county contains a lot of dissolved calcium and other minerals essential for good health. Unfortunately, the high mineral content doesn't make for clear ice. That is because minerals turn into solid white particles when frozen.

DOES CLOUDY TAP WATER MEAN THERE'S SOMETHING WRONG?

Not necessarily. Water in distribution pipelines is under pressure. This means "air" is dissolved in the water. When the water flows from the faucet the air is released and may form tiny bubbles. These bubbles are easily seen in a glass of water and will slowly rise and disappear. If your water remains cloudy, call your water utility to investigate the cause.

DON'T I HAVE TO BUY BOTTLED WATER TO CUT BACK ON SODIUM?

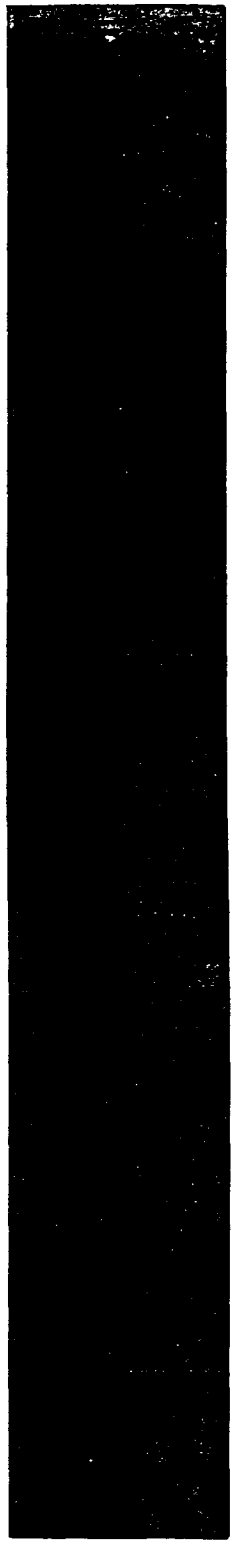
No. Nearly all the sodium people consume each day comes from food, not water. If you are limited to 1,000 milligrams sodium per day you can drink tap water. A diet restricted to 500 milligrams or less per day means you should find out the sodium content of your drinking water—whether it's tap water or bottled water. Contact the company you pay your water bills to for tap water sodium content. Do not purchase bottled water that does not state the sodium content. One bottled water shown in our test on the next page had six times the amount of sodium found in tap water.

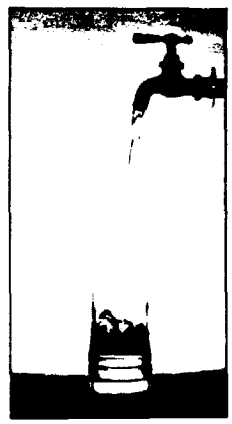
WHAT ABOUT ADD-ON FILTERS?

The only reason to buy a filter for municipally-supplied water in Santa Clara County is to change the taste, not for health reasons. The very best filters on the market can remove detectable levels of trihalomethanes and organic chemicals of the type that have been found in a handful of Santa Clara Valley's hundreds of major drinking water wells. The levels of these compounds are extremely low; any tap water that may contain them is safe and meets all drinking water standards. If you do own a filter, be very careful to change the filter medium—usually activated carbon—at least as often as recommended by the manufacturer. If you don't, the filter itself will harbor bacteria; this will endanger your health if the bacteria levels are too high.

WHAT ABOUT BACTERIA IN TREATED TAP WATER COMPARED TO BOTTLED WATER?

A recent test comparing bottled water to this District's treated imported water revealed that treated water has far less bacteria than most bottled water tested. Look at the results of that test in this brochure. Bacteria levels in some bottled water ranged from five to 2,300 times greater than treated water. Municipal water supplies are regularly tested for bacteria and must meet very rigid standards.





WHAT DOES THE TABLE MEAN?

Simply put, it showed that tap water was better than some bottled water and not quite as good as some others. But the bottom line is that tap water produced at our treatment plants is perfectly safe. And that the most important "contaminant" in water—bacteria—is almost nonexistent in treated tap water. There is little difference between bottled water and municipally-supplied tap water in Santa Clara County. Except that bottled water costs 500 to 7,000 times more than high-quality water coming out of your tap.

LABORATORY TEST: TAP VS BOTTLED WATER

Brand	Bacteria[1] per milliliter	THM[3] mg/1[4]	Sodium mg/1	Chloride mg/1	Arsenic mg/1[6]	Nitrates mg/1[7]	Total Dissolved Minerals mg/1	Taste Rating[8]	Hardness mg/1
1	1	nd[5]	14	17	nd	0.1	142	3	106
2	5	nd	3	6	nd	0.8	308	3	300
3	< 1[2]	nd	19	13	nd	1.0	155	2	96
4	6	nd	2	6	nd	< 0.1	8	3	nd
5	< 1	nd	12	13	nd	< 0.1	90	5	62
6	2300	nd	189	194	0.14	< 0.1	620	4	16
7	27	nd	nd	5	nd	< 0.1	< 1	3	nd
8	< 1	nd	nd	nd	nd	0.1	2	2	nd
9	40	nd	5	24	nd	0.6	52	3	34
10	860	nd	4	1	nd	< 0.1	9	2	4
Treated Imported Water	1	0.04	32	31	nd	< 0.1	268	4	190

Bottled water: 1, 2, 3, 5, 6, 10 Distilled on site: 4 Vending machine: 7, 8, 9

1. Heterotrophic plate count
2. The symbol < means less than
3. Trihalomethane (THM) maximum contaminant level, 0.10 mg/1
4. Milligrams per liter, mg/1, are equivalent to parts per million, ppm.
5. nd, none detected
6. Maximum contaminant level is 0.05 mg/1
7. Maximum contaminant level as nitrogen is 10 mg/1
8. Taste panel used a scale of 1 to 9: 1 = very acceptable 5 = maybe acceptable, 6 to 9 = not acceptable.

Test results were based on one sample from different brands purchased randomly on November 7, 1985.
Test was conducted at Santa Clara Valley Water District's Rinconada Water Treatment Plant.

Santa Clara Valley Water District • 5750 Almaden Expressway • San Jose, CA 95118 • (408) 265-2600

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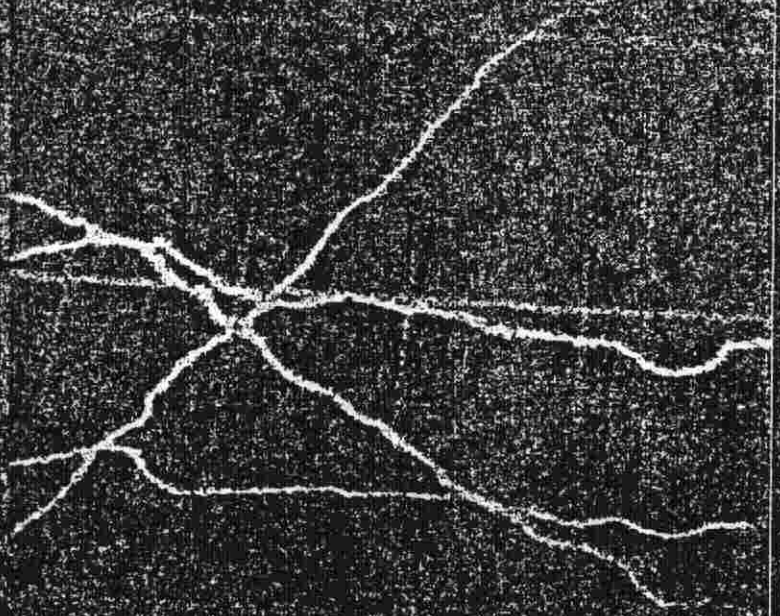
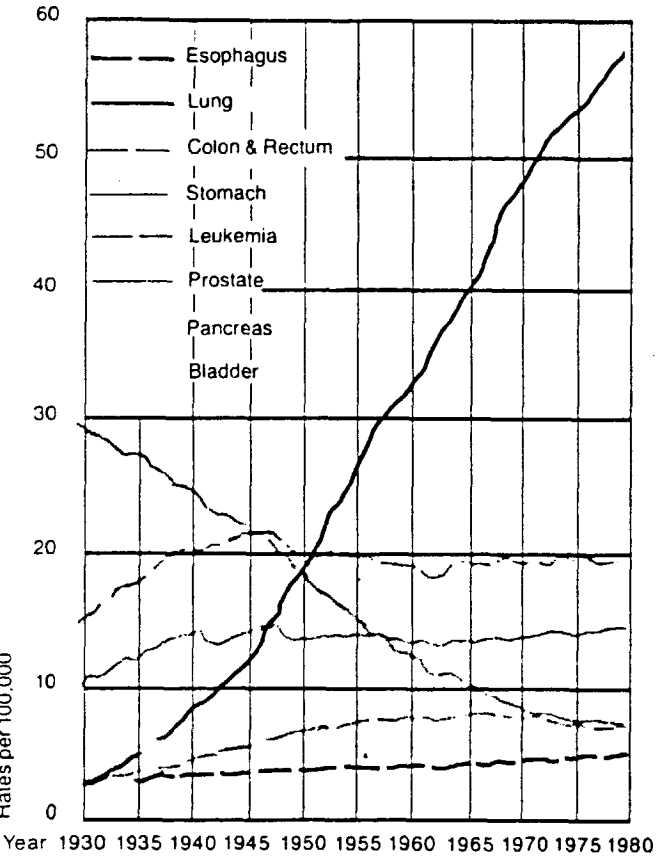
Cancer in the United States: Is There an Epidemic?

A Report by the American Council on Science and Health



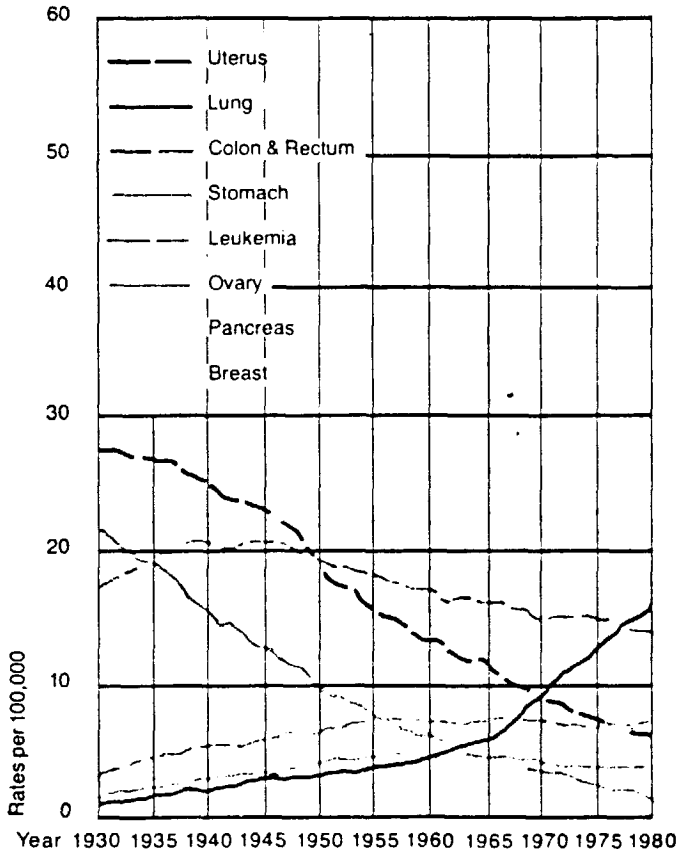
ıure 20 Age Adjusted Male Cancer Death Rates* per 100,000 Population, Selected Body Sites, United States, 1930-1980



*Standardized on the Age Distribution of The 1940 U.S. Census Population

Source: Silverberg, E., Cancer Statistics, 1980, *CA-A Cancer Journal for Clinicians*, 30(1): 23, 1980.

Figure 21 Age Adjusted Female Cancer Death Rates* per 100,000 Population, Selected Body Sites, United States, 1930-1980



*Standardized on the Age Distribution of The 1940 U.S. Census Population

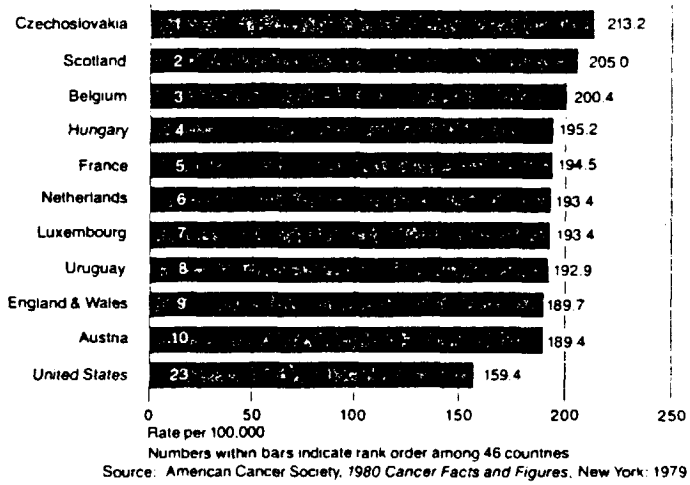
Source: Silverberg, E., Cancer Statistics, 1980, *CA-A Cancer Journal for Clinicians*, 30(1): 23, 1980.

An International Comparison

It is widely believed that the United States has a high cancer death rate compared with other countries. One network television program on cancer opened with the statement: "The news tonight is that the United States is number one in cancer. The National Cancer Institute estimates that if you're living in America your chances of getting cancer are higher than anywhere else in the world."

However, information collected by the World Health Organization and analyzed by the American Cancer Society gives a much different view. In a comparison of cancer death rates in 46 countries, the U.S. ranked 23rd for male and 19th for female cancer deaths. Czechoslovakia holds the dubious honor of being "number one" followed by Scotland, Belgium, Hungary and France (Figure 22). According to this survey, the U.S. white male death rate, was 159 per 100,000.

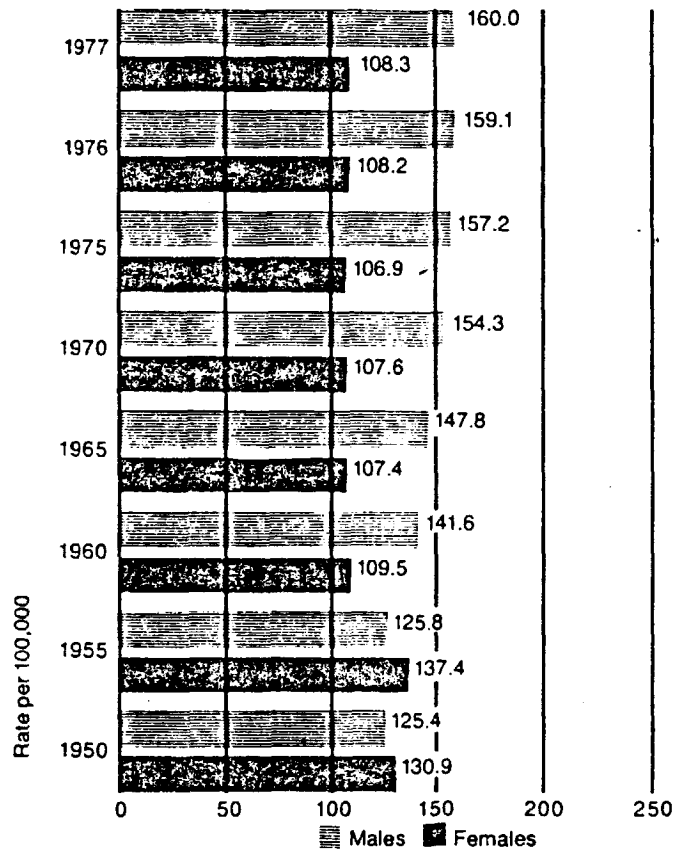
Figure 22 Age Adjusted White Male Cancer Death Rates per 100,000 population, Selected Countries, 1974-1975



Numbers within bars indicate rank order among 46 countries

Source: American Cancer Society, *1980 Cancer Facts and Figures*, New York: 1979

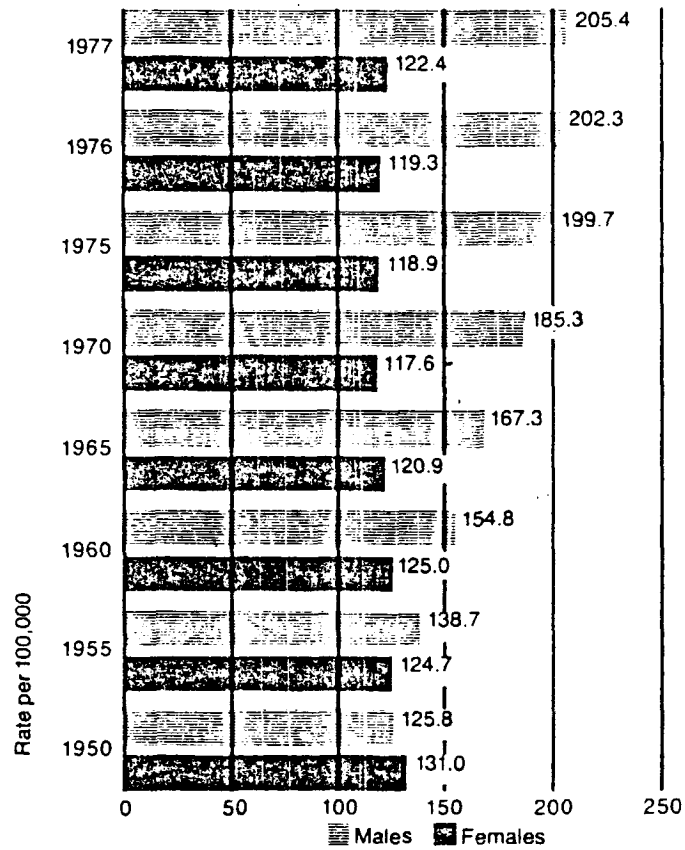
Figure 17 Age Adjusted Cancer Death Rates* per 100,000 Population by Sex for the White Population, All Sites Combined, 1950-1977



*Age Adjusted to 1940 Census population

Source: U.S. Department of Health, Education and Welfare, *Health: United States 1979*, DHEW No. (PHS) 80-1232, Washington, D.C.: 1980.

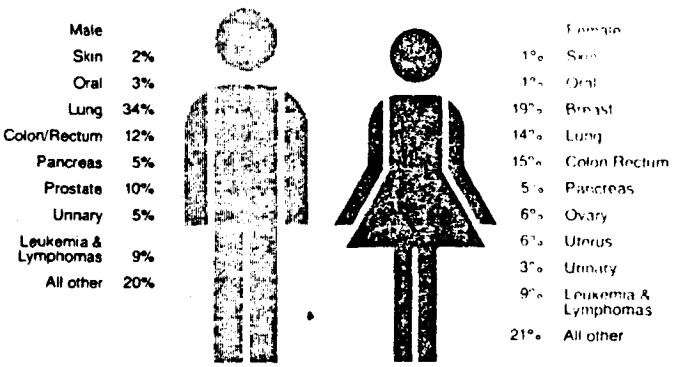
Figure 18 Age Adjusted Cancer Death Rates* per 100,000 Population by Sex for the Nonwhite Population, All Sites Combined, 1950-1977



*Age Adjusted to 1940 Census population

Source: U.S. Department of Health, Education and Welfare, *Health: United States 1979*, DHEW No. (PHS) 80-1232, Washington, D.C.: 1980.

Figure 19 1978 Cancer Deaths by Site and Sex



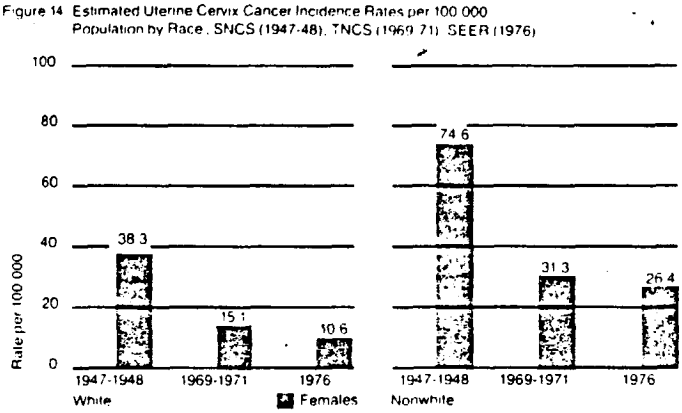
Source: American Cancer Society, *1980 Cancer Facts and Figures*, New York: 1979.

As is evident in Figures 20 and 21, the only cancer deaths that qualify as "epidemic" are those from lung cancer. The rapid increase in lung cancer deaths is most evident for men, but has also occurred in recent years for women as well. This delayed increase in female lung cancer death rates is consistent with the rise in female cigarette smoking that followed World War II. In contrast, men began smoking in large numbers after World War I, almost 30 years earlier. The usual latency period for lung cancer is 20 to 30 years which accounts for the delayed increase in the female rates. Table 2 summarizes the recent trends in the specific cancer death rates for men and women.

Cervix

The incidence of cervical cancer has decreased substantially since 1947 in both white and nonwhite females (Figure 14). Among whites, it declined from 38 in 1947 to 11 per 100,000 in 1976. Among nonwhites, cervical cancer incidence deceased from 75 to 26 per 100,000 during the same time period. Most, if not all of this decline can be explained by use of the Pap test, which can detect precancerous changes in uterine tissue before they become cancerous and thus allow for surgical treatment or other therapy.

Figure 14 Estimated Uterine Cervix Cancer Incidence Rates per 100,000 Population by Race, SNCS (1947-48), TNCS (1969-71), SEER (1976)

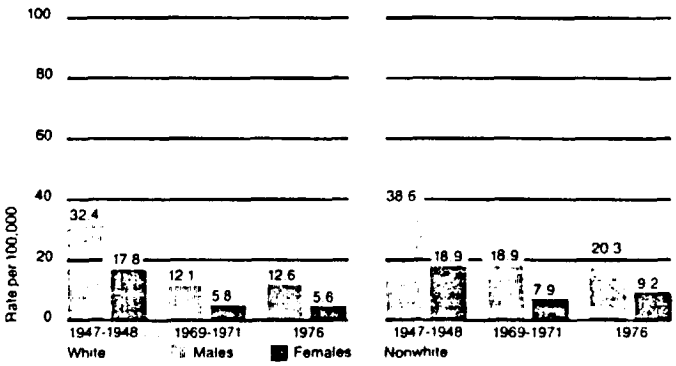


Source: Devesa, S.S. and D.T. Silverman, Cancer incidence and mortality trends in the United States, 1935-1974, *J. Natl. Cancer Instit.*, 60(3):545, 1978; Pollack, E.S. and J.W. Horm, Trends in cancer incidence and mortality in the United States, 1969-76, *J. Nat. Cancer Instit.*, 64 (5):1091, 1980.

Stomach

Stomach cancer incidence also declined substantially for all sex and race groups during the period 1947-1971 (Figure 15). The combined rates for males and females dropped from 25 to 9 per 100,000. Between 1971 and 1976, U.S. stomach cancer incidence has remained stable at the lowest level in the world. The cause of this decline is unknown, but many believe it is related to the widespread use of refrigeration and antioxidant food additives rather than salting to preserve food. In other countries where salting and pickling are still the main forms of food preservation, stomach cancer rates are considerably higher than those in the U.S.

Figure 15 Estimated Stomach Cancer Incidence Rates per 100,000 Population by Race and Sex, SNCS (1947-48), TNCS (1969-71), SEER (1976)



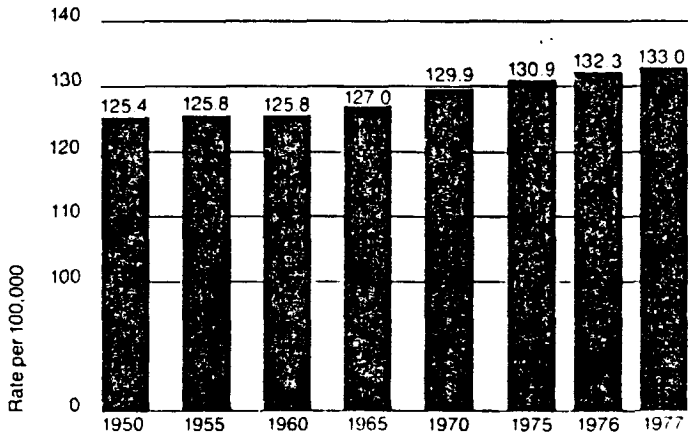
Source: Devesa, S.S. and D.T. Silverman, Cancer incidence and mortality trends in the United States: 1935-1974, *J. Natl. Cancer Instit.*, 60(3):545, 1978; Pollack, E.S. and J.W. Horm, Trends in cancer incidence and mortality in the United States, 1969-76, *J. Nat. Cancer Instit.*, 64 (5):1091, 1980.

U.S. Cancer Mortality

Cancer is the second leading cause of death in the United States after diseases of the heart and circulatory system.

The American Cancer Society estimates that about 405,000 Americans will die of cancer in 1980. Of these, 101,000, or 25 percent, will die of lung cancer. Data from the National Center for Health Statistics indicate there has been a gradual rise in the combined age adjusted cancer death rate since 1950 (Figure 16). In general, the cancer death rate has increased among men and decreased among women. Yet except for the large increases in lung cancer deaths, age adjusted death rates for other types of cancer are leveling off, and in some cases declining. Figures 17 and 18 summarize the recent trends in the combined death rates for whites and nonwhites.

Figure 16 Age Adjusted Cancer Death Rates* per 100,000 Population, All Sites, All Sexes and Races, United States, 1950-1977.



* Age adjusted to 1940 Census population

Source: U.S. Department of Health, Education and Welfare, *Health: United States 1979*, DHEW No. (PHS)80-1232, Washington, D.C.: 1980.

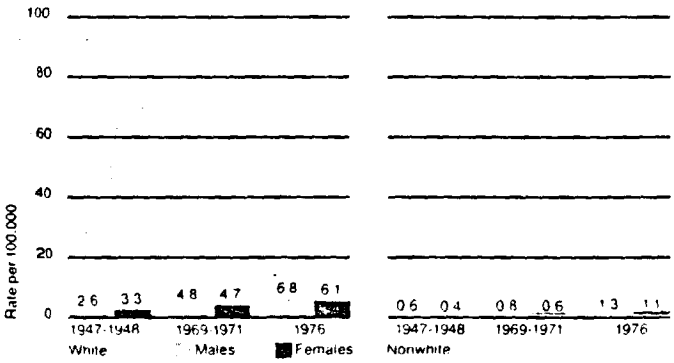
These changes in cancer death rates are due in part to the decrease in certain forms of cancer, especially stomach and cervical cancer. They are also the result of the increased use of screening methods that can detect cancers early, when therapy can be more successful. Some of the decrease can also be attributed to improved medical and surgical treatments for diagnosed cancers. These improvements have increased the survival rates for several forms of cancer, particularly leukemia, Hodgkin's disease and breast cancer in young women. On the other hand, survival rates for lung and pancreatic cancers remain very low.

Lung cancer is the most common cause of cancer deaths among men, followed by colon-rectum and prostate cancers. Among women, breast cancer is the leading cause of cancer deaths followed by colon-rectum and lung cancers. Figure 19 shows the proportion of all cancer deaths for specific forms of the disease.

Melanoma

The incidence of melanoma, a malignant skin cancer, has increased in all groups since 1947 (Figure 10). Among white males, it increased from 3 to 7 per 100,000 during the period 1947-1976. Among white females, melanoma incidence increased from 3 to 6 per 100,000 in 1976. Although slight increases in melanoma incidence have also been reported for nonwhites, this form of cancer is rare among dark-skinned individuals. Geographic variation in melanoma incidence suggests that it may be due in part to exposure to solar radiation, but this relationship is still uncertain.

Figure 10 Estimated Melanoma Incidence Rates per 100,000 Population by Race and Sex. SNCS (1947-48), TNCS (1969-71), SEER (1976)

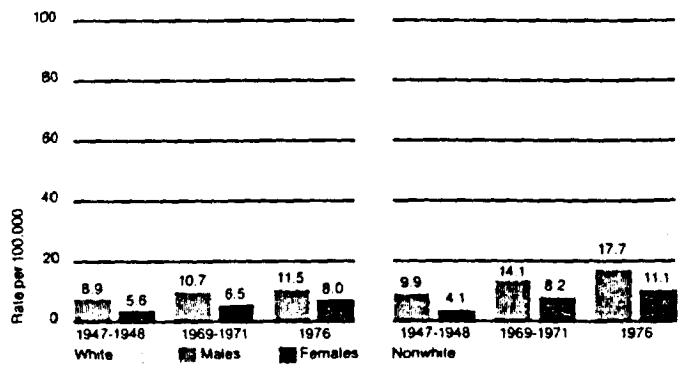


Source Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.* 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.* 64 (5):1091, 1980.

Pancreas

The incidence of pancreatic cancer increased in all sex and race groups since 1947 (Figure 11). Among white males, pancreatic cancer incidence increased from 9 per 100,000 in 1947 to 12 per 100,000 in 1976. For white females, incidence rose from 6 to 8 per 100,000 during the period 1947-1976. Among nonwhite males, pancreatic cancer incidence increased from 10 in 1947 to 18 per 100,000 in 1976. For nonwhite females, it increased from 4 to 11 per 100,000.

Figure 11 Estimated Pancreatic Cancer Incidence Rates per 100,000 Population by Race and Sex. SNCS (1947-48), TNCS (1969-71), SEER (1976)

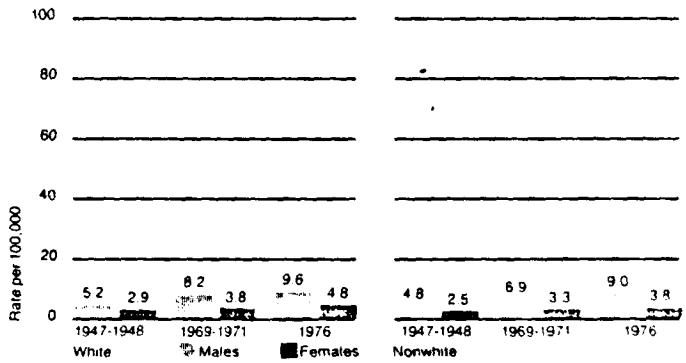


Source: Devesa, S.S. and D.T. Silverman, Cancer incidence and mortality trends in the United States: 1935-1974, *J. Natl. Cancer Instit.*, 60(3):545, 1978; Pollack, E.S. and J.W. Horm, Trends in cancer incidence and mortality in the United States, 1969-76, *J. Nat. Cancer Instit.*, 64 (5):1091, 1980.

Kidney

The incidence of kidney cancer has increased among males and females in both race groups (Figure 12). Among white males, it rose from 5 to 10 cases per 100,000 during the period 1947-1976. For nonwhite males, incidence increased from 5 to 9 per 100,000 during this same period. Increases in female incidence during 1947-1976 were substantially less than those for males, suggesting differential exposure to some carcinogenic agent.

Figure 12 Estimated Kidney Cancer Incidence Rates per 100,000 Population by Race and Sex. SNCS (1947-48), TNCS (1969-71), SEER (1976)

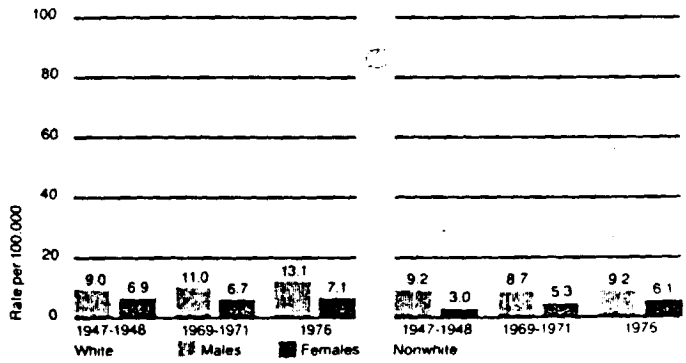


Source Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.*, 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.*, 64 (5) 1091, 1980.

Leukemia

Leukemia incidence increased among white males and nonwhite females during the period 1947-1976 (Figure 13). In nonwhite females the rate doubled from 3 to 6 per 100,000. During this same period, the incidence for white females and nonwhite males has remained relatively constant.

Figure 13 Estimated Leukemia Incidence Rates per 100,000 Population by Race and Sex. SNCS (1947-48), TNCS (1969-71), SEER (1976)



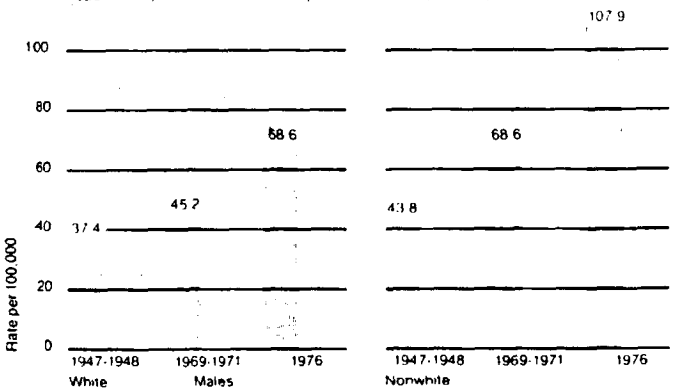
Source Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.*, 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.*, 64 (5) 1091, 1980.

One report has suggested there may be two different forms of malignant breast tumors. One form is thought to behave in a relatively benign manner compared with the other, and has little effect on breast cancer mortality. During the 1970's, many women became more aware of breast cancer because of the publicity over the breast cancer diagnoses of Betty Ford, Marvella Bayh and Happy Rockefeller. The increase in self-examination and other early detection methods may therefore have uncovered more of the relatively benign cancer types. This possibility may explain the recent increase in breast cancer incidence.

Prostate

Prostate cancer incidence has increased substantially among white and nonwhite males (Figure 7). Among whites, it increased from 37 to 69 per 100,000 during 1947-1976. Among nonwhites, prostate cancer incidence increased from 44 to 108 cases per 100,000 population during the same time period. These increases may again reflect better diagnosis of prostate cancer in its early stages, and for nonwhites, better access to medical care. Since prostate cancer occurs more in older males, longer male life expectancy will also allow for the discovery of new cancer cases although another illness or disease may actually cause death.

Figure 7 Estimated Prostate Cancer Incidence Rates per 100,000 Population by Race SNCS (1947-48) TNCS (1969-71), SEER (1976)

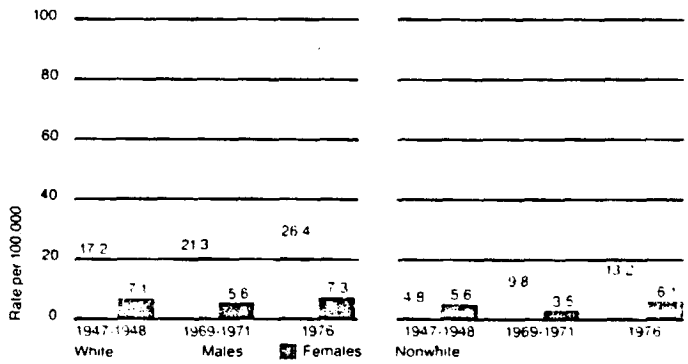


Source Devesa, S.S and D.T Silverman. Cancer incidence and mortality trends in the United States 1935-1974. *J Natl Cancer Instit*, 60(3) 545, 1978. Pollack, E.S and J.W Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J Nat Cancer Instit*, 64 (5) 1091, 1980.

Bladder

For males, bladder cancer incidence increased from 1947 to 1976 (Figure 8). Among white males, it increased from 17 to 26 per 100,000. Among nonwhite males, bladder cancer increased from 5 in 1947 to 13 per 100,000 in 1976. Female bladder cancer incidence decreased slightly from 7 in whites and 6 in nonwhite in 1947 to 6 and 4 per 100,000, respectively, in 1971. Since 1971, female bladder cancer has increased to 7 per 100,000 in whites and 6 per 100,000 in nonwhites.

Figure 8 Estimated Bladder Cancer Incidence Rates per 100,000 Population by Race and Sex SNCS (1947-48) TNCS (1969-71) SEER (1976)



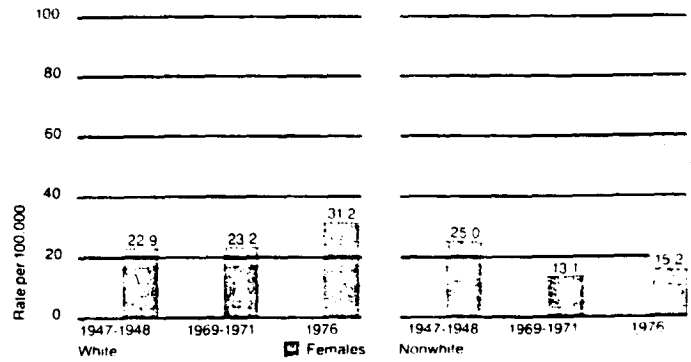
Source Devesa, S.S and D.T Silverman. Cancer incidence and mortality trends in the United States 1935-1974. *J Natl Cancer Instit*, 60(3) 545, 1978. Pollack, E.S and J.W Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J Nat Cancer Instit*, 64 (5) 1091, 1980

These increases in male bladder cancer are likely due to cigarette smoking and occupational exposures to certain toxic chemicals. Among females, the recent increases are probably due to smoking alone. In general, bladder cancer is far more likely to occur in males than females.

Uterus (Other Than Cervix)

The incidence of cancer of the uterine corpus increased among whites from 23 in 1947 to 31 per 100,000 in 1976 (Figure 9). Among nonwhites, incidence substantially decreased during the period 1947-1971, then increased slightly during 1971-1976. Research has suggested that these increases may be due to the long term use of estrogen compounds in treating menopausal symptoms.

Figure 9 Estimated Cancer Incidence Rates per 100,000 Population by Race Uterus corpus and Uterus Not Otherwise Specified SNCS (1947-48) TNCS (1969-71), SEER (1976)



Source Devesa, S.S and D.T Silverman. Cancer incidence and mortality trends in the United States 1935-1974. *J Natl Cancer Instit*, 60(3) 545, 1978. Pollack, E.S and J.W Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J Nat Cancer Instit*, 64 (5) 1091, 1980

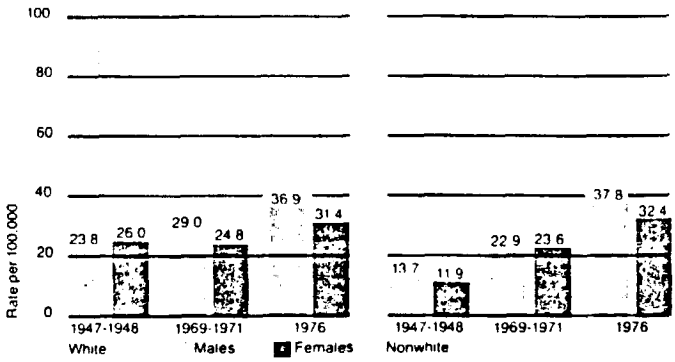
An even greater increase has been noted among nonwhite males. In 1947, nonwhite male incidence was estimated at 23 per 100,000; by 1976 it had increased to 113 per 100,000, or more than 500 percent. These large increases are believed to be due to the effects of cigarette smoking, although some of the increase for nonwhites may be explained by a lack of medical care in the past. Nonwhites had fewer contacts with the health care system in 1947 than they did after legislation of Medicaid in 1965. This suggests that the number of new cases identified in 1947 was lower than it should have been.

Lung cancer among women has also steadily increased since 1947. The American Cancer Society estimates that **by 1983 lung cancer will replace breast cancer as the leading cause of cancer deaths among women.** Among white females, lung cancer incidence increased from 7 in 1947 to 24 per 100,000 in 1976. Among nonwhite females, incidence rose from 5 to 26 per 100,000 in 1976. At present, lung cancer incidence is increasing at a faster rate for females than for males. Indeed, a substantial proportion of the overall increase in cancer incidence during the 1970s can be explained by the dramatic surge in female lung cancer cases. This increase is also believed due to the increase in female cigarette smoking following World War II.

Colon

Colon cancer incidence among white males increased from 24 per 100,000 in 1947 to 37 in 1976 (Figure 4). Among nonwhite males, incidence increased from 14 in 1947 to 38 per 100,000 in 1976. Nonwhite female incidence also increased during this period from 12 to 32 per 100,000.

Figure 4 Estimated Colon Cancer Incidence Rates per 100,000 Population by Race and Sex: SNCS (1947-48), TNCS (1969-71), SEER (1976)



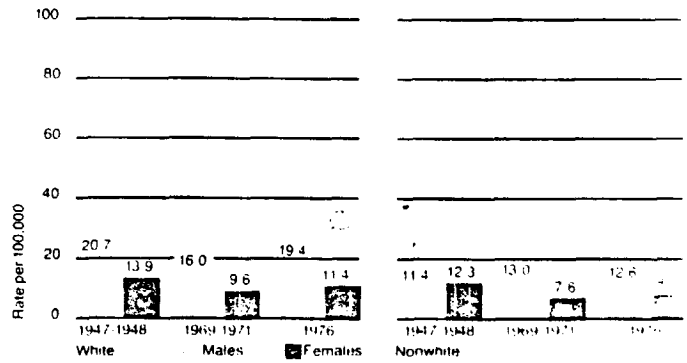
Source: Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.*, 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.*, 64 (5):1091, 1980

Colon cancer incidence among white females decreased slightly during the period 1947-1971 from 26 to 25 per 100,000. Since 1971, this incidence has increased to 31 per 100,000.

Rectum

The incidence of cancer of the rectum among white males and females and nonwhite females decreased from 1947 to 1971, then increased between 1971 and 1976 (Figure 5). Among nonwhite males, however, incidence increased slightly until 197 then decreased.

Figure 5 Estimated Rectal Cancer Incidence Rates per 100,000 Population by Race and Sex: SNCS (1947-48), TNCS (1969-71), SEER (1976)

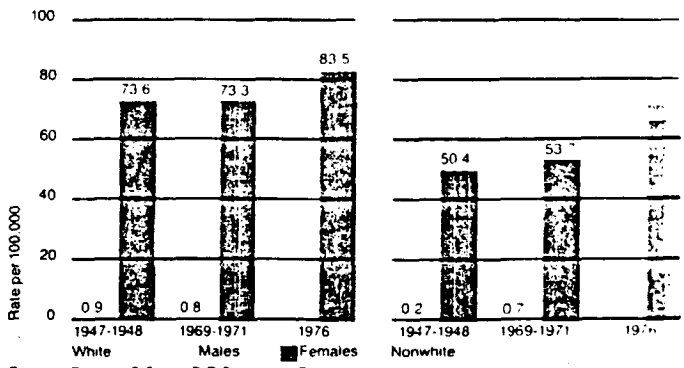


Source: Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.*, 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.*, 64 (5):1091, 1980

Breast

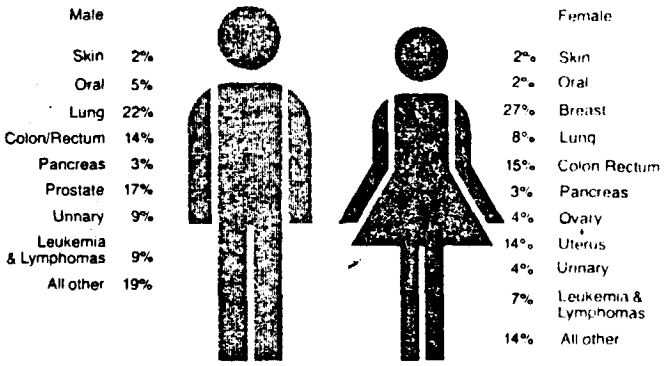
The breast is the leading site of cancer incidence among women. In whites, breast cancer incidence increased from 74 to 84 per 100,000 during 1947-1976 (Figure 6). Among nonwhites it increased from 50 to 67 cases per 100,000 population during the same time period.

Figure 6 Estimated Breast Cancer Incidence Rates per 100,000 Population by Race and Sex: SNCS (1947-48), TNCS (1969-71), SEER (1976)



Source: Devesa, S.S. and D.T. Silverman. Cancer incidence and mortality trends in the United States: 1935-1974. *J. Natl. Cancer Instit.*, 60(3):545, 1978. Pollack, E.S. and J.W. Horm. Trends in cancer incidence and mortality in the United States, 1969-76. *J. Nat. Cancer Instit.*, 64 (5):1091, 1980

Figure 2 1980 Estimated Cancer Incidence by Site and Sex*



* Excluding non-melanoma skin cancer and carcinoma in situ

Source: American Cancer Society, *1980 Cancer Facts and Figures*, New York: 1979.

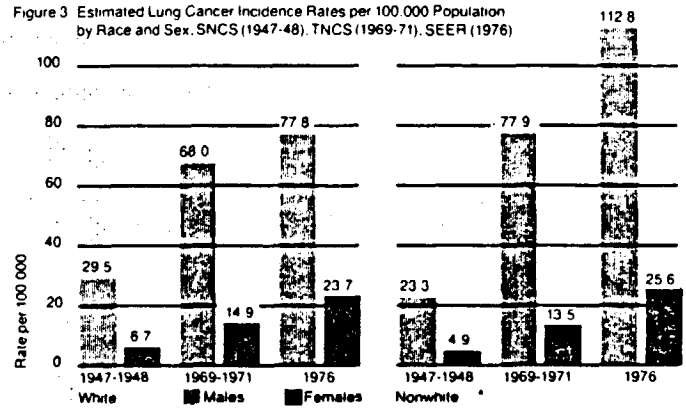
As with all statistical data, several factors will influence the interpretation of these estimates. First, as knowledge about cancer increases, changes occur in medical diagnosis. (There are currently more than 100 known types of human cancer.) Past incidence surveys may have either under or over-reported certain kinds of cancer because of these diagnostic changes.

Second, the survey areas from which data are collected also change with time. For example, two southern cities with large black populations (Atlanta and New Orleans) were added to the SEER network in 1974 and 1976. As a result, the estimates of cancer incidence among blacks from the past surveys cannot properly be compared with the newer data. And as noted earlier, the SEER program adjusts its data to a different standard population than the earlier National Cancer Surveys. These and other methodological differences suggest that the incidence data for 1971-1976 may be somewhat higher than they would be if the pre-1971 techniques were used. Therefore any small increases or decreases should be interpreted cautiously.

Lung

Since 1947 the greatest increase in cancer incidence has been for lung cancer. In 1947, white male incidence was estimated at 30 per 100,000 population. By 1976, this rate had risen to 78, an increase of more than 160 percent (Figure 3).

Figure 3 Estimated Lung Cancer Incidence Rates per 100,000 Population by Race and Sex, SNCS (1947-48), TNCS (1969-71), SEER (1976)



Source Devesa, S.S. and D.T. Silverman, Cancer incidence and mortality trends in the United States: 1935-1974, *J. Natl. Cancer Instit.*, 60(3):545, 1978, Pollack, E.S. and J.W. Horm, Trends in cancer incidence and mortality in the United States, 1969-76, *J. Nat. Cancer Instit.*, 64 (5):1091, 1980

Table 1 Estimated Cancer Incidence Rates per 100,000 Population by Race and Sex, Selected Body Sites, SNCS (1947-48)*, TNCS (1969-71), SEER (1976)*****

Cancer Site	Total	White Males	White Females	Nonwhite† Males	Nonwhite† Females
All Sites Combined					
SNCS	288.9	283.7	305.0	225.6	273
TNCS	277.7	309.0	256.8	330.2	231
SEER		374.0	301.2	452.1	280
Lung					
SNCS	17.6	29.5	6.7	23.3	4
TNCS	39.2	68.0	14.9	77.9	13
SEER		77.8	23.7	112.8	25
Colon					
SNCS	23.8	23.8	26.0	13.7	1
TNCS	26.4	29.0	24.8	22.9	23
SEER		36.9	31.4	37.8	32
Rectum					
SNCS	16.6	20.7	13.9	11.4	12
TNCS	12.2	16.0	9.6	13.0	7
SEER		19.4	11.4	12.6	8
Breast					
SNCS		0.9	73.6	0.2	50
TNCS		0.8	73.3	0.7	53
SEER			83.5		66
Prostate					
SNCS		37.4		43.8	
TNCS		45.2		68.6	
SEER		68.6		107.9	
Bladder					
SNCS	11.3	17.2	7.1	4.8	5
TNCS	11.7	21.3	5.6	9.8	3
SEER		26.4	7.3	13.2	6
Uterus Corpus and Uterus NOS‡					
SNCS			22.9		25
TNCS			23.2		13
SEER			31.2		15
Melanoma					
SNCS	2.7	2.6	3.3	0.6	0
TNCS	4.3	4.8	4.7	0.8	0
SEER		6.8	6.1	1.3	1
Pancreas					
SNCS	7.1	8.9	5.6	9.9	4
TNCS	8.7	10.7	6.5	14.1	8
SEER		11.5	8.0	17.7	11
Kidney					
SNCS	4.0	5.2	2.9	4.8	2.5
TNCS	5.7	8.2	3.8	6.9	3.3
SEER		9.6	4.8	9.0	3.8
Leukemia					
SNCS	7.6	9.0	6.9	9.2	3.0
TNCS	8.4	11.0	6.7	8.7	5.3
SEER		13.1	7.1	9.2	6.1
Uterine Cervix					
SNCS			38.3		74.6
TNCS			15.1		31.3
SEER			10.6		26.4
Stomach					
SNCS	25.2	32.4	17.8	38.6	18.9
TNCS	9.1	12.1	5.8	18.6	7.9
SEER		12.6	5.6	20.3	9.2

*SNCS: Second National Cancer Survey, 1947-1948, rates adjusted to age distribution of 1950 Census population.

**TNCS: Third National Cancer Survey, 1969-1971, rates adjusted to age distribution of 1950 Census population.

***SEER: Surveillance, Epidemiology and End Results, 1976, rates adjusted age distribution of 1970 Census population.

†: Nonwhite rates for SEER program are for black population only

‡: Not otherwise specified.

Source: Devesa, S.S. and D.T. Silverman, Cancer incidence and mortality trends in the United States: 1935-1974, *J. Natl. Cancer Instit.*, 60(3):545, 1978; Pollack, E.S. and J.W. Horm, Trends in cancer incidence and mortality in the United States, 1969-76, *J. Natl. Cancer Instit.*, 64(5):1091, 1980.

, Francisco, and Seattle) and the entire commonwealth of Puerto Rico. New Jersey and New York have also established cancer registries to monitor new cases and cancer deaths, but these data are not included in the SEER reporting system.

The American Cancer Society also publishes annual information on cancer incidence. Using data from the SEER program, the ACS estimates the number of new cancer cases that will occur in each state. These estimates can be misleading, however, because they are not related to a fixed population.

For example, the cover of the ACS report *1980 Cancer Facts and Figures* shows the estimated number of new cancer cases that will occur in each state in 1980. California leads the country with an estimated 76,000 new cases and is followed by New York with 71,000 cases and Pennsylvania with 49,000. Because these estimates are not related to their state populations, it is not clear if cancer occurs more frequently in these states than in others.

When incidence rates are calculated, using state population estimates for 1975*, the order is reversed. Pennsylvania leads with an incidence rate of 413 new cases per 100,000 population, followed by New York with 393 and California with 358 new cases per 100,000.

Cancer death rates are published by the National Center for Health Statistics, the American Cancer Society and the National Cancer Institute. Each of these agencies uses a different standard population for presenting mortality data.

The National Center for Health Statistics collects crude cancer mortality information and adjusts it to the age distribution of the 1940 Census population. Because cancer occurs primarily among older persons, it is important to take into account the proportion of each age group in computing a single death or incidence rate. Age adjusting permits comparisons of rates from different years without the influences of a continuously aging population.

The American Cancer Society uses the information collected by the NCHS and prepares its own analysis of cancer death rates. The ACS also uses these data to estimate the number of cancer deaths that will occur during the following year. But because these cancer death rates are not age adjusted, they are not comparable with the NCHS cancer death rates.

In 1975 the National Cancer Institute published a report, *U.S. Cancer Mortality by County: 1950-1969*. This study calculated cancer death rates for each county in the continental U.S. according to sex and race. These rates were age adjusted to the 1960 Census population, a different standard than that used by

Bureau of Census, *County and City Data Book 1977*, Washington, D.C.: 1978.

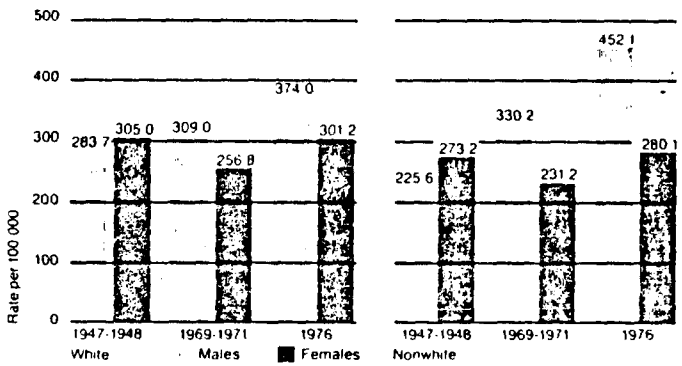
statistics.

U.S. Cancer Incidence*

The American Cancer Society estimates that 785,000 new cases of cancer will be diagnosed in 1980. If current rates prevail, one in four Americans now living will eventually develop cancer, although many will die of other causes. For the 24-year period 1947-1971, the composite age adjusted cancer incidence rate **declined** slightly even though the total number of new cases increased. However, between 1971 and 1976, the most recent period for which data are available, age-adjusted incidence rates have **increased** about 1.3 percent annually.

In general, cancer incidence has decreased among women and persons under the age of 45. Incidence has increased since 1947 among men and among persons 45 and older. Figure 1 shows how the combined cancer incidence rates have changed for men and women during the period 1947-1976. Again, the differences in age adjusting standards for each survey period require caution in drawing any firm conclusions from this information.

Figure 1 Estimated Cancer Incidence Rates per 100,000 Population by Race and Sex. SNCS (1947-48) TNCS (1969-71) SEER (1976)



Source Devesa, S S and D T Silverman Cancer incidence and mortality trends in the United States 1935-1974 *J Natl Cancer Instit* 60(3) 545 1978 Pollack E S and J W Horm Trends in cancer incidence and mortality in the United States 1969-76 *J Nat Cancer Instit* 64 (5) 1091 1980

Some types of cancer occur more frequently than others. Among men, lung cancer is now the most common form followed by prostate and colon-rectum cancers. Among women, breast cancer is the leader followed by colon-rectum and uterine cancers. Figure 2 shows estimates of the proportion of all cancers that occur at each major body site. Table 1 shows the changes in cancer incidence for selected body sites for the period 1947-1976.

*Incidence rates in this section are taken from the 1947-1948 Second National Cancer Survey (SNCS), the 1969-1971 Third National Cancer Survey (TNCS) and the 1976 data of the SEER program

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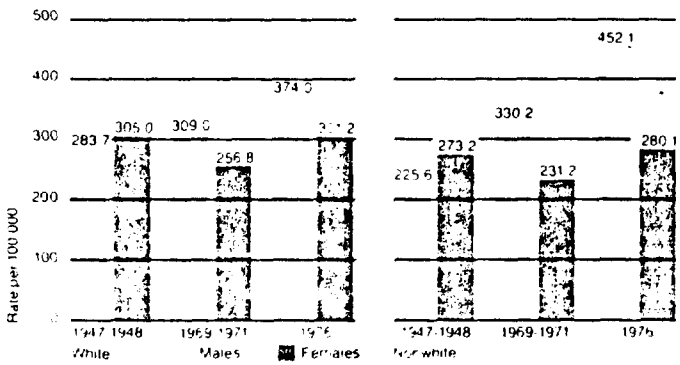

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Cancer and Diet

Bruce N. Ames' remarkable summary (23 Sept., p. 1256) of the evidence that cancer and cardiovascular and other degenerative diseases are of metabolic origin comes as welcome support for the hitherto-little-noticed contentions by Totter (*1*), Handler (*2*), and Fridovich (*3*) that oxygen radicals may be an important proximate cause of cancer.

The thrust of Ames' article would seem to be that cancer is essentially a natural aging process. No matter what we eat, the huge flood of oxygen radicals produced in many metabolic processes overwhelms all but the most heavy external carcinogens, such as tobacco in heavy smokers. To be sure, anticarcinogenic substances are of benefit, but to choose a noncarcinogenic diet would probably be equivalent to starving to death.

The implications of Ames' findings are broad and fall into three categories. First, our preoccupation with small effluents of carcinogens resulting from various industrial processes represents a serious misdirection of resources. This was revealed by Totter in 1980 (*1*), when he showed that overall cancer mortality in 19 countries, when corrected for completing risks, was not correlated with degree of industrialization, as measured by per capita energy use.

Second, the Delaney amendment, which seeks to eliminate the last trace of artificial carcinogen in food, seems to be targeting a tiny part of the carcinogenic burden and ignoring the major carcinogen, the ubiquitous oxygen radical. In short, the Delaney amendment may be based on wrong science and be wrong policy.

Finally, if we concede that cancer, like death itself, is "natural," then our primary focus in cancer research ought to shift far more toward early detection and extirpation of tumors. This, I believe, would require rethinking of the National Cancer Institute's underlying strategy, which at present seems to be dominated by the belief that cancer, unlike death itself, is a preventable disease.

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On page 1260 of his article "Dietary carcinogens and anticarcinogens" Ames refers to "dietary selenium (usually selenite)." The term "selenite" could cause confusion because geologists know the mineral selenite, a variety of gypsum ($CaSO_4 \cdot 2H_2O$) containing no selenium. Ames must be referring to a compound of selenium when he uses the term "selenite." I doubt that the mineral selenite would inhibit tumor or counter the oxidative toxicity of mercuric salts.

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Perhaps the most provocative thing in Ames' provocative article is his placing of the figs in the family Umbelliferae. It is often said that disciplinary crossovers can reinvigorate static fields by bringing new insights unfettered by conventional wisdom. It remains to be seen if Ames' dietary pre- and proscriptions have as much impact on American life-styles as his creative taxonomy is likely to have on the family Moraceae.

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In his article "Dietary carcinogens and anticarcinogens," Ames states (p. 1258) that "high dietary fat is a promoter and a presumptive carcinogen," citing among his references the recent National Academy of Sciences (NAS) report *Diet, Nutrition, and Cancer* (*1*). The NAS report does state that "most of the data suggest that dietary fat has promoting activity"; however, this report does not refer to fat as "a presumptive carcinogen." Rather, the report notes that "there is not enough evidence to warrant the complete exclusion of an effect on initiation."

Ames writes that "the amount of ingested oxidized fat may be appreciable." Neither of the references he cites (*2, 3*), however, provides direct evidence in support of this statement. Shorland *et al.* (*2*) demonstrate that vitamin E supplementation to calves retarded lipid oxidation of some muscle tissue but not others during frozen storage. No estimates are provided regarding how much oxidized fat humans typically ingest. A perusal of *Autoxidation in Food and Biological Systems*, edited by Simic and Karel (*3*), reveals the same facts. There are no direct estimates of the amounts of oxidized fat ingested by humans, and it is well recognized that the unpalatable nature of rancid fats precludes their ingestion in significant quantities.

We strongly disagree with Philip H. Abelson's assertion that "the colon and digestive tract are exposed to many fat-derived carcinogens" (Editorial, 23 Sept., p. 1249). Unsaturated fatty acids in dietary fats are subject to chemical reactions (oxidation, polymerization, hydrolysis) that can occur to a limited extent during deep-fat frying. The extent of these reactions, however, depends largely on frying conditions, principally the temperature, aeration, and duration. Many of the studies used to support the implication that oxidation that can occur during cooking "form[s] mutagens, promoters, and carcinogens" were performed under exaggerated conditions that are unrealistic and not indicative of actual conditions. It is the usual practice of restaurants to discard frying fat when prolonged frying causes excessive foaming of the hot fat or when undesirable flavor or dark color develop. This being the case, Abelson's statements that "rancid fats are possible causative agents of colon and breast cancer in humans" and that "rancid fats should not be part of the diet" are unnecessarily alarming to prudent users of heated fat or other fat-containing products.

In support of the safety of fats heated under more realistic conditions, a 2-year animal feeding study by Nolen *et al.* (*4*) showed that animals consuming used frying fats as the sole source of fat in the diet throughout their life-span thrived as well as control animals consuming the same fat that had not been subject to frying conditions. Furthermore, if "the colon and digestive tract are [truly being] exposed to many fat-derived carcinogens," we should be seeing increasing colon and breast cancer mortality in the United States as a result of the marked increases in vegetable oil (much of it highly unsaturated) consumption since the early 1900's (*5*). In fact, however, data from the American Cancer Society indicate that age-adjusted mortality rates for both colon and breast cancer have remained essentially unchanged since 1940 (*6*).

Ames notes that "[s]ome fatty acids, such as $C_{22:1}$ and certain *trans* fatty acids, appear to cause peroxisomal proliferation because they are poorly oxidized in mitochondria and are preferentially oxidized in the peroxisomes." Data are not accumulating, however, to substantiate such a theory.

Citing the paper of Enig *et al.* (*7*), which has been criticized (*8*), Ames states that "Americans consume about 12 g of *trans* fatty acids a day and a similar amount of unnatural *cis* isomers, . . . mainly from hydrogenated vegetable fats." We believe these estimates of

consumption are excessive and are not supported by reliable data. A more reasonable estimate of consumption of "unusual" *cis* and *trans* positional isomers has been suggested by Emken to be around 9 grams per day (not 24 grams per day, as suggested by Enig *et al.*) or about 6 to 8 percent of total fatty acid intake (*9*). When one considers that the fatty acid composition of adipose tissue reflects that of the diet and that a range of from 2.0 to 5.8 percent *trans* fatty acids has been reported in human adipose tissue (*10*), an adult male consuming his recommended dietary allowance of 2700 calories per day (*11*) of a diet providing 40 percent of the calories as fat would ingest around 2.4 to 7 grams of *trans* fatty acids per day.

Contrary to the disputed hypotheses of Enig *et al.* (*7*), there are no reliable data relating *trans* fatty acids to tumor development. A study by Brown (*12*) not cited by Ames indicated no unusual incidence of tumors in mice treated with dimethylhydrazine (or with saline) and then fed a diet high in *trans* fatty acids for 17 months.

Finally, Ames mentions the disagreement between the NAS report (*1*) and a critique of this report (*13*) by the Council for Agricultural Science and Technology (CAST) on the appropriateness of recommending reduced fat consumption to the American public. In doing this, he indirectly quotes the CAST report as saying that, "until we know more . . . about which types of fats are dangerous, it is premature to recommend dietary changes" (*13*). However, the CAST report does not state that certain "types of fats are dangerous." We believe there are insufficient reliable data to justify the suggestion that certain fats in the current American diet represent a substantial cancer risk.

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We commend Ames for his review of natural dietary toxins, but not for concluding that, rather than reducing exposure to environmental and occupational carcinogens, "dietary practices are the most promising area to explore" for reducing cancer risks. Ames' article, moreover, is flawed by substantial errors, omission of relevant data, and reliance on tenuous hypotheses. These limitations are more significant in view of the major public health implications of Ames' article and the accompanying editorial by Abelson, press release, and publicity in the mass media.

Ames' position that there is no evidence for generalized recent increases in U.S. or U.K. cancer rates, other than for cancers attributed to tobacco, is based on epidemiological analyses that, with tenuous justification, exclude people over the age of 65 and also blacks of all ages and attribute a near exclusive tobacco etiology to cancers of various organs in addition to the lung (*1*). In fact, overall cancer rates have increased sharply since 1970 (*2*). Incidence and mortality rates in the United States, age standardized to 1970, have risen sharply since the late 1960's particularly for persons over 60, blacks of all ages, and a wide range of occupational subgroups (*2–4*). From 1969 to 1976, mortality rates increased for white and black males by 8 percent and 17 percent, respectively, and for white and black females by 4 percent and 6 percent, respectively. While this increase was pronounced for lung cancer—21 percent and 32 percent for white and black males, respectively, and 74 percent and 56 percent for white and black females, respectively—increases also occurred in other organs, including, for whites, the prostate (11 percent), male and female kidney (5 percent), and female breast (4 percent); sharper increases were noted for less common cancers, including those of brain, liver, esophagus, and multiple myeloma. Incidence rates rose more rapidly than mortality on an overall basis and for cancers of various organs, such as the colon, bladder, kidney, skin (melanoma), uterus, female breast, and prostate, besides lung (*2*); for whites, cancers of sites other than the lung accounted for approximately 70 percent of the increase. The most recent data show persistence of these trends through 1980 (*5*). These trends are consistent with the theory that past exposure to industrial carcinogens, whose production have increased exponentially since the 1940's, are responsible for recently increasing cancer burdens (*3, 4*).

The assertion that smoking is responsible for essentially all lung cancer, and thus accounts for almost all recent increases in cancer rates, is negated by substantial evidence (*3*), including (i) the more than doubling of lung cancer rates among nonsmokers over the last two decades, with the proportion of these cancers in nonsmokers approaching 20 percent (*3, 6*); (ii) the sharply increasing incidence of adenocarcinoma of the lung, which is less closely related to smoking than are squamous and oat cell carcinomas (*7*); (iii) over the last three decades (*8*), the decline in the proportion of smoking males and the tar content of cigarettes, while lung cancer mortality increased at a rate that cannot be accounted for by cohort effects; (iv) the strong positive associations, largely independent of smoking habits, between lung cancer and exposure to a wide range of occupational carcinogens, including vinyl chloride, mustard gas and chloromethylmethylether, and carcinogenic processes, such as copper smelting and uranium, zinc, and lead mining (*3, 4*); (v) lung cancer rates in black men that are now about 40 percent higher and have been increasing more rapidly than in whites over the last 30 years, although blacks smoke less and start smoking later in life (*4, 9*); (vi) lung cancer rates that are almost equal in white and black women, although the proportion of whites smoking more than one pack a day is twice that of blacks (*9*); (vii) a threefold increase in lung cancer rates among women between 1950 and 1975, a steeper increase than could be accounted for by the modest rise in their smoking prevalence (*8*); (viii) the major geographic variations in mortality rates due to cancers of the lung (besides other organs) that have been associated with workplace and community air pollution (*10*) and are not explainable by differences in smoking patterns; (ix) the shift of the highest lung cancer rates from northeastern to southeastern and southcentral states after World War II industrialization of the South; and (x) the divergent trends and directions observed between cancers of the lung, on the one hand, and, on the other hand, of other organs, including the esophagus, buccal cavity, and pharynx (*4*), which have also been strongly associated with cigarette smoking (*1*). These considerations in no way

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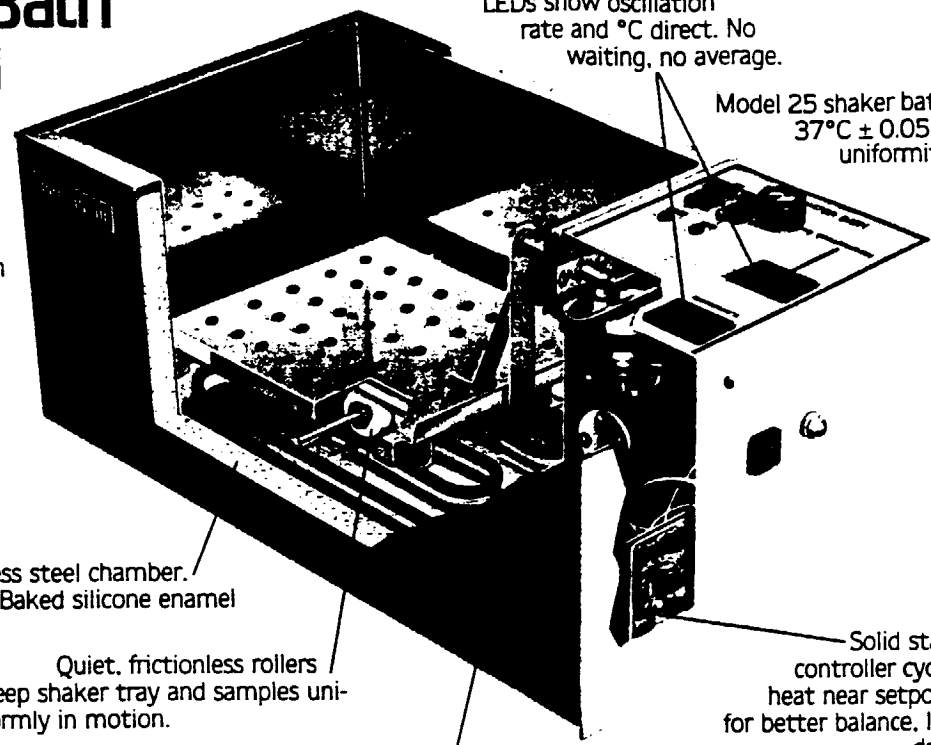

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detract from the critical importance of tobacco as a major cause of preventable disease and death.

In his statement that high-dose exposure to occupational carcinogens "*might* also turn out to be important for particular groups of people" [emphasis added], Ames does not acknowledge the substantial literature on occupational cancer. According to a 1978 federal estimate, occupational exposure just to asbestos and five other carcinogens could, on a worst case basis, account for 18 to 38 percent of all male cancers in coming decades (*11*). Even outspoken critics of these estimates, whose analyses Ames cites, concede that "the minimum proportion of all current cancer deaths attributable to occupation can hardly be less than 2% or 3%" (*1*), 4000 to 6000 male deaths per annum. Asbestos and coke plant workers both have lung cancer rates five to ten times those of appropriate controls (*11*). Some 10 million workers are now potentially exposed to 11 "high volume human carcinogens," and there are major excesses of cancers throughout a wide range of occupational groups, including oil refinery and petrochemical workers, rubber and tire workers, welders and metal-trades workers (*4*), and atomic plant workers (*12*). These studies are all the more important as two- to fivefold excesses in cancer rates have generally been necessary before they could be detected by standard epidemiological techniques (*13*).

Contrary to Ames, substantive studies have documented the carcinogenic effects of urban air pollution or some related urban factor. Accordingly, the World Health Organization concluded that "it is probable that some urban atmospheric factor is involved [in the etiology of lung cancer], resulting from the air pollution from car exhausts, fumes from heating systems and industrial fumes" (*14*); automobile exhaust contains a wide range of carcinogens, many common to tobacco smoke. In addition, many epidemiological studies have documented large geographical variations in standardized cancer mortality rates, on an overall and organ-specific basis, with higher rates in communities located near smelters, petrochemical plants and facilities producing nuclear weapons, and in communities with high levels of atmospheric pollution (*10, 15*); definitive epidemiological evidence of carcinogenic and reproductive hazards from proximity of residence to hazardous waste landfills or industrial impoundments is not yet available, although preliminary data from sites such as Woburn, Massachusetts, are highly suggestive (*16*).

Ames dismisses the possibility that carcinogenic synthetic pesticides, marketed since the 1940's, may contribute substantially to cancer rates, as their dietary intake is claimed to be 10,000 times lower than that of age-old "nature's pesticides." There is, however, much evidence to the contrary. For example, a number of widely used chlorinated hydrocarbon pesticides have accumulated by many orders of magnitude in certain foods to levels comparable to those inducing cancer in small groups of experimental animals (*17*). Chub and trout in Lake Michigan have been found with aldrin and dieldrin residues above 0.3 part per million, and similar residues of chlordane and heptachlor have been found in the Great Lakes and in Long Island and New York City lakes; in 1983 Montana health officials warned against eating game contaminated with concentrations of heptachlor epoxide more than 100 times the Environmental Protection Agency's (EPA's) "acceptable intake level." Aldrin and dieldrin were found to be carcinogenic at dietary concentra-

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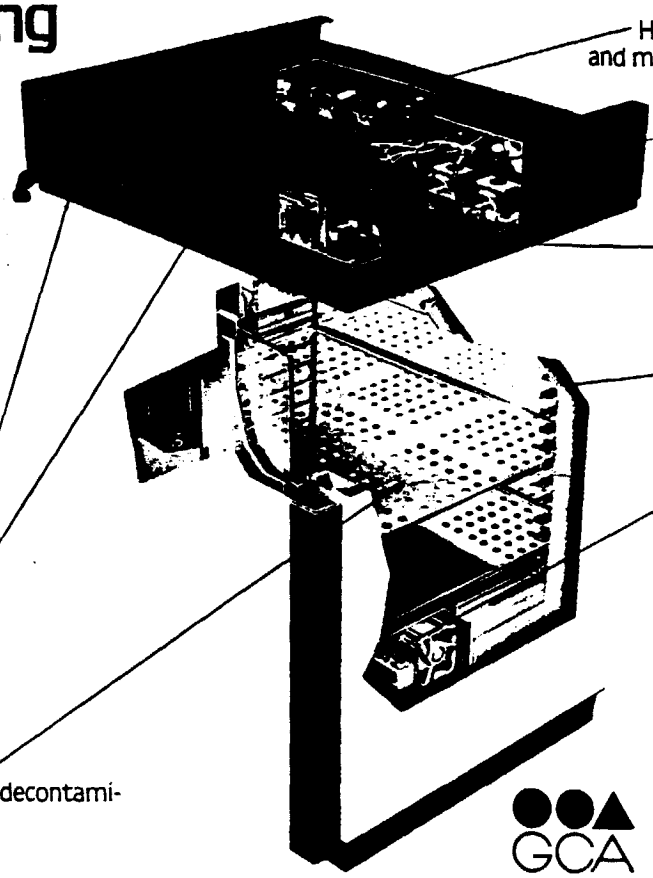

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tions of between 0.1 and 20 parts per million in five separate rodent bioassays, and residues of chlordane and heptachlor have been found in concentrations in human fat similar to those found in rats in whom carcinogenic effects had been induced by these pesticides (*18*). By all principles of extrapolation, such exposures would be expected to result in a significant excess of human cancers. The widespread use of chlordane and heptachlor for termite treatment represents additional major carcinogenic exposures. Indoor chlordane concentrations greater than an arbitrary interim guideline of 5 micrograms per cubic meter have led to the evacuation of more than 1500 contaminated homes at Air Force bases across the country (*19*) and to the petition by a New York State citizens' group, after the finding in April 1983 that 63 percent of 443 treated homes were contaminated, to ban the use of chlordane for termite treatment. Exposure to 5 micrograms per cubic meter of chlordane, approximately 50 micrograms per day for an average adult, according to EPA extrapolations that considerably underestimate risk for several reasons, including neglect of high-dose flattening, would be expected to increase lifetime cancer risks by as much as 0.1 to 0.5 percent (*20*).

Ames' position on the significance of dietary burdens of carcinogenic synthetic pesticides is not supported by recent data on ethylene dibromide (EDB) residues, with concentrations up to 5000 parts per billion in flour and citrus pulp. EPA estimated, again using procedures that minimize risk, that lifetime exposures to "realistic worst case" dietary concentrations of 31 parts per billion of EDB would result in cancer risks of from 10^{-4} to 10^{-3} (*21*), about 300 to 3000 deaths per year; occupational risks were estimated to be as high as 40 percent. Ames has also objected to the regulation of EDB, saying that the "trace of the carcinogen EDB now allowed in food is insignificant" (*22*); this in spite of the fact that available noncarcinogenic alternatives include aluminum phosphide for grains and cold storage for fruits and vegetables.

The minimal references by Ames to problems of poorly regulated exposures to a wide range of environmental and occupational carcinogens are in contrast to his exaggerated emphasis of the roles of high-fat and low-fiber diets and of charred foods as "major risk factors," although evidence for such risks, where not negative, is generally inconclusive. A recent report concludes that "in the only human studies in which the total fiber consumption was quantified, no association was found between total fiber consumption and colon cancer" (*23*). The position that high fat consumption is a major cause of breast and colon cancer is based on experimental and epidemiological studies (*1*, *24*). However, this evidence is weak and inconsistent (*3*, *25*). There appear to be no data on the correlation between the proportion of fat in the diet, the critical variable examined in the animal experiments, and rates of colon and breast cancers on a nation-by-nation basis; while those rates are strongly correlated with absolute fat consumption, this correlation is equally good with other measures of industrialization, such as per capita energy production (*3*). Moreover, up to 20-fold increases in dietary fat were generally necessary to increase tumor yields in rodents after the administration of carcinogens, whereas between-country differences in total fat consumption are generally less than a factor of 2 (*3*). Finally, no evidence was found in two major case control studies of an associa-

tion between fat consumption and breast cancer rates (*26*). These considerations do not denigrate the importance of a prudent diet in the promotion of health nor the need for research in this area which could lead to future cancer prevention strategies; a low-fat and high-fiber diet not only decreases intake of fat-soluble synthetic carcinogenic contaminants but also reduces risks of cardiovascular disease and diverticulitis.

Evidence on the qualitative and quantitative significance in generalized diets of Ames' examples of "nature's pesticides" and on their carcinogenicity is unimpressive. For instance, conclusions about the carcinogenicity of pepper are based on the results of a single questionable study (*27*), and the inference that mushrooms are carcinogenic is based on the identification in certain mushroom extracts of unstable diazonium compounds that are carcinogenic in mice only after artificial in vitro stabilization.

The implicit identification of mutagens with carcinogens, the implication of an identity in their underlying mechanisms, the blurring of the distinction between different types of mutagens, the identification of quantitative mutagenicity with the results of Ames' bacterial assay, and the derivation of carcinogenic potency from quantitative mutagenicity data are all of questionable validity (*28*). Many mutagens are inactive in carcinogenesis tests, and many carcinogens are inactive in short-term tests for mutagenicity (*29*); glutathione is positive in the Ames test (*30*), although Ames recognizes it as an anticarcinogen and an antimutagen. Furthermore, recent evidence has suggested that gross mutagenic events, such as chromosome translocations, are more likely to be crucial in carcinogenesis than are the point mutations or deletions detected in the Ames assay (*28*). Moreover, while somatic mutations are likely to be involved in carcinogenesis, epigenetic events also appear critical.

Ames' discussion of free radicals and the potential anticarcinogenic effects of antioxidants is speculative and of dubious relevance. Even one of the authors cited in support of the thesis that carotenoid antioxidants are protective in smokers has admitted that various studies revealed only "a slightly lower than average incidence of cancer among people with above average intake of β-carotene" and that even this slim association may be artifactual (*31*). A recent large-scale case control study (*32*) produced no evidence "relating intake or serum levels of antioxidant vitamins to a reduced cancer risk."

Evidence for major carcinogenic effects of trace natural components of U.S. diets is speculative. Strategies based on this hypothesis offer little hope for cancer prevention, and the hypothesis affords no basis for Ames' trivializing the importance of reducing exposure to occupational and other environmental carcinogens. Understandably, such strategies are applauded by corporations resisting regulation of their carcinogenic products and processes and seeking, with others, to explain away cancer causation largely in terms of diet and faulty life-style (*1*). Strangely, Ames' current proposals appear at variance with his strongly argued recent positions (*33*). These include warnings that EDB is "a potent carcinogen" whose presence as an impurity in tris-BP [tris (2,3-dibromopropyl) phosphate] is one of the reasons why this flame retardant "should not be used"; that there are "enormous possible [carcinogenic] risks" from inadequately tested industrial chemicals, such as flame retardants; that a "steep increase in the human cancer rate from [industrial] chemicals may soon occur . . . as the 20- to 30-year lag time for chemical carcinogenesis in humans is almost over"; that "tens of thousands of man-made chemicals have been introduced into the environment in the last few decades—with widespread human exposure—to low but disturbing doses of these carcinogens" and that such chemicals should be tested for mutagenicity and carcinogenicity; and that priorities must be established to "minimize human exposure to these chemicals" (*33*). Clearly there is substantial evidence that, besides smoking, involuntary exposures to occupational and industrial environmental carcinogens are major and generally avoidable contributors to the burgeoning national cancer burden and to a wide range of other chronic diseases. Vigorous public health measures are essential to reduce such exposures.

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Weinberg and I are in agreement that cancer and heart disease appear to be in large part degenerative diseases of old age, that oxygen radicals generated during normal metabolism are likely to be major contributors to this aging process, and that it is unlikely we are going to eliminate them. I also agree that Fridovich, Totter, and Handler have made major contributions to the field.

We also agree that every meal contains natural carcinogens, and it is unlikely we are going to eliminate all of them. However, I do not think that this knowledge makes it any less important to work toward cancer prevention. By identifying smoking as a major cause of lung cancer and heart disease, we have furnished people with the knowledge that they can live 8 years longer on average by not smoking heavily. The incidence of stomach cancer is high in Japan and low in the United States, while colon and breast cancer incidence are high in the United States and low in Japan. This may be due to a limited number of dietary components, and if we could identify them, we might be able to prolong the life span of the people affected in both countries. Understanding some of the main causes of cancer may be the first step in preventing cancer, and although causes and mechanisms are complex, with more knowledge we should be able to sort out some of the major risks in our diet and intervene in many ways, both to minimize significant carcinogens and to maximize anticarcinogenic defenses. I also agree that the preoccupation with tiny amounts of man-made pollution has been blown up out of proportion.

Ingmanson rightly points out that selenite is another name for the crystalline form of the mineral gypsum ($CaSO_4 \cdot 2H_2O$). The etymology is from the Greek for moonstone, "probably an allusion to the soft moon-like reflection of light from some of its faces" (*1*). The selenite I meant is the SeO_3^{2-} anion (analogous to sulfite and tellurite). The name of the element selenium is also derived from the Greek word for moon, selene. Selenite also means "a supposed inhabitant of the moon" (*2*); presumably there will not be any confusion with this last meaning.

Hunter says that "there are insufficient reliable data to justify the suggestion that certain fats in the current American diet represent a substantial cancer risk." The situation is confusing because there are so many types of fat and the evidence so far does not prove cause and effect. I referenced the considerable epidemiological literature associating high fat consumption with colon and breast cancer and the considerable body of animal experiments implicating high fat with cancer. The National Academy of Sciences committee (which also reviewed the field), and more recently the American Cancer Society, have advised the American public that it would be prudent to reduce their fat intake to lower cancer risk. It was important to point out the controversy as to where prudence begins and to mention the disagreements with this view. Recent reviews on nutrition and cancer also discuss fat (*3*). Most scientists would emphasize that the evidence linking fat to cancer is much less secure than that implicating cigarettes, alcohol, or asbestos with cancer. I had hoped that a discussion of plausible molecular mechanisms for a fat-cancer connection might provide some testable hypotheses. I discussed cyclopropenoid fatty acids, rancid fat, and peroxisome oxidation of certain fats. Newmark *et al.* (*4*) and Welsch and Aylsworth (*5*) have other explanations. All of these mechanisms are plausible, but we do not know which, if any, are correct.

Fat rancidity products in the diet still appear to be a possible source of mutagens and carcinogens that could contribute to colon and breast cancer. I listed in my article some of the carcinogenicity and mutagenicity data on the variety of hydroperoxides, enals, epoxides, and other reactive chemicals produced by the rancidity reaction. Appreciable amounts of lipid oxidation products may exist in palatable food. For example, Tsai *et al.* (*6*) have found significant amounts of cholesterol epoxide (a mixture of α and β) in commercial dried eggs, scrambled egg mix, and dried whole egg products containing additives, each averaging about 20 parts per million (ppm), although some samples reached eight times this. Cholesterol epoxide is a weak alkylating agent, induces sarcomas at the injection site in rats and mice, is positive in a sister chromatid exchange test, transforms hamster embryo cells, induces chromosome damage in human fibroblast cultures, and is mutagenic in hamster cells (*7, 8*). Concentrations in human breast fluid, prostate secretions, or serum samples from particular people can be enormous (*8, 9*), although it is not clear whether the source is endogenous oxidation or the diet. We need more research on the extent of epoxide destruction by the acid in the stomach. In addition, lipid hydroperoxides are present in heated fat that is reused. A number of hydroperoxides have been shown to be mutagens and carcinogens, and others are likely to be, due to their generation of oxygen radicals. I discussed ionizing radiation as a mutagen-carcinogen that is active because it generates oxygen radicals, and I also referred to the carcinogenicity of hydrogen peroxide and fatty acid hydroperoxides. Even a small amount of oxidation (for example, a peroxide number as low as 2) which could be found commonly in cooking oil in restaurants and in fat (*10*), would represent a level of 1200 ppm (if it were a triglyceride hydroperoxide). Meat can also have a fair amount of rancidity. I mentioned Shorland's article (*11*) because it reviews some of the literature on rancidity in meat: "In contrast to fresh intact meat, cooked and uncooked ground meat becomes rancid within 48 hours at 4°C. . . . This phenomenon has been described . . . as 'warmed over' flavor. . . ." Rancidity products (as measured by malondialdehyde reaction) were found to be increased in ground meat stored in the refrigerator and in the urine of people who consumed the meat (*12*). I gave references to both sides of the trans fatty acid controversy, and I find Hunter's additional comments useful.

The letter from Epstein and his cosignatories implies that my inquiry into natural dietary carcinogens and anticarcinogens trivializes the importance of reducing exposure to the carcinogens of occupation and pollution and that, therefore, I am aiding the corporations, which Epstein *et al.* imply are the true causes of cancer. They also criticize me for changing my mind and seem to misunderstand the chief purposes of my article. One way in which biology advances is by the formulation of new hypotheses which can then be tested and either rejected, accepted, or (more commonly) modified and converted into the next generation of more specific and more testable hypotheses. It is through this process that scientists change their minds, which is, in fact, desirable. I was prompted to write the article in order