Letters

Paleolithic Diet, Evolution, and Carcinogens

Philip H. Abelson (Editorial, 31 July, p. 473) and Bruce N. Ames *et al.* (Articles, 17 Apr., p. 271) observe that cancer is a complex of diseases with multiple causes, ranging from carcinogens and hormonal factors to chronic infectious diseases and dietary patterns. Moreover, Ames *et al.* advise that naturally occurring carcinogens in the food supply are generally more toxic than industrial carcinogens, excepting workplace exposures. This interpretation of greater toxicity of food-borne carcinogens derives from the HERP [*H*uman *E*xposure dose/*R*odent *P*otency dose] index of Ames *et al.*, which uses data from animal studies of carcinogenicity and finds alcohol and peanut butter more potent than pesticide residues.

While the work of Ames *et al.* presents an interesting use of toxicological data, it should not be construed as the final word on the role of synthetic organic carcinogens in producing cancer patterns in humans. The relative contribution of different synthetic and natural toxicants to human evolution and to current cancer and other disease patterns is a complex matter. A National Research Council (NRC) report (*1*) noted that many of the nondietary toxicants in foods are not known to be harmful to normal healthy human beings when the foods are prepared in time-honored ways. Adequate cooking reduces or destroys the harmful properties of the cyanogenetic glycosides in the lima bean, the goitrogens in certain vegetables, thiaminase in fish, and avidin in the egg. After ripening, the ackee fruit and grapefruit lose their toxic components.

Some observations from studies of Paleolithic nutrition may also be relevant, as widely varying foods were available to evolving hominids at least 4 million years ago. (*2*). Ames *et al.* note that some pyrolysis products are potent carcinogens. However, fire-cooked wild game meats have been consumed by humans for at least 700,000 years; for example, in Lantian, China (*3*), along with a variety of plants (*4*).

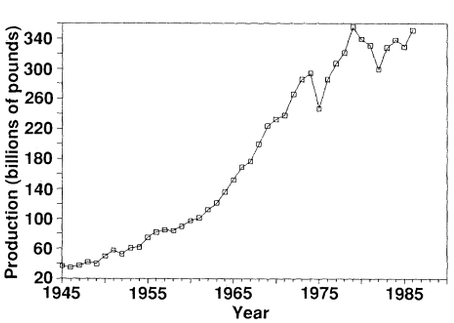

Fig. 1. Production of synthetic organic chemicals, including tar and primary products from petroleum and natural gas, 1945 to 1986.

A recent visit with my son Aaron to the expanded exhibit at the Hall of Fossils of the Smithsonian Institution's Museum of Natural History provided some relevant information. Reconstructions of the earliest archeological sites of human ancestors indicate that the larger, more robust form of Australopithecus, *Homo robustus*, died out about 1 million years ago and probably depended on vegetable foods, as its huge molar teeth and massive jaws are well adapted for such a rough diet. A sagittal crest (bony ridge of the top of the skull) and protruding cheek bones anchored the strong chewing muscles. The hominids from which we evolved had teeth that were adapted for an omnivorous diet of vegetables and meat and lived about 1.2 to 3 million years ago. Moreover, the range of early diets was extensive, from protein rich diets of far northern peoples to the vegetable-laden diets of the Australian Kalahari.

To be sure, materials causing chronic illnesses that are commonly expressed in postreproductive persons would not have a selective influence on the evolution of human genotypes. However, such materials could have had major effects on human development. Experimental data suggest that few carcinogens are not also toxic to reproduction (*5*). Thus, exposure to food-borne toxicants in early humans may have selected out genotypes that produced spermatocytes, oocytes, embryos, and fetuses with susceptibility to toxic constituents of foods. Early pregnant humans may have experienced spontaneous abortions due to prenatal and other exposures to carcinogens in the food supply, which would have produced genetic resistance in the human genome.

Nearly four decades ago, J. B. S. Haldane argued that diseases are responsible for much of the observed biochemical and genetic variability of wild populations, insofar as the struggle against disease plays an important evolutionary role (*6*). Reasoning that a small biochemical change provides a host species a substantial degree of resistance, Haldane argued that it is an advantage to a species to be biochemically diverse.

Whatever the role of evolution may prove to be, humans have been eating complex foods far longer than they have been exposed to synthetic, organic carcinogens. Moreover, some cancer patterns in the United States have changed markedly and recently in ways that are unlikely to be related to changes in food consumption. Other cancers, such as breast cancer, appear closely related to patterns of dietary fat consumption (*7*). But several cancers, with no known or suspected nutritional basis, have been increasing. Moreover, some food-related cancers, including stomach cancer have been declining in many industrial countries (*8*). In the United States cancers in persons under age 45 have also declined markedly in recent years (*9*). In contrast, multiple myeloma, lung cancer, and brain cancer have increased at least 50% from 1968 to 1978 in white and nonwhite persons aged 75 to 84. (*9, 10*). From 1975 to 1984, the age-adjusted U.S. cancer mortality rate rose from 162.2 to 170.7 per 100,000 individuals; during this same time, the death rate per 100,000 for nonlung cancer changed from 125.4 to 125.1 (*11*).

In light of these complex patterns, serious research needs to be done on possible changes in the environment in the past that could account for these patterns. Whether recent chemical exposures are linked with changing cancer patterns in the elderly remains an open question. However, in the past three decades, production of synthetic organic chemicals grew exponentially (Fig. 1). This older cohort includes persons who have lived long enough to experience cancers that may be associated with such exposures.

As Ames *et al.* point out, the range of variation in worldwide cancer patterns is substantial, running at least sixfold, and many cancers occur with even greater variation (*8*). Diet alone is unlikely to explain all of this variation, nor are changes in diet likely to be involved with some of the specific changes noted above.

The relative roles of food and nonfood carcinogens are unclear. It is highly likely that the impact of the latter may differ qualitatively from that of the former. Also synergies may occur between them, with newer compounds enhancing the toxicity of longer established compounds. In light of the relatively recent increase in the volume of production of some carcinogenic and other hazardous substances, it is not now possible to determine the extent to which exposures to such chemicals will influence future cancer rates. Prudent public policy dictates that additional research be conducted on the relative potencies of these materials for humans.

DEVRA LEE DAVIS
Board on Environmental Studies and Toxicology,
National Research Council,
2101 Constitution Avenue, NW,
Washington, DC 20418

REFERENCES

1. National Research Council, *Toxicants Occurring*

Naturally in Foods (National Academy of Sciences, Washington, DC, 1966).
2. S. B. Eaton and M. J. Konner, *N. Engl. J. Med.* **312**, 283 (1985).
3. J. D. Clark and J. W. K. Harris, *Afr. Archaeol. Rev.* **3**, 3 (1985).
4. A. B. Stahl, *Curr. Anthropol.* **25**, 151 (1984).
5. D. L. Davis, *Toxic Subst. J.* **1**, 205 (1979).
6. J. B. S. Haldane, *On Being the Right Size and Other Essays* (Oxford Univ. Press, Oxford, England, 1985).
7. National Research Council, *Diet, Nutrition and Cancer* (National Academy of Sciences, Washington, DC, 1983).
8. *Cancer Incidence on Five Continents* (International Agency for Research on Cancer, Lyon, France, 1976), vol. 3.
9. S. S. Devesa *et al. J. Natl. Cancer Inst.* **79**, 701 (1987).
10. D. L. Davis, A. D. Lilienfeld, A. Gittelsohn, M. E. Scheckenbach, *Toxicol. Ind. Health* **2**, 127 (1986).
11. J. C. Bailar, III, *Issues Sci. Technol.* **4**, 16 (1987).

Response: Davis takes issue with our documentation that carcinogenic hazards from current levels of pesticide residues or water pollution are likely to be of minimal concern relative to the background levels of natural substances. She indicates that humans, as opposed to rats or mice, may have developed *specific* resistance to these natural chemicals, since we have been selected by evolution to deal with plant toxins or cooked food. This is unlikely, because, as we discussed in our article, both rodents and humans have developed many types of *general* defenses against the large amounts and enormous variety of toxic chemicals in plants (nature's pesticides). These defenses include the constant shedding of the surface layer of cells of the digestive system, the glutathione transferases for detoxifying alkylating agents, the active excretion of hydrophobic toxins out of liver or intestinal cells (*1*), numerous defenses against oxygen radicals (*2*), and DNA excision repair. The fact that defenses appear to be mainly general, rather than specific for each chemical, makes good evolutionary sense and is supported by various studies. Experimental evidence indicates that these general defenses will work against both natural and synthetic compounds, since basic mechanisms of carcinogenesis are not unique to either.

We also pointed out that humans ingest about 10,000 times more of nature's pesticides than man-made pesticides. Relatively few of nature's pesticides that we are eating have been tested for carcinogenicity, but about half of the naturally occurring substances that have been tested in rats and mice are carcinogens. We also pointed out that the modern diet is vastly different from that of a few thousand years ago or of primitive man (*3*). Davis dismisses dietary and other life-style factors too readily as potential causes of cancer that do not change; they do change all of the time. For example, as part of the back-to-nature movement we are eating canavanine in alfalfa sprouts, carcinogenic hydrazines in raw mushrooms, and carcinogens in herb teas. Cooking food does destroy some carcinogens but also makes others, such as the variety of nitrosamines and nitropyrenes formed when food is cooked in gas ovens, a relatively recent invention. Davis' argument that natural selection eliminated all hazards from carcinogens acting late in life because they are reproductive toxins is not supported by good evidence and appears unlikely.

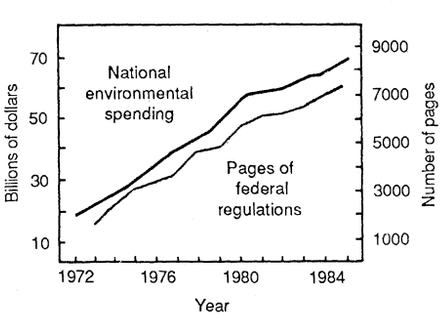

Fig. 1. Expenditures for environmental protection (*8*).

We have discussed why "risk assessment" based on worst-case scenarios may not have much to do with biological reality for either synthetic or natural chemicals. Linear extrapolations from results at the maximum tolerated dose may enormously exaggerate risks at low dose if, as appears to be true, an important aspect of carcinogenesis is cell proliferation, which may frequently result from the high (maximally tolerated) doses of test chemicals administered in rodent bioassays (*4*). Concern with very low doses is even more likely to be misplaced for agents suspected of causing birth defects, because of a threshold effect. In this respect it would be useful to compare rodent data for particular synthetic chemical pollutants with those for a representative set of natural chemicals, analogous to our HERP index comparisons. One important comparison to be made would be that between alcohol and other rodent teratogens. Alcohol is a leading cause of mental retardation in humans (fetal alcohol syndrome), and such a comparison would put possible teratogenic hazards into perspective.

The key issue is not that production of synthetic chemicals has gone up markedly in recent years, but whether the tiny amounts of pesticide residues or water pollutants we are ingesting are likely to be important in human cancer. In our ranking, such exposures are very low compared with the background of natural carcinogens, but we also pointed out that workplace exposures often rank high (*5*).

Davis contends that the incidence of brain tumors and multiple myelomas in the elderly has clearly increased. However, Doll and Peto, in a detailed analysis of the causes of human cancers, convincingly point out why such apparent increases may be due to recent improvements in diagnosis (*6*). Peto concluded, in commenting on this matter (*7*, p. 283), that "Future trends may differ substantially from recent trends, of course, but at present the U.S. data contain no clear evidence for any generalized increase in cancer over and above that due to the delayed effects of tobacco. Opposite conclusions by other commentators appear to derive chiefly from methodological oversights."

From a policy perspective, we discussed in our article that it is prudent to consider the benefits of modern technology and also the alternative substances that might replace regulated compounds. Modern chemicals commonly replaced more hazardous substances, for example, chlorinated solvents replaced flammable solvents. Modern technology, which concomitantly causes the increase in production of synthetic chemicals, has contributed in important ways to our steadily increasing life-span. Currently, as a society our expenditures on pollution abatement and control are more than $80 billion annually (Fig. 1), despite the uncertainty of whether environmental pollutants at parts-per-billion levels have public health significance. We believe that the potential carcinogenic hazards of pollutants should be evaluated in the context of background level exposures to natural substances until science makes the further understanding of mechanisms clearer, as we emphasized in our article.

BRUCE N. AMES
Department of Biochemistry, University of California, Berkeley, CA 94720
LOIS SWIRSKY GOLD
Lawrence Berkeley Laboratory, Berkeley, CA 94720

REFERENCES

1. F. Thiebaut *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 7735 (1987).
2. B. N. Ames, in *Detection Methods for DNA-Damaging Agents in Man* (International Agency for Research on Cancer, Lyon, France, in press).
3. L. A. Cohen, *Sci. Am.* **257**, 42 (November 1987).
4. J. A. Swenberg *et al.*, *Environ. Health Perspect.*, in press.
5. L. S. Gold, G. M. Backman, N. K. Hooper, R. Peto, *ibid.*, in press.
6. R. Doll and R. Peto, *The Causes of Cancer* (Oxford Univ. Press, Oxford, England, 1981).
7. R. Peto, in *Quantification of Occupational Cancer*, R. Peto and M. Schneiderman, Eds. (Banbury Report 9, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, 1981), pp. 269–284.
8. J. Hirschhorn, *Serious Reduction of Hazardous Waste* (Office of Technology Assessment, Washington, DC, 1986), figure 1, p. 8.

Definition Required

Concerning "Science and mutual self-interest" by David Dickson and Colin Nor-