LETTERS

Agricultural Research System

According to the editorial page, "*Science* serves its readers as a forum for the presentation and discussion of important issues related to the advancement of science. . . ." In that context *Science* is to be congratulated for the article by Nicholas Wade in the 5 December 1975 issue (News and Comment, p. 959) concerning agricultural research. On the other hand, *Science* readers are entitled to more objectivity than is demonstrated in that article. The quotes attributed to me are in error as well as being misleading. Even more serious are the remarks concerning Assistant Secretary of Agriculture Robert W. Long. A similar article by the same author (News and Comment, 17 Jan. 1975, p. 150) drew comments from within the Department as well as outside, with assurances that Long is a capable administrator of agricultural research programs and is highly respected by the agricultural research community.

R. L. LOVVORN
Cooperative State Research Service, U.S. Department of Agriculture, Washington, D.C. 20250

I much regret that Lovvorn feels he has been misquoted. Misunderstandings are always possible, but I do not believe that the quotations attributed to him are in error.—NICHOLAS WADE

Carcinogenicity Tests

In his capacity as chairman of the AAAS Committee on Scientific Freedom and Responsibility, John Edsall is in a position to influence public policy; because of his stature as a distinguished researcher, he is in a position to influence scientific thought. He notes in his letter of 18 July 1975 (p. 174) the finding that some carcinogens are mutagenic in bacteria (*1*). This has been interpreted to mean that those carcinogens cause cancer by somatic mutation and has been taken by many as support for the venerable hypothesis that the malignant transformation of cells is a mutational event. In addition, the screening of compounds for their capacity to cause bacterial mutations has been adopted by a number of laboratories as a means of indicating carcinogenic potential. The implied relation between mutagenesis and carcinogenesis (*2*) still needs careful scrutiny with regard to its scientific validity and also because of its implications for public policy.

Unfortunately, an enormous variety of materials has been shown to be carcinogenic if applied persistently enough in the right places at the right times. A classic example is "solid state" carcinogenesis, in which a variety of inert, insoluble materials are carcinogenic if implanted under the skin in the form of continuous sheets, but not if implanted in the form of pellets (*3*). Excessive application of normal steroid hormones causes cancer, as does the simple transplantation of some endocrine organs into the spleen of the same animal (*4*). It is difficult to accept mutagenesis as the origin of these cancers.

A simple listing of agents as carcinogens has little meaning unless accompanied by a quantitative indication of carcinogenic potency and the conditions under which these were determined. The hazards involved in readily accepting a screen for carcinogenic hazard based on other biological effects are illustrated in a recent article by Wood *et al.* (*5*). Benzo[*a*]pyrene is a potent carcinogen and a widespread environmental pollutant. Its carcinogenic activity has been attributed to its metabolic products. The 4,5-oxide was highly mutagenic in bacterial tester strains, but benzo[*a*]pyrene itself and the 7,8- and 9,10-oxides had no significant mutagenic activity. However, only benzo[*a*]pyrene and the 7,8-oxide produced tumors, while the 4,5-oxide induced few, if any, tumors in mice [see note added in proof of (*5*)]. In other words, the screen missed the carcinogens and implicated the noncarcinogen.

Acceptance of screening for carcinogenicity by determining mutagenicity lends tacit support to the hypothesis that malignant transformation of cells is caused by somatic mutation. This hypothesis has been tested explicitly in several experiments and has been found wanting in each case. Transplantation into frog eggs of nuclei from frog carcinoma cells results in normal swimming tadpoles (*6*). This shows that the carcinoma nuclei had the normal genomic complement, capable of making every functional tissue of the tadpole. This is the same type of evidence which has served as the basis for general acceptance of the idea that cell and tissue differentiation are epigenetic phenomena (*7*). Heidelberger's group (*8*) has shown that the powerful carcinogenic hydrocarbon methylcholanthrene, at concentrations which cause no significant cell death, produces malignant transformation in 100 percent of the clones of mouse prostate cells in culture. This would certainly be an extraordinary outcome if the malignant transformation were caused by mutations, which occur at extremely low frequencies in clearly defined situations. Finally, Braun (*9*) has shown that single cells of the crown gall tumor of tobacco give rise to normal tobacco plants when grafted to cut stem ends of tobacco. They yield seeds which are generatively normal in every respect. While one may argue that plant tumors are not equivalent to animal tumors, they are certainly more closely related than are bacterial mutations.

There are other types of evidence which are inconsistent with assuming a genetic basis for the malignant transformation (*10*). Perhaps none of the tests can be considered conclusive by itself, but together they make a far weightier case *against* a mutational origin of the malignant transformation than does the evidence *for* such an origin. Unfortunately, there is no clearly established mechanism for obtaining a heritable change in cells other than a change in the genetic complement of the cell, although some have been considered (*11*). It is inescapable, however, that such a mechanism must exist to explain the stable differentiation of cells which have identical nuclear genomes (*7*).

I have no argument with the desirability of screening for mutagens in the environment by a simple and economical test. However, to use this kind of screening as a test for carcinogenicity is a bit like looking under the lamppost for the coin lost a block away because of the availability of light. For the present, we must still assume the hard and expensive task of looking for carcinogens by determining a compound's carcinogenic action because that is the only way we can know what we have found.

HARRY RUBIN
Department of Molecular Biology, University of California, Berkeley 94720

References

1. B. N. Ames, F. D. Lee, W. E. Durston, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 782 (1973); B. N. Ames, W. E. Durston, E. Yamasaki, F. D. Lee, *ibid.*, p. 2281.
2. W. Burdette, *Cancer Res.* **15**, 201 (1955).
3. B. Oppenheimer, E. Oppenheimer, E. Stout, I. Danishefsky, *Science* **118**, 783 (1953).
4. W. Gardner, C. Pfeiffer, J. Trentin, in *Physiopathology of Cancer*, F. Homburger, Ed. (Harper, New York, 1959), p. 152.
5. A. W. Wood, R. L. Goode, R. L. Chang, W. Levin, A. H. Conney, H. Yagi, P. M. Dansette, D. M. Jerina, *Proc. Natl. Acad. Sci. U.S.A.* **72**, 3176 (1975).
6. R. McKinnell, B. Deggins, D. Labat, *Science* **165**, 394 (1969).
7. J. Gurdon and V. Uehlinger, *Nature (London)* **210**, 1240 (1966).
8. S. Mondal and C. Heidelberger, *Proc. Natl. Acad. Sci. U.S.A.* **65**, 219 (1970).
9. A. Braun, *ibid.* **45**, 932 (1959).
10. See B. Mintz and K. Illmensee [*ibid.* **72**, 3585 (1975)] for the most recent and most unequivocal case.
11. T. Sonneborn, in *The Nature of Biological Diversity*, J. Allen, Ed. (McGraw-Hill, New York, 1963), p. 165; H. Rubin, in *Major Problems in Developmental Biology*, M. Locke, Ed. (Academic Press, New York, 1966), p. 317.

For the last 10 years I have been involved in the development and validation of a rapid, sensitive, and economical test method (using *Salmonella* bacteria and mammalian microsomal enzymes) for de-