U.S. population is marginally folate-deficient. There is also epidemiological evidence that folate deficiencies cause birth defects in humans. Accumulating epidemiological evidence indicates that vitamins E and C and betacarotene are major protective factors against both cancer and heart disease, yet a sizable percentage of the public is deficient in these antioxidants. Choline deficiency increases cancer rates in rats (7). In addition, calorie reduction dramatically lowers mitogenesis rates and spontaneous tumor rates in rodents. Protein reduction lowers spontaneous tumor rates in rats. Ad libitum feeding, which encourages overeating, is routinely done in bioassays; overeating increases spontaneous tumor rates, and a variation in food intake is important in tumor incidence (*8*). Human cancers can be due to a variety of factors, such as dietary imbalances, hormones, and chronic infections, that are not likely to be uncovered by screening chemicals in rodents, even if we knew which chemicals to test (*9*).

The NTP strategy to analyze mechanisms is a useful change. Increased mitogenesis rates are clearly important in mutagenesis, and we believe that also adding routine measurements of mitogenesis to the 13-week toxicology study and the 2-year bioassay would provide information that would improve dose setting, interpretation of experimental results, and risk assessment. Such information may help to distinguish among rodent carcinogens, for example, between butadiene and sodium saccharin, for which the risk at doses a hundred times below the MTD appears to be vastly different. The work of Cunningham *et al.* at the NTP is a good example of how mechanism studies help to differentiate among chemicals. Their experiments showed that with two pairs of mutagenic isomers (1- versus 2-nitropropane and 2.4- versus 2.6-diaminotoluene), one isomer a carcinogen and the other not, only the carcinogen was mitogenic (*10*). It may be that half the rodent carcinogens are not acting as genotoxins in vivo and that their risk at low doses is zero, but we should look for compounds like butadiene that may be carcinogens at doses as low as 100 times below the MTD (*4*). If there are super carcinogens (*5*), butadiene is a possible example. Butadiene and vinyl chloride are DNA cross-linking agents, and it would be of interest to see whether this property is important in unusual activity at low doses. Studies of mechanisms, including mitogenesis, should help to clarify this. It is clear that the mechanisms of action for all rodent carcinogens are not the same and that one cannot use a simple linearized risk assessment model for all of them.

Rall states that it is a "myth" that testing at the MTD can result in effects that are unique to the high dose and cites the analysis of Hoel *et al.* We think that it is not a myth and that there is accumulating evidence to support mitogenesis effects unique to high doses for particular chemicals analyzed, for example, formaldehyde, melamine, and saccharin. One-half the MTD (which is the "low" dose in a bioassay) is a high dose and can also result in mitogenesis. Our point is that rodent bioassays provide virtually no information about low doses because they are conducted at the MTD and one-half the MTD, both high and close to one another in comparison to low-dose human exposures. It is a rare chemical that is tested across a range of doses. With only two doses and a control in cancer tests, information about dose-response is limited. Even at these two high doses, 44% of the positive sites in NTP bioassays are statistically significant at the MTD, but not at one-half the MTD (among 365 positive sites analyzed in the Carcinogenic Potency Database). Because the NTP bioassays do not measure mitogenesis, Hoel *et al.* (*11*) used an indirect, but inadequate, method to examine the issue. We have discussed the details of this inadequacy (*4, 12*).

Rall cites a recent paper (*13*) that purports to show an overall increase in cancer mortality rates; however, eminent epidemiologists dispute the interpretation (*14*).

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REFERENCES

1. L. S. Gold, G. M. Backman, N. K. Hooper, R. Peto, *Environ. Health Perspect.* **76**, 211 (1987).
2. S. M. Cohen and L. B. Ellwein, *Science* **249**, 1007 (1990).
3. D. W. Gaylor, *Regul. Toxicol. Pharmacol.* **9**, 1101 (1989).
4. B. N. Ames and L. S. Gold, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 7772 (1990); B. N. Ames, M. Profet, L. S. Gold, *ibid.*, p. 7777; *ibid.*, p. 7782.
5. L. Bernstein, L. S. Gold, B. N. Ames, M. C. Pike, D. G. Hoel, *Fundam. Appl. Toxicol.* **5**, 79 (1985); L. Zeise, R. Wilson, E. Crouch, *Risk Analysis* **4**, 187 (1984); C. C. Travis, S. A. Richter Pack, A. W. Saulsbury, M. W. Yambert, *Mutat. Res.* **241**, 21 (1990).
6. J. T. MacGregor, R. Schlegel, C. M. Wehr, P. Alperin, B. N. Ames, *Proc. Natl. Acad. Sci. U.S.A.* **87**, 9962 (1990).
7. S. J. James and L. Yin, *Carcinogenesis* **10**, 1209 (1989); P. M. Newberne, V. Suphiphat, M. Locniskar, J. L. V. deCamargo, *Nutr. Cancer* **14**, 175 (1990).
8. F. J. C. Roe, *Mutagenesis* **4**, 407 (1989); *Fundam. Appl. Toxicol.*, in press.
9. S. Preston-Martin, M. C. Pike, R. K. Ross, P. A. Jones, B. E. Henderson, *Cancer Res.* **50**, 7415 (1990); R. Peto, in *Assessment of Risk from Low-Level Exposure to Radiation and Chemicals*, A. D. Woodhead, C. J. Shellabarger, V. Pond, A. Hollaender, Eds. (Plenum, New York, 1985), pp. 3–16.
10. M. L. Cunningham, H. B. Matthews, *Environ. Mol. Mutagen.* **15** (suppl. 17), 14 (1990); M. L. Cunningham, R. Maronpot, J. Foley, H. B. Matthews, *Toxicologist* **10**, 181 (1990).
11. D. G. Hoel, J. K. Haseman, M. D. Mugon, J. Humm, E. E. McConnell, *Carcinogenesis* **9**, 2045 (1988).
12. B. N. Ames and L. S. Gold, *Science* **250**, 644 (1990); *Chem. Eng. News*, in press.
13. D. L. Davis, D. G. Hoel, J. Fox, A. Lopez *et al.*, *Lancet* **336**, 474 (1990).
14. F. Doyon, *ibid.*, p. 1262; S. Freni, *ibid.*, p. 1263.

Cold Spring Harbor

Leslie Roberts' quotes of my comments in her News & Comment article "Cold Spring Harbor turns 100" (26 Oct., p. 496) misrepresent what I feel about Cold Spring Harbor's new neuroscience center. I may well have said that such a big jump in the size of the laboratory "is enough to give one sleepless nights" and that it will be "a problem to populate that huge building," but I certainly did not wish to imply that James Watson might fail in this latest endeavor. He has shown in the past an astonishing ability to pick people and make projects flourish, and I have absolutely no doubt that once more he will be successful.

I would also like to comment on the impression given by the article of the financial history of the laboratory. A major crisis occurred just before I became director in 1963. At that time the laboratory was in debt by an amount roughly equal to 50% of its annual budget. When I arrived, the summer program was just beginning and the cash reserve was enough to meet 2 weeks of payroll. That was what gave *me* sleepless nights. By the time Watson became director, in 1968, we had paid off the debt, increased the budget by 30% a year, and built up a reasonable cash reserve. The main problem he faced was to attract good scientists when he could not offer them financial security. The development of the laboratory over the past 22 years will always be seen as a monument to his success.

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Erratum: In the seventh paragraph (column 3) on page 1204 of Marcia Barinaga's Research News article "Biology goes to the movies" (30 Nov.), the diameter of the microtubules observed by Nina and Robert Allen and their colleagues should have been given as 25 nanometers, not 25 angstroms.

Erratum: In the report "Broadly neutralizing antibodies elicited by the hypervariable neutralizing determinant of HIV-1" by K. Javaherian *et al.* (14 Dec., p. 1590), the headings for tables 4 and 5 on page 1592 were incorrectly interchanged.