sively increasing the prior probabilities of success along the way. In retrospect, adding an expenditure of $\$18 \times 10^6$ on β-carotene research (Bailey's estimate) to the $\$4 \times 10^6$ for the trial still leaves the enterprise looking extremely cost-effective, even if the only benefit of that research had been to identify β-carotene as a potential human anticarcinogen.

As stated in my article, I agree with Rall's observation that bioassays may have value in developing a scientific database for future priority-setting. I would take issue only with his conclusion that testing is, therefore, "necessary." Priorities do need to be set, and we must not lose sight of the primary objective of protecting the public health. In the same vein, I agree that negative studies may have value, but urge only that we be explicit that the value of such study results is "confidence" or reassurance and not cancer prevention. Indeed, one advantage of an explicit approach to priority-setting is to reveal the value judgments and beliefs that motivate a decision to perform any given study.

The fact that β-carotene is one of only a few dietary constituents that are ready for trials does not diminish the conclusion about the cost-effectiveness of that trial. Certainly I am not prepared to argue that all such trials of dietary constituents would be as cost-effective. However, recent epidemiologic and laboratory findings do suggest that rather large investments in applied research on dietary agents are likely to be cost-effective (*1*).

By the same token, the bioassay of *p*-dichlorobenzene may not be the most cost-effective among all those of industrial chemicals. However, the dichlorobenzenes, not toluene, were selected by the EPA from among the first set of nominees by the Interagency Testing Committee to be the subject of the first draft testing rules advanced by EPA. (No draft rules have yet been made final.)

As for the particular estimates of the percent reduction in cancer mortality with β-carotene, I stand by my estimates as consistent with Peto's review (17 of 20 studies he reviewed found relative risk of 1.3 or greater in the target organs examined) and subsequent studies. One advantage of my proposed approach is that it invites those who have different judgments to enter those in the model. Nonetheless, as demonstrated by the sensitivity analysis in my article, even if the estimates of cancer reduction were believed to be overstated by a factor of 2, 3, or more, the basic conclusions of the analysis would stand. Indeed, if β-carotene reduces cancer mortality by only a few percent, the major drawback to the trial would not be the size of its potential health impact (which would still be great) but its ability to detect such a small relative mortality difference.

The model is intended to be a guide to decision-making in the face of uncertainty and resource constraints, not a source of scientific truth. Thus, its conclusions in any particular instance should not be regarded as cast in stone and may change as new data become known. Moreover, scientists may disagree about the estimates entering into the model. (For example, it is my personal judgment that, absent any particular structure-activity hypothesis or ominous short-term test results, the prior probability that *p*-dichlorobenzene is a human carcinogen is not more than 10 percent. Rall's opinion is different and should be reflected in his use of the model.) What is important is that these underlying judgments be made explicit and debated openly in the priority-setting process. I am delighted that this model has already begun to stimulate such explicit, open discussion.

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References

1. B. N. Ames, *Science* **221**, 1256 (1983).

The Cover's Message

I couldn't disagree more with James C. Nofziger (Letters, 4 Nov., p. 456): I had no trouble distinguishing the message in the cover of 23 September from the burden of the article by Bruce N. Ames (23 Sept., p. 1256). The cover, crudely literated, says, "there are interesting, surprising, and paradoxical relationships between eating and dying." In its present context, it also says, "to learn about some of them, look in this magazine." I think this is a fine way for a cover to function, even on a scientifically objective journal.

More generally, I think your covers are often remarkably witty and subtle (wit and subtlety are important to good science), especially the last two Halloween covers and last year's Christmas cover.

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