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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

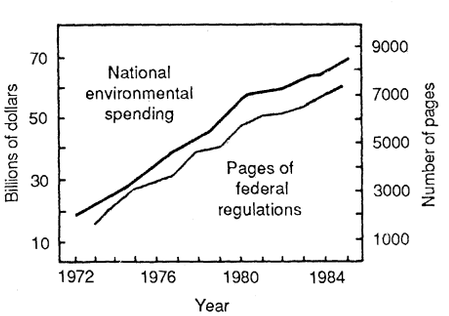

Fig. 1. Expenditures for environmental protection (*8*).

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.

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.

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Definition Required

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

man (News & Comment, 4 Sept., p. 1101), I know what "self-interest," "mutual interest," "common interest," and even "common self-interest" mean, but what is "mutual self-interest"?

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California's Proposition 65: A Reply

The recent editorial of Philip H. Abelson (25 Sept., p. 1553) concerning California's Proposition 65, the Safe Drinking Water and Toxic Enforcement Act of 1986, painted an unrealistically woeful picture. The implementation is being carried out in a manner that will not encumber industry with unnecessary burdens, yet it will protect the state's sources of drinking water and provide information to Californians about chemicals to which they are exposed.

The California Health and Welfare Agency is the agency responsible for the implementation of the Act. A Scientific Advisory Panel, consisting of 12 members from academia and industry, recommends to the agency those chemicals that are to be listed as chemicals known to the state to cause cancer or reproductive toxicity. Contrary to Abelson's views, it is unlikely that common table salt will be listed as a reproductive toxicant.

The 15,000 items on supermarket shelves will not require warnings. The public's first statewide introduction to warnings will be with regard to the reproductive toxicity of ethanol in alcoholic beverages. In this case, warnings will be required by 1 October 1988. Similar warnings for alcoholic beverages are already in place in Los Angeles and San Diego, the result of local actions. Labels are not required by the Proposition, nor by the agency's proposed regulations.

The Health and Welfare Agency has issued proposed regulations that address naturally occurring substances. The presence of such chemicals in food will not constitute an exposure under the Proposition. The agency intends to recognize regulatory levels for carcinogens and reproductive toxicants that are regulated by state and federal agencies, to the extent that they provide the same level of human health protection required by the Proposition.

California is implementing Proposition 65 in a manner that is fair, predictable, and based on a firm scientific foundation. When fully implemented, it will serve to complement existing laws concerned with environmental and public health protection. Those who comply with existing laws and regulations will, in most cases, be in compliance with Proposition 65. Those, however, who fail to comply with existing laws designed to protect the public health will also be out of compliance with Proposition 65. Such activities, if not addressed by government enforcement agencies, would be the most likely targets for the "bounty hunter" provisions of the Proposition.

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Cholesterol Guidelines

The report (*1*) of an expert panel of the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute (NHLBI) announced on 5 October and discussed by Leslie Roberts (Research News, 23 Oct., p. 482) exaggerates the risks of coronary heat disease (CHD) from total serum cholesterol values and magnifies the predicted benefits of following the guidelines proposed. Although there is some evidence that a "desirable level" of serum cholesterol is less than 200 milligrams per deciliter (mg/dl), there is no convincing evidence that 199 mg/dl is less risky for CHD than 210 mg/dl (*2*). The range of 200 to 239 mg/dl is a gray area of mild risk reaching twice the baseline risk at 240 mg/dl.

The range of 200 to 239 mg/dl under no imaginable circumstance could be considered to be "borderline high." This is analogous to saying that a systolic blood pressure of 121 to 139 millimeters (mm) of mercury and a diastolic blood pressure of 81 to 89 mm are "borderline high." Borderline values in clinical medicine are single values that demarcate negligible risk from measurable risk. The usually accepted borderline value for blood pressure is 140/90 mm of mercury; for fasting blood sugar, 100 mg/dl; and for serum cholesterol, greater than 240 mg/dl. Most physician-scientists believe that values of serum cholesterol of 240 to 280 mg/dl constitute moderate risk and greater than 280 mg/dl, high risk.

Recommending that more than 25% of the adult population of this country go on fat-modified diets for cholesterol values in the gray zone is, in my opinion, a gross exaggeration of the hazards. If other risk factors are present, it might be important to do so. Furthermore, both low-density lipoprotein cholesterol and high-density lipoprotein (HDL) cholesterol should be measured because of the protective action of HDL cholesterol above 40 mg/dl. Most are agreed that intervention should begin at 240 mg/dl, first with diet and then with drugs, if necessary. It is also important to realize that in the moderate range of serum cholesterol, reduction of smoking and hypertension are more important than reduction of cholesterol levels (*3*).

With regard to the benefits of reduction of serum cholesterol, NHLBI director Claude Lenfant is quoted as saying that "If adopted, these recommendations could result in 300,000 fewer heart attacks each year." Since there are about 800,000 initial heart attacks per year in the United States (and about 550,000 deaths from coronary heart disease per year), this number represents a 40% reduction in initial heart attacks. None of the intervention studies, which have involved 36,000 persons worldwide with diet, or drugs, or both, has achieved a 40% decrease in heart attacks. Furthermore, these studies show only a slight reduction in mortality from CHD, with no change in all-cause mortality (*4*). These intervention trials, furthermore, have shown only a 5 to 13% change in serum cholesterol as a result of dietary modification over 6 to 8 years.

All of us are most concerned with developing strategies for the prevention of coronary heart disease. It is unjustifiable, however, to magnify the benefits of reduction of serum cholesterol, particularly for those persons at low risk.

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Liability Insurance and Litigation

The article by Peter Huber on "Injury litigation and liability insurance dynamics" (2 Oct., p. 31) asserts that the reason for the current crisis in liability insurance is an increase in liability law, inducing "mushrooming litigation" and an "avalanche of suits," leading to "unexpectedly large" payouts by insurance companies, thus caus-