LETTERS

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.

ALVIN M. WEINBERG
Institute for Energy Analysis, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, Tennessee 37830

References and Notes

1. J. R. Totter, *Proc. Natl. Acad. Sci. U.S.A.* **77**, 1763 (1980).
2. P. Handler, dedication address presented at the Northwestern University Cancer Center, Evanston, Ill., 18 May 1979.
3. I. Fridovich, *Science* **201**, 875 (1978); subsequent personal communication.

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.

DALE E. INGMANSON
Department of Natural Science, College of Sciences, San Diego State University, San Diego, California 92182

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.

ARTHUR M. SHAPIRO
Department of Zoology, University of California, Davis 95616

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.

J. EDWARD HUNTER
Biological Subcommittee,
Institute of Shortening and Edible Oils,
Inc., 1750 New York Avenue, NW,
Washington, D.C. 20006

References

1. National Research Council, *Diet, Nutrition, and Cancer* (National Academy Press, Washington, D.C., 1982).
2. F. B. Shorland *et al.*, *J. Agric. Food Chem.* **29**, 863 (1981).
3. M. G. Simic and M. Karel, Eds., *Autoxidation in Food and Biological Systems* (Plenum, New York, 1980).
4. G. A. Nolen *et al.*, *J. Nutr.* **93**, 337 (1967).
5. R. M. Marston and S. O. Welsh, *Natl. Food Rev.* **21**, 17 (1983).
6. American Cancer Society, *Cancer Facts & Figures—1983* (American Cancer Society, New York, 1982).
7. M. G. Enig *et al.*, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **37**, 2215 (1978).
8. T. H. Applewhite, *ibid.* **38**, 2435 (1979); J. C. Bailar III, *ibid.*, p. 2435; W. H. Meyer, *ibid.*, p. 2436.
9. E. A. Emken, *J. Am. Oil Chem. Soc.* **58**, 278 (1981).
10. J. B. Ohlrogge *et al.*, *J. Lipid Res.* **22**, 955 (1981).
11. Food and Nutrition Board, *Recommended Dietary Allowances* (National Academy of Sciences, ed. 9, Washington, D.C., 1980).
12. R. R. Brown, *Cancer Res.* **41**, 3741 (1981).
13. Council for Agricultural Science and Technology, *Diet, Nutrition, and Cancer: A Critique* (Special Publication 13, Council for Agricultural Science and Technology, Ames, Iowa, 1982).

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

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-

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.

SAMUEL S. EPSTEIN
JOEL B. SWARTZ*
Department of Preventive Medicine and Community Health, University of Illinois Medical Center, Chicago 60680

*Cosignatories: Eula Bingham, University of Cincinnati Medical School; Donald Dahlsten, University of California, Berkeley; Susan Daum, Albert Einstein College of Medicine, New York; John Gofman, University of California, Berkeley; Robert Harris, Princeton University; Joseph Highland, Princeton University; Ruth Hubbard, Harvard University; Marvin Legator, University of Texas Medical Branch, Galveston; Kenneth Miller, Oil, Chemical and Atomic Workers, Washington, D.C.; Rafael Moure and Michael Silverstein, International Union, United Auto Workers, Detroit, Michigan; Glenn Paulson, National Audubon Society, New York; Marvin Schneiderman, Bethesda, Maryland; Joseph Wagoner, Springfield, Virginia; George Wald, Harvard University; and Bailus Walker, Commonwealth of Massachusetts.

References

1. R. Doll and R. Peto, *J. Natl. Cancer Inst.* **66**, 1191 (1981).
2. *Trends in Mortality 1971–1975* (Series DH1, U.K. Office of Population Censuses and Surveys, London, 1978), No. 3; E. Pollack and J. Horm, *J. Natl. Cancer Inst.* **64**, 1091 (1980).
3. S. S. Epstein, *The Politics of Cancer* (Anchor, New York, 1979); S. S. Epstein and J. B. Swartz, *Nature (London)* **289**, 127 (1981).
4. D. L. Davis, K. Bridbord, M. Schneiderman, *Teratogen. Carcinogen. Mutagen.* **2**, 105 (1982).
5. E. Sondik (National Institutes of Health), personal communication to Congressman J. Conyers.
6. J. Enstrom, *J. Natl. Cancer Inst.* **62**, 755 (1979).
7. C. Harris, *Cancer Chemother. Rep.* **4**, 59 (1973), part 3; E. Wynder and S. Stellman, *Cancer Res.* **37**, 4608 (1977); J. Wagoner, P. Infante, D. Bayliss, *Environ. Res.* **21**, 15 (1980).
8. *Smoking and Health: A Report of the Surgeon General* (Government Printing Office, Washington, D.C., 1979); J. Harris, *J. Natl. Cancer Inst.* **71**, 473 (1983).
9. *Advance Data from Vital and Health Statistics of National Center for Health Statistics* (No. 52, Department of Health, Education, and Welfare, Washington, D.C., 19 September 1979); *Health United States* (No. [PHS] 83-1232, Department of Health and Human Services, Washington, D.C., December 1982).
10. J. Mason and F. McKay, *Atlas of Cancer Mortality for U.S. Counties: 1950–1969* (Department of Health, Education, and Welfare, Washington, D.C., 1975); *Atlas of Cancer Mortality for U.S. Counties among U.S. Non-Whites* (Department of Health, Education, and Welfare, Washington, D.C., 1976); W. J. Blott, L. A. Brinton, J. F. Fraumeni, Jr., B. J. Stone, *Science* **198**, 51 (1977); B. Carnow, *Environ. Health Perspect.* **22**, 17 (1978); L. S. Robertson, *ibid.* **36**, 197 (1980).
11. K. Bridbord *et al.*, "Estimates of the fraction of cancer in the United States related to occupational factors" (National Cancer Institute, National Institute of Environmental Health Sciences, and National Institute for Occupational Safety and Health, Washington, D.C., 1978).
12. G. W. Kneale, T. E. Mancuso, A. M. Stewart, *Br. J. Ind. Med.* **38**, 156 (1981).
13. J. Stellman and S. Stellman, paper presented at the annual meeting of the American Society for Preventive Oncology, Chicago, Ill., 6 and 7 March 1980.
14. U. Mohr, D. Schmahl, L. Tomatis, *IARC (Int. Agency Res. Cancer) Sci. Publ. 16* (1977).
15. C. Johnson, paper presented at the AAAS Annual Meeting, Washington, D.C., 1982.
16. S. W. Lakagos, B. J. Wessen, M. Zelen, unpublished manuscript.
17. Office of the General Counsel, Environmental Protection Agency, "Respondent's brief, proposed findings, and conclusion on suspension" in re Shell Chemical Company *et al.*, Consolidated Aldrin/Dieldrin Hearing (FIFRA Dockets 145 *et al.*, Washington, D.C., 16 September 1974); S. Epstein, *Sci. Total Environ.* **4**, 1 (1975).
18. Office of the General Counsel, Environmental Protection Agency, "Respondent's final brief" in re Velsicol Chemical Corporation *et al.*, Chlordane and Heptachlor (FIFRA Docket 384, Washington, D.C., 8 December 1975); S. Epstein, *Sci. Total Environ.* **6**, 103 (1976).
19. *An Assessment of the Health Risks of Seven Pesticides Used for Termite Control* (National Academy Press, Washington, D.C., 1982).
20. *Ambient Water Quality Criteria for Chlordane* (Environmental Protection Agency, Washington, D.C., 1980).
21. "Ethylene dibromide: Position document 2/3" (Environmental Protection Agency, Washington, D.C., 1980).
22. B. Ames, *Wall Street J.*, 14 February 1984, p. 30.
23. *Diet, Nutrition, and Cancer* (National Academy Press, Washington, D.C., 1982), pp. 8–5.
24. B. Armstrong and R. Doll, *Int. J. Cancer* **15**, 617 (1975).
25. J. Berg, in *Persons at High Risk of Cancer: An Approach to Cancer Etiology and Control*, J. Fraumeni, Jr., Ed. (Academic Press, New York, 1975), pp. 201–224; K. Carroll, *Cancer Res.* **35**, 3374 (1975).
26. R. Phillips, *Cancer Res.* **35**, 3513 (1975); A. B. Miller *et al.*, *Am. J. Epidemiol.* **107**, 499 (1978).
27. J. M. Concon, D. S. Newburg, T. W. Swerczek, *Nutr. Cancer* **1**, 22 (1979).
28. I. Weinstein, M. Wigler, C. Pietropaolo, in *Origin of Human Cancer*, H. Hiatt, J. Watson, J. Winston, Eds. (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1977), pp. 751–

772; I. Weinstein *et al.*, in *Carcinogens: Identification and Mechanisms of Action*, A. Griffin and C. Shaw, Eds., (Raven, New York, 1979), pp. 399–418; H. Rubin, *J. Natl. Cancer Inst.* **64**, 995 (1980); J. Cairns, *Nature (London)* **289**, 353 (1981); R. Sager, *Chromosome Mutation and Neoplasia* (Liss, New York, 1983), p. 333.
29. S. J. Rinkus and M. S. Legator, *Cancer Res.* **39**, 3289 (1979).
30. H. Glatt, M. Protić-Sabljić, F. Oesch, *Science* **220**, 961 (1983).
31. R. Peto, R. Doll, J. D. Buckley, M. B. Sporn, *Nature (London)* **290**, 201 (1981).
32. W. C. Willett *et al.*, *N. Engl. J. Med.* **310**, 430 (1984).
33. A. Blum and B. N. Ames, *Science* **195**, 17 (1977); B. N. Ames, *ibid.* **204**, 587 (1979).

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

to draw together five areas of research:

1) The standard epidemiological view that dietary factors may be important in the etiology of certain types of cancer (*3, 13, 14*).

2) The awareness that increasing numbers of *natural* products are being identified as carcinogens in rodent studies and the realization that many of these compounds are present in very large amounts in the diet relative to the amounts of man-made carcinogens.

3) The finding in recent years of a large number of mutagens formed on cooking food and also among the group of natural pesticides present in plants and molds, many of which appear in the human diet in large amounts. A number of these mutagens have now been tested and shown to cause cancer in laboratory animals. These mutagenicity findings may be much more representative of the dietary hazards to which humans are exposed than the findings of animal cancer tests, in which very few chemicals are examined each year, almost all of which are man-made.

4) The relation between cancer and aging in animals of widely different life spans, such as rodents and humans, suggesting that cancer is a degenerative disease of old age. Of relevance to aging is the recent interest in the generation of oxygen radicals, a destructive process in normal metabolism, which leads to DNA damage and other damage in cells and could be a major force in both aging and cancer. Also relevant are the contributions of the radiobiologists who have demonstrated that the oxygen radicals produced by radiation appear to account for a good part of its mutagenicity and carcinogenicity.

5) The finding by many cancer researchers that a variety of nutritional factors can have a marked anticarcinogenic effect in rodents (for example, an azo dye gives 90 percent of the rats cancer, but only 14 percent of the animals get cancer if 4 ppm of a selenium-containing salt is added to the diet) (*15*). Many of the substances found to be anticarcinogenic in rodent experiments, such as selenium, β-carotene, vitamin E, and ascorbate, are components of our normal antioxidant defenses. Many epidemiological studies now implicate dietary factors as being possibly protective against cancer, with some evidence pointing toward antioxidants such as selenium and β-carotene.

I restricted my article to *dietary* carcinogens and anticarcinogens because, as I stated, "whether or not any recent changes in lifestyle 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." In addition, I felt that there were certain unifying concepts in this area. I was not addressing future risks or that fraction of cancer today which might be caused by viruses, hormones, occupation, or pollution. I was not attempting to belittle these areas, as these and other causes are of concern (*13, 14, 16*). Doll and Peto (*13, 16*), for example, ascribe to occupational factors about 12 percent of all lung cancer deaths, plus a smaller percentage of other cancer deaths (totaling about 4 percent of all cancer deaths), and the emergence of such factors may have contributed to certain cancer trends—for example, over the last few decades the annual number of asbestos-induced U.S. lung cancer deaths has risen from perhaps a few hundred to perhaps a few thousand and is likely to continue to increase for some time yet. This increase is caused by the delayed effects of past heavy exposures and not the present asbestos levels, which are much reduced. Whether occupation causes about 4 percent of current cancer, as indicated by Doll and Peto and other leading epidemiologists (*13, 16*), or even double that, is irrelevant to my article. As indicated by Epstein *et al.*, I have previously advocated, and still do, vigilance in the area of man-made carcinogens and mutagens stemming from occupation and pollution (*17*).

Epstein and his cosigners state that a generalized increase in cancer not related to tobacco is in progress, even though the most distinguished epidemiologists who have studied the available data on national trends have come to exactly the opposite conclusion. The question of trends appears to have arisen because, in arguing that some important determinants of cancer are likely to await discovery among long-established aspects of the American way of life, I noted that "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," a conclusion that I drew after discussing the work of Doll and Peto (*13*) with many leading epidemiologists. If lung cancer is not included, the overall cancer death rates have declined, not only according to Doll and Peto (*13, 16*), who, incidentally, did evaluate blacks and people over 65 (*13*, p. 1272), contrary to Epstein's statement, but also according to both the American Cancer Society (*18*) and the recent thorough study by the Environmental Protection Agency and the National Cancer Institute (NCI) of three decades of cancer (*19*). The recent NCI SEER data (*20*) also show no convincing evidence of any increases in the major cancers except for lung cancer, while liver, stomach, and uterine cervix cancer are declining. The argument by Epstein *et al.* for an increase is based on earlier and superseded SEER data.

The statements by Epstein *et al.* that 20 percent of lung cancer cases occur in nonsmokers and that lung cancer is increasing in this group both appear to be incorrect. Two recent representative studies of the very high lung cancer areas of South Louisiana and the petrochemical area near Houston show that only about 3 to 6 percent of lung cancer patients are people who have never smoked (*21*). The arguments by Epstein *et al.* about blacks and lung cancer are not supported by these studies; for example, for black males in South Louisiana, 97.6 percent of the lung cancer patients were smokers or ex-smokers, while the figure for white males was 97.7 percent. The study in Louisiana also showed a sizable modifying factor of diet: smokers who rarely ate fresh fruits and vegetables had a 30 percent higher risk from lung cancer for a given amount of smoking, in agreement with the results of Hirayama (*22*) in Japan on the influence of diet on cancer induced by cigarette smoking, which I quoted. There is no good evidence for any appreciable increase in lung cancer in nonsmokers (*23*): The conclusion by Epstein *et al.* is based on an earlier, flawed (*13*) study.

Thus, only one major cancer rate, that of lung cancer, is increasing, and this appears to be largely attributable to smoking; the rates of liver, stomach, and uterine cervix cancer are decreasing. Breast and colorectal cancer rates (both associated with high fat) have been fairly constant for decades. Some less common types of cancer are becoming more prevalent, but the causes still have to be determined. We cannot assume that these are due to occupation or pollution, although some may turn out to be. In the case of esophageal cancer in blacks, for example, an epidemiological investigation by NCI implicated high alcohol consumption as a major risk factor and a good diet as a protective factor (*24*).

The most authoritative and thorough study of causes of cancer in America (*16*) suggests that diet and life-style are major contributors to cancer and that the contribution of occupation and pollution are only a very small percentage of the cause of the major human cancers. This study

(Continued on page 757)

(Continued from page 670)

discredits many of the arguments of Epstein *et al.* in detail. The estimates by Doll and Peto agree with those of other leading epidemiologists (*13*) and also are consistent with the analyses of cancer in different countries and immigrant groups (*14*), although everyone agrees there are uncertainties in the figures. The range of human intake of fat is more than Epstein *et al.* state, and the many animal tests showing an effect of fat were often over a comparable range (*3*). Breast cancer rates are not so closely correlated with industrial society. Modern industrial societies such as Japan and the United States have an ever-increasing life span and a lower overall cancer rate than many less industrialized societies, such as Finland and New Zealand (*25*). Czechoslovakia (after Luxembourg) has the highest cancer rate in the world (*25*) and does not have any corporations. The calculations that Epstein *et al.* refer to stating that 18 to 38 percent of the cancer in coming decades will be caused by asbestos and five other carcinogens appear to inappropriately assume that anyone with *any* exposure to asbestos would have the same risk as a person with *massive* exposure. These estimates have been shown to be erroneous in other ways as well (*13, 15*) and have been effectively criticized by a good number of the world's leading epidemiologists (*26*).

Epidemiologists studying urban air pollution have had a difficult time demonstrating any measurable effect on cancer because of the larger effects of small differences in smoking (*27*). In Contra Costa County, California, a possible connection between air pollution due to several refineries and excess cancer was widely publicized for several years. The connection evaporated when a more detailed epidemiological study showed that the excess cancer was explainable by the higher smoking rate in blue-collar workers, who made up a higher percentage of the population in the area (*28*). In this study, as in those discussed above, only 3 percent of the males with lung cancer had never smoked, and green vegetable consumption showed a marked protective effect. I pointed out in my article that one would have to breathe in Los Angeles smog for about a year to inhale an amount of burnt material equal to that inhaled by a smoker in one day. Therefore, one has to be suspicious of superficial associations with refineries, smelters, and so forth, until precise adjustments are made for both duration and amount of smoking. I also pointed out that the major human intake of browned and burnt material, even more than smoking, comes from cooked food, which is also full of mutagens and carcinogens, although it is ingested rather than inhaled, and we do not know the human risk from this.

Epstein *et al.* dismiss the whole area of dietary anticarcinogens, despite the fact that many leading scientists think it is one of the most promising areas in cancer research. There is a vast literature on oxygen radicals in pathology, and there is a large and striking literature on anticarcinogens in animal tests and on dietary protective factors in people. Although this is an inherently difficult area, the impact on prevention of cancer could be great. We hope our own work on noninvasive measurement of the high endogenous flux of oxidative DNA damage in individual humans (and the much higher rate in rats) may help to open up new approaches to measuring the effects of antioxidant modifying factors in humans and to the understanding of the contribution of the aging process to cancer (*29*).

Epstein *et al.* seem to have a double standard about carcinogens. They emphasize only industrial chemicals or pollution and belittle or ignore the evidence concerning the many natural carcinogens, mutagens, and teratogens discussed in my article, as evidenced by their comments on mushrooms, pepper, and fat. Toth, an expert on the carcinogenicity of man-made hydrazines, has also published numerous papers on the carcinogenicity of many mushroom hydrazines (*30*). Gyromitrin, a carcinogen in mice (*31*), is present in large amounts (500 ppm, dry weight) in the widely eaten false morel and has recently been shown to massively alkylate the DNA of rats (*31*). The mushroom contains several other carcinogenic hydrazines, including *N*-methyl *N*-formylhydrazine, which is both potent and stable (*30*). The common commercial mushroom *Agaricus bisporus* contains agaritine, a hydroxymethyl phenylhydrazine derivative (3000 ppm, 45 milligrams per mushroom (*30*). A metabolic product of agaritine, a diazonium compound, is highly reactive and mutagenic and was found to cause stomach tumors in mice at low doses of both the sulfate and tetrafluoroborate salt (*30*). Agaritine is not appreciably destroyed by cooking and, when eaten, is distributed in tissues, where it is converted to the reactive mutagenic diazonium metabolite by cytochrome P-450 (*30*). The diazonium metabolite is also present in the mushroom (about 2 ppm) as it is formed from agaritine by enzymes in the mushroom (*30*). Epstein *et al.* dismiss the mushroom work because the diazonium compound was found to be a carcinogen when tested as a salt, an irrelevant argument in view of all of the findings about agaritine and the fact that the diazonium ion would be the chloride salt in the stomach in any case. Toth has recently identified another carcinogen in *Agaricus*, *p*-hydrazinobenzoic acid (10 ppm, 150 micrograms per mushroom) (*30*). Gyromitrin and some other natural pesticides cause lung tumors when fed to mice (*30*). Lung tumors may conceivably be caused in humans by natural carcinogens as well as by smoking and by the occupational hazards listed by Epstein *et al.* The positive cancer test on pepper was done by skin painting and is not a very elegant test, but it is statistically significant for each of three sites: skin, lung, and liver. Piperine, the major natural pesticide in black pepper (present at 10 percent of its weight), is closely related in structure to the known natural carcinogens safrole, estragole, and methyleugenol, which are also widely distributed in spices and plant oils. The test should be repeated, although, unfortunately, no government agency seems very interested in doing cancer tests on natural products. Toth has also shown that capsaicin, the pungent material in hot pepper, is a mutagen, and he has some preliminary evidence for its carcinogenicity in mice (*32*).

Epstein *et al.* call all of these "trace natural components." My article was full of numbers showing that the amounts are not traces. Nature's pesticides are present at parts per hundred and parts per thousand, while man-made pesticides are present at parts per million and parts per billion. We are eating more than 10,000 times more of nature's pesticides than of man-made pesticides. The arguments of Epstein *et al.* about man-made pesticides do not invalidate this calculation. His calculations are based on rare, highly contaminated foods or people, while mine are based on Food and Drug Administration values for man-made pesticide residues.

Epstein *et al.* criticize my discussion of mutagens as potential carcinogens. There are 3000 laboratories using our test alone, and there are many other kinds of mutagenicity tests in which cells from mammals are used. Over the last 10 years, more than 5000 compounds, natural as well as man-made, have been

tested, and an amazing variety of mutagens in the natural world have surfaced. These include superoxide, hydrogen peroxide, and aldehydes generated by our normal metabolism; products of lipid rancidity; products of cooking food such as the brown color on our toast; many of nature's pesticides; and the aroma of butter (diacetyl). We cannot ignore this new information, as it is telling us something important about nature. There are good reasons for thinking that mutagens are potential carcinogens and that DNA damage is of concern in itself. Our test is successful at detecting carcinogens as mutagens (80+ percent) and has been improved since validation (*33*). In many cases its mutagens have later been found to be carcinogens in rodents (for example, natural metabolic products such as hydrogen peroxide and formaldehyde, natural pesticides such as allyl isothiocyanate from mustard, many pyrolysis products from cooking, nitropyrenes from diesel exhaust, and synthetic substances such as ethylene dibromide, hair dye components, and the flame retardant tris-BP). Recent evidence on oncogenes also supports a mutation–DNA damage hypothesis as one aspect of cancer causation (*34*). The identification of mutagens aids epidemiology in its search for hypotheses to test, serves as a bioassay for active principles in complex mixtures (for example, the mutagenic pyrolysis products from cooking, later shown to be carcinogens), and is a way of investigating active forms of carcinogens. Of course, it is far from a perfect guide. We need to understand promotion as well, although I pointed out recent evidence for an oxygen radical connection. We know that some chemical carcinogens are missed by mutagenicity tests, but the battery of short-term test systems agree with each other quite well and detect a remarkable percentage of the known carcinogens. Agents that are known to cause deletions, translocations, and chromosomal rearrangements, such as x-rays, are also detected by our test system (*33*). Whether there are many significant carcinogens that cause translocations and are not detected as mutagens in short-term tests remains to be seen. Glutathione, as pointed out by Epstein *et al.*, is converted to a mutagen by kidney homogenate (but not liver homogenate). This may be due to an enzyme specific for kidney that generates oxygen radicals from O_2 and glutathione (*35*), but this is not relevant to the role of glutathione as an antioxidant or the value of mutagenicity tests.

Epstein and his colleagues may be drawing the wrong conclusion from the results coming out of animal cancer tests. The National Cancer Institute–National Toxicology Program animal cancer bioassay test program, which is the most thorough and extensive source of tests, is looking at only a small portion of the chemicals in the world. The current cost is more than $500,000 per chemical, so it is difficult to test many chemicals. The tests are almost exclusively done on man-made chemicals and therefore, of course, find man-made carcinogens. Out of about 200 chemicals tested by NCI in 8 years, 60 percent were judged carcinogenic, 33 percent noncarcinogenic, and 7 percent inadequately tested (*36*). The high percentage of carcinogens found is somewhat disturbing, as the conventional wisdom is that carcinogens are very rare. This discrepancy could be accounted for by the fact that more suspicious chemicals are being tested. It also could be that carcinogens are more common than we think. We have no idea of what the true percentage of carcinogens is among chemicals in general (including natural ones) when tested at the maximum tolerated dose in rodents. Even if it is 10 percent, our current regulatory policies, which assume carcinogens are rare, are in trouble. I pointed out that we are ingesting enormously more in both number and amount of natural pesticides and other natural toxic molecules (and traditional mixtures such as cooked food) than we are of man-made substances. Plants have been devising nasty chemicals to kill off insects and animals throughout all of evolution.

There is no reason to think nature is any more benign than man. We already know about natural carcinogens, such as psoralens, aflatoxins, sterigmatocystins, pyrrolizidine alkaloids, safrole, asbestos, radioactive potassium in our body, radon coming up from the ground into our houses, mushroom hydrazines, hydrogen peroxide made during normal metabolism, and sunshine. The same detoxification and activation mechanisms appear to operate on both man-made and natural chemicals. Animal cancer testing will not be able to catch up with the large number of mutagens being uncovered. Therefore, it might be reasonable to plan on doing animal cancer testing on those natural mutagens that we eat in largest amounts to see how many are rodent carcinogens and to provide a benchmark of the natural hazard for setting priorities relative to man-made carcinogens.

Much fear of traces of man-made carcinogens is based on ignoring the natural background of carcinogens and using "worst case" assumptions in extrapolating risk from the most sensitive rodent (when the chemical is given at the maximum tolerated dose) to low-dose human exposure. This quantitative extrapolation is viewed with great unease by much of the toxicological and epidemiological community because there is little scientific support underlying it (*13*). It is an extrapolation based on ideas of prudence, not on firm science (*13, 37, 38*). This is true, of course, for both natural and man-made carcinogens. We cannot validate these extrapolations. In a few cases, individual extrapolations from rats to man can be examined, although not very satisfactorily (*38*). In cases such as ethylene dibromide (EDB) (*39*), aflatoxin (*38, 40*), and vinyl chloride (*38*), the extrapolations appear to markedly overestimate the risk to man. We assume a linear response with dose, but we do not know if this is true. We have no basis for assuming metabolism in rodents and humans is the same. We do not know if we can extrapolate cancer risk from short-lived species such as rodents to long-lived species such as man because of the cancer-longevity connection (my article discusses this). Antioxidant defenses can differ markedly from rodents to humans (*41*). We know that some dietary changes make great differences in cancer incidence in rodent tests, but we do not understand which are the dietary protecting factors that appear to influence cancer risks so markedly in human epidemiology studies. We do not understand promotion or the interaction of carcinogens. Thus, it is time to do the same types of worst case risk calculations on natural chemicals as well as man-made chemicals before deciding what our priorities are. I emphasized that

> To identify a substance, whether natural or man-made, as a mutagen or a carcinogen, is just a first step. Beyond this, it is necessary to . . . quantitate the approximate magnitude of the risk. . . . [T]he rapid progress of science and technology . . . should help to dispel confusion about how important health risks can be identified among the vast number of minor risks.

Epstein *et al.* distort my statement on EDB (*42*), which was in favor of the EPA standards and much more stringent occupational standards. Aluminum phosphide (phosphine gas), the suggested alternative of Epstein *et al.* to EDB for grain fumigation, is both extremely toxic to humans and flammable, and, despite their statement, it has not been tested for carcinogenicity (*43*).

Epstein and his cosigners offer sup-

port for the idea that cancer is basically a political problem, that it is "corporate cancer," and that the solutions are not scientific, since we already know what we need to know to solve the problem politically. Yet their fundamental hypotheses and beliefs are wrong or likely to be wrong. If we follow their advice, we will ignore the major area of diet as a source of both protective factors and risk factors for cancer. We will continue to be preoccupied instead only with industrial sources of cancer, trying to eliminate smaller and smaller risks even though the alternatives to these have unknown risks. Pollution is not being neglected when the budget of the EPA is equal to that of NCI, nor are occupational hazards when we have large government agencies such as the Occupational Safety and Health Administration and the National Institute of Occupational Safety and Health. Smoking, which causes 30 percent of cancer and 25 percent of heart disease, is largely neglected: we subsidize tobacco farmers. Understanding cancer mechanisms may turn out to be among the most cost-effective ways to reduce the burden of cancer that is not related to tobacco, and for the present the key questions are scientific, not political.

I would like to correct some errors and omissions in my article. I omitted a paper reviewing the carcinogenicity of the herbs comfrey and coltsfoot (*44*), which contain the very potent carcinogenic pyrrolizidine alkaloids that are widespread in plants. The use of comfrey is increasing markedly with the new interest in returning to natural herbs and the increase in health food stores. I overlooked the extensive work of Janzen and others (*45*) on the biological role of plant toxins and of Morton (*46*) on the connection between tannins in plants and esophageal cancer in a number of countries. I also overlooked a paper on the plasma levels in humans of the potato toxins in which the toxicology of these compounds was reviewed (*47*). Also overlooked were the natural mutagens in ginger (*48*) and in corn, rye, and wheat (*49*) and the work on the formation of mutagens by the reaction of sugars with amino acids (nonenzymatic browning or Maillard reaction) during the cooking of food (*50*). It was a single dose of 400 micrograms per gram, not 400 nanograms per gram, of the mushroom diazonium derivative that caused the appreciable cancer in mice. I would also like to call attention to the paper of Birnboim (*51*) on the role of oxygen radicals in strand breaks and promotion, which I overlooked, and to the book in which it appears, which has many papers of relevance. I also apologize to Shapiro and my numerous botanist correspondents for misclassifying figs.

BRUCE N. AMES

Department of Biochemistry,
University of California,
Berkeley 94720

References and Notes

1. *Encyclopedia Brittanica*, 11th Edition (1910).
2. *Oxford Universal Dictionary* (Oxford Univ. Press, New York, 1955).
3. W. C. Willett and B. MacMahon, *N. Engl. J. Med.* **310**, 697 (1984); J. H. Weisburger, B. S. Reddy, W. S. Barnes, E. L. Wynder, *Environ. Health Perspect.* **50**, 101 (1983); E. Wynder, *Cancer Res.* **43**, 3024 (1983); S. Graham, *Epidemiol. Rev.* **5**, 38 (1983). See also K. K. Carroll, *J. Environ. Pathol. Toxicol.* **3**, 253 (1980).
4. H. Newmark, M. C. Wargovich, W. R. Bruce, *J. Natl. Cancer Inst.*, in press.
5. C. W. Welsch and C. F. Aylsworth, *ibid.* **70**, 215 (1983).
6. L. S. Tsai, K. Ijichi, C. A. Hudson, J. J. Meehan, *Lipids* **15**, 124 (1980); *Proc. 39 Inst. Food Tech. Meet.* (abstr.) 164 (1979); *ibid.*, unpublished manuscript. This work is discussed to some extent by L. L. Smith [in *Autoxidation in Food and Biological Systems*, M. G. Simic and M. Karel, Eds. (Plenum, New York, 1980), pp. 119–132]. Tsai *et al.* also show a solution to the problem. They found that direct gas-fired heating of eggs gave much higher epoxide values than indirect heating. NO_2, produced by gas flames, is known to be an effective inducer of oxidation reactions in lipids, and it would be simple for the industry to switch over to indirect heating. The beer industry switched from direct to indirect heating of malt promptly after nitrosamines were discovered in beer and were found to be caused by the NO_2 reacting with the malt. The changeover was perhaps speeded up by the full-page advertisements of Coors, in which they compared the nitrosamine content of their competitors' beers with their own, which had negligible levels because it was produced by an indirect heating method.
7. F. Bischoff, in *Advances in Lipid Research*, R. Paoletti and D. Kritchevsky, Eds. (Academic Press, New York, 1969), vol. 7, pp. 165–244; A. Sevanian and A. R. Peterson, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
8. N. L. Petrakis, L. D. Gruenke, J. C. Craig, *Cancer Res.* **41**, 2563 (1981); N. L. Petrakis *et al.* in *Banbury Report 13. Indicators of Genotoxic Exposure* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1982), pp. 67–82. These papers review the toxicology.
9. M. F. Gray, T. D. V. Lawrie, C. J. W. Brooks, *Lipids* **6**, 836 (1971).
10. J. A. Thompson *et al.*, *Food Technol. (Chicago)* **21**, 405 (1967); C. W. Fritsch, D. C. Egberg, J. S. Magnuson, *J. Am. Oil Chem. Soc.* **56**, 746 (1979).
11. F. B. Shorland *et al.*, *J. Agric. Food Chem.* **29**, 863 (1981).
12. E. A. Jacobson, H. L. Newmark, R. P. Bird, W. R. Bruce, *Nutr. Rep. Int.* **28**, 509 (1983).
13. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, New York, 1981). Also available in *J. Natl. Cancer Inst.* **66**, 1191 (1981).
14. J. Higginson, *Environ. Mutagen.* **5**, 929 (1983).
15. A. H. Daoud and A. C. Griffin, *Cancer Lett.* **9**, 299 (1980).
16. R. Peto and M. Schneiderman, Eds., *Banbury Report 9. Quantification of Occupational Cancer* (Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1981).
17. B. N. Ames, *Science* **204**, 587 (1979).
18. *Cancer Facts and Figures, 1984* (American Cancer Society, New York, 1984).
19. W. B. Riggan *et al.*, *Cancer Mortality Rates and Trends, 1950–1979* (Environmental Protection Agency–National Cancer Institute, Washington, D.C., 1984).
20. S. S. Devesa, E. S. Pollack, J. L. Young, Jr., *Am. J. Epidemiol.* **119**, 274 (1984).
21. P. Correa, L. W. Pickle, E. Fontham, Y. Lin, W. Haenszel, *Lancet* **1983-II**, 595 (1983); P. Correa, L. W. Pickle, E. Fontham, N. Dalager, Y. Lin, W. Haenszel, W. D. Johnson, in *Proceedings, International Lung Cancer Update Conference*, M. Mizell and P. Correa, Eds. (Verlag Chemie International, Deerfield Beach, Fla., in press); P. Buffler, L. W. Pickle, T. J. Mason, C. Contant, in *ibid.*
22. T. Hirayama, *Nutr. Cancer* **1**, 67 (1979).
23. L. Garfinkel, *J. Natl. Cancer Inst.* **66**, 1061 (1981).
24. R. G. Ziegler *et al.*, *ibid.* **67**, 1199 (1981).
25. M. Segi, *Age-Adjusted Death Rates for Cancer for Selected Sites (A-Classification) in 52 Countries in 1973* (Segi Institute of Cancer Epidemiology, Nagoya, Japan, 1978).
26. E. Efron, *Am. Spect.* **17**, 10 (1984).
27. F. E. Speizer, *Environ. Health Perspect.* **47**, 33 (1983). Speizer estimates that air pollution causes less than 2 percent of all lung cancers.
28. D. F. Austin, *Epidemiological Study of the Incidence of Cancer as Related to Industrial Emissions in Contra Costa County, California* (Final Report to the Environmental Protection Agency, Washington, D.C., 1982).
29. R. Cathcart, E. Schwiers, R. L. Saul, B. N. Ames, *Proc. Natl. Acad. Sci. U.S.A.*, in press.
30. B. Toth, in *Carcinogens and Mutagens in the Environment*, H. F. Stich, Ed. (CRC Press, Boca Raton, Fla., 1984), pp. 99–108; T. Lawson and B. Toth, *Am. Assoc. Cancer Res. Abstr.* **24**, 77 (1983); *Eur. J. Cancer Clin. Oncol.* **19**, 1296 (1983); B. Toth, personal communication. In one cancer test by Toth, agaritine itself was not found to be carcinogenic in mice.
31. A. Meier-Bratschi *et al.*, *J. Agric. Food Chem.* **31**, 1117 (1983).
32. B. Toth and E. Rogan, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **43**, 594 (1984).
33. D. E. Levin, L. J. Marnett, B. N. Ames, *Proc. Natl. Acad. Sci. U.S.A.*, in press; D. E. Levin *et al.*, *ibid.* **79**, 7445 (1982).
34. E. Santos *et al.*, *Science* **223**, 661 (1984).
35. C. H. Schmelzer *et al.*, *Arch. Biochem. Biophys.* **228**, 681 (1984).
36. K. C. Chu, C. Cueto, Jr., J. M. Ward, *J. Toxicol. Environ. Health* **8**, 251 (1981); D. Salsburg, *Fund. Appl. Toxicol.* **3**, 63 (1983).
37. F. C. Roe, *Nature (London)* **303**, 657 (1983).
38. *Assessment of Technologies for Determining Cancer Risks from the Environment* (Office of Technology Assessment, Washington, D.C., 1981).
39. J. C. Ramsey, C. N. Park, M. G. Ott, P. J. Gehring, *Toxicol. Appl. Pharm.* **47**, 411 (1978).
40. L. Stoloff, *Nutr. Cancer* **5**, 165 (1983).
41. B. N. Ames, R. Cathcart, E. Schwiers, P. Hochstein, *Proc. Natl. Acad. Sci. U.S.A.* **78**, 6858 (1981).
42. What I said in the reference Epstein cites is: "As pesticides go, it is a potent carcinogen in rodents. The new standards set for EDB are useful and overdue and should keep industry from getting sloppy. The Ruckelshaus standards seem pretty reasonable while EDB is being phased out. On the other hand, the risk to workers using EDB could be significant. The government's air standards until recently were such that workers were allowed to breathe in an amount of EDB roughly equivalent to eating a million ounces of bread a day with EDB residues of 30 parts per billion (the new Ruckelshaus standard for bread). Two studies of workers who were breathing in close to this amount of EDB for decades showed no increase in cancer. But because of the limitations of these studies, I and others fought to get California to lower the allowable level for workers. In 1982, California lowered the allowable level for workers by more than 100-fold. Our experience with asbestos and radium has taught us we can't ignore occupational carcinogenic hazards."
43. U. Hackenberg [*Toxicol. Appl. Pharmicol.* **23**, 147 (1972)] has done a cancer test only on food fumigated with phosphine gas, not on phosphine gas at high dose.
44. I. Hirono, H. Mori, M. Haga, *J. Natl. Cancer Inst.* **61**, 865 (1978).
45. G. A. Rosenthal and D. H. Janzen, Eds., *Herbivores: Their Interaction with Secondary Plant Metabolites* (Academic Press, New York, 1979). This book has many interesting articles on defense toxins in plants; D. H. Janzen, *Am. Nat.* **111**, 691 (1977).
46. J. F. Morton, in *Recent Advances in Phytochemistry*, vol. 14, *The Resource Potential in Phytochemistry*, T. Swain and R. Kleiman, Eds. (Plenum, New York, 1980), chap. 3, pp. 53–73.
47. J. A. Matthew *et al.*, *Food Chem. Toxicol.* **21**, 637 (1983).
48. H. Nakamura and T. Yamamoto, *Mutat. Res.* **122**, 87 (1983).
49. T. Ishizaki, Y. Hashimoto, K. Shudo, T. Okamoto, *Tetrahedron Lett.* **23**, 4055 (1982); Y. Hashimoto, K. Shudo, T. Okamoto, *Mutat. Res.* **66**, 191 (1979).
50. K. Shinohara *et al.*, *Mutat. Res.* **122**, 279 (1983).
51. H. C. Birnboim, in *Radioprotectors and Anticarcinogens*, O. F. Nygaard and M. G. Simic, Eds. (Academic Press, New York, 1983), pp. 539–556.