Letters

National Security

In his recent letter (24 Dec., p. 1270) commenting on articles by William J. Broad (News and Comment, 19 Nov., p. 769) and by Hans Bethe (*1*), Edward Teller makes some statements about me and my views. He is basically correct about my views on the superbomb program; his statements about my general views are not correct.

Far from being "unwilling to acknowledge any danger," I believe the United States and the world face two very serious and closely connected problems. The common shorthand name for one is the Russian Threat; the common shorthand name for the other is the Nuclear Arms Race, with a Nuclear Holocaust as its logical final result. In our search for solutions to either one of these problems it is absolutely essential to take the other into account, and it is truly dangerous to propose and carry out programs designed to mitigate one of these problems that ignore or exacerbate the other. Unfortunately, many people in high places and at both extremes do just that, and the net result has been a steady worsening of our absolute national security position for at least the last 30 years.

For 25 years I have believed and said that the United States seriously undervalues and underutilizes nuclear arms control and disarmament as a major means for coping with its national security problems, and I have supported programs and worked in projects designed to rectify that situation. Similarly, for my entire career, I have supported programs and worked on projects whose main or sole purpose has been to improve the quality of Western military preparedness, and I still do.

Teller also speaks of "self-delusion." I suppose all of us are vulnerable to it from time to time, but surely one of the outstanding delusions of recent times has been the notion that a technological means for defending the nation against a general nuclear attack is just around the corner. This grand self-delusion has been shared by a number of technologists (including Teller) for at least 25 years now, but to date the record clearly shows that they have been quite wrong. Of course, it is conceivable that among the discoveries and inventions yet to be made will be one which will in fact lead to a solution to this problem. Like Bethe and Teller, I believe that would be a good thing, and I have always supported work intended to lead to such a possibility. However, I believe it is very unlikely that an effective general defense will be invented in the foreseeable future. I further believe, along with most others who have had experience with this particular technological issue, that if the necessary "breakthrough" does turn up, it will probably not involve either nuclear fission or fusion in an essential way.

HERBERT F. YORK
Science, Technology and Public Affairs, University of California, San Diego, La Jolla 92093

References

1. H. A. Bethe, *Los Alamos Science* (Fall 1982), pp. 43–53.

Homology

In evolutionary studies, homology implies common ancestry. When the biochemist Margoliash (*1*) in 1969 defended that simple and historically correct usage, he had been arguing against an earlier contention of protein chemists. They had stated, in effect, that "homology" should merely be a synonym for "similarity" because the evolutionary biochemist "has not and cannot have any independent experimental evidence relative to the question of ancestral genes" (*2*). Now with DNA sequences, one can reasonably evaluate the probability that two genes shared a common ancestor. Margoliash's stricture stands with even more force today.

Yet many concerned with DNA, protein, or karyotype evolution have not heeded the century of usage of the term homology in evolutionary biology. A recent extremely interesting report in *Science* concerned chromosomal comparisons of human, gorilla, chimpanzee, and orangutan (19 Mar., p. 1525). Unfortunately, the authors wrote that comparisons of chromosomes "have revealed a general homology of chromosomal bands in the four species and suggested a common ancestor for chimpanzee, gorilla, and man." This is the cart before the horse. Similarity in karyotype banding (or sequence comparisons) can lead to the inference of a common ancestor, in which case, if the inference is accepted, the structures (or sequences) can be referred to as homologous. If these similarities were owing to convergence caused by similar function or simply chance, they would only be analogous to each other. The advantage for the confinement of homology in papers with evolutionary implications to mean similarity by common ancestry is that it prevents what were rightly referred to as "insidious misunderstandings" (*1*).

THOMAS J. M. SCHOPF
Department of the Geophysical Sciences, University of Chicago, Chicago, Illinois 60637

References

1. E. Margoliash, *Science* **163**, 127 (1969).
2. W. P. Winter, K. A. Walsh, H. Neurath, *ibid.* **162**, 1433 (1968).

Ranking Carcinogens for Regulation

When I compare the ranking scheme proposed for regulating carcinogens by Robert A. Squire (20 Nov. 1981, p. 877) to one which employs the fitting of mathematical models, I find that most of the factors considered important by Squire could be included more objectively in a mathematical model approach. The most surprising feature of his ranking system is the lack of weight given to carcinogenic potency. In fact, two chemicals that are identical in their carcinogenic effect, except that one is 1 million times more potent than the other, could be given the same recommendation for regulation in Squire's system (if, for example, 0.75 gram per kilogram of body weight per day of one carcinogen caused the same response as 0.75 microgram per kilogram per day of another). Most any data-fitting scheme, on the other hand, would lead to the correct conclusion that, all other things being equal, the allowable exposures of the more potent carcinogen should be 1/1,000,000 of those allowable for the less potent one. If malignant neoplasms are deemed to be important, then those could be used in fitting a model. It would seem that the absolute numbers of neoplasms are more important than the ratio of malignant to nonmalignant. According to Squire's ranking system, finding 10 malignant and no nonmalignant neoplasms would be more cause for concern than finding 10 malignant and 50 nonmalignant ones—which seems illogical.

It is possible to incorporate negative

data into model-fitting approaches. Whenever a chemical is unequivocally carcinogenic in at least one species (this would have to be true before Squire's ranking method would be employed), a model-fitting approach that utilizes both positive and negative data could objectively account for negative data. This seems preferable to simply awarding a score based upon whether one or two species are affected, particularly since negative findings can be due to limitations in experimental design.

Regulatory action must take account of not only the carcinogenic potency of a chemical but also the numbers of humans exposed and their exposure levels. With a model-fitting approach there is a built-in procedure for doing this; the ranking system approach would require still further arbitrary rules. A related problem is the fact that the regulatory actions recommended by Squire for different classes of carcinogens are stated very generally; examples include "restrict or ban," "no action," "labeling," and "public education." These recommendations beg the issue; regulatory agencies need to know *how much* to restrict use. To answer this question regulators would undoubtedly be led back to a model-fitting approach.

The chief criticism of the model-fitting approach—and a valid one—is that the shape of the dose-response curve at low doses is impossible to determine experimentally, and different models, fit to experimental carcinogenicity data, often lead to vastly different estimates of low dose risks. Perhaps this difficulty could be mitigated by admitting that we don't know how to protect human health to the levels of 10^{-6} or 10^{-5} lifetime risks and to begin paying more attention to comparisons of carcinogenic potencies rather than absolute levels of risk. At any rate, the data ranking system proposed by Squire doesn't solve this problem; instead, it appears to create some additional ones. It seems likely that any such formula for ranking data would be subject to similar criticisms.

KENNY S. CRUMP
Science Research Systems, Inc.,
1201 Gaines Street,
Ruston, Louisiana 71270

We consider the validity of the scoring system proposed by Squire for the purpose of ranking the tumorigenic potential of known animal carcinogens to be questionable; this is due to an inherent weakness which, in many cases, will cause it to fail.

Briefly, a scoring system is applied by the author to six factors which are considered to be relevant parameters of the carcinogenicity of a substance; the final score is then derived by summing up the six scores arithmetically. It must be stressed that, although a set of six individual scores can adequately describe the biological behavior of a carcinogen, their sum does not. Several different combinations of them (each of these combinations representing a carcinogen with defined biological properties) will yield an identical final score if the proposed procedure is applied. Consequently, substances whose carcinogenicity varies greatly in nature and degree will be merged into a seemingly homogeneous class so that their individual qualities are blurred.

For the proposed ranking procedure, an unequivocal assignment of a single rank to a given set of relevant individual scores apparently does not exist.

E. FRÖHLICH
R. HESS
Toxicology, Ciba-Geigy Ltd.,
CH-4002 Basle, Switzerland

The comments by Crump and by Fröhlich and Hess about my ranking system approach for animal carcinogens are among several constructive opinions I have received. A major reason for my devising a ranking scheme is the fact that mathematical models utilize only dose-response data and ignore most of the biological information derived from animal tests that is relevant to risk assessment. If, indeed, other biological factors can be incorporated into mathematical models, this may be the optimal approach. However, in my experience, statisticians have been reluctant to consider graduated observations.

Crump's point about carcinogenic potency receiving inadequate attention is based upon the possibility of two chemicals having an identical effect in all the factors included in my system, except dose-response. This has never occurred in my experience, and precisely because chemicals vary so widely in all their effects, not only in dose-response, the model approach as currently employed is inadequate for risk assessment.

Crump's second point on absolute numbers of neoplasms (or animals with specific neoplasms) is well taken, and I agree that this is an important oversight. I have tentatively modified the system since publication to include an additional factor based upon the proportion of animals with the neoplasms in question in treated versus control groups. The P value resulting from statistical analysis of the tumor incidences may be a useful way to handle this. For example, a very low P value of $< .001$ would receive more weight than a P value of $< .05$. The number of animals affected by a carcinogen, the degree of tumor progression (malignancy), and the dose-response relationship are all reflections of carcinogenic potency in the test animals and, I agree, should be represented in the system.

Crump's comment on human exposure is an important one, and this factor could be incorporated into a ranking system. However, I considered it to be part of the next step, that is, the regulatory decision. As Crump points out, "how much to restrict" is a critical question, but it is a judgment based not only on risk but also on populations affected, patterns of use, benefits, economic considerations, and other factors that are not addressed in my article.

As indicated by Crump, a weakness of the model-fitting approach is the lack of information at low dose exposure. However, a greater weakness, as indicated above, is that models ignore much of the relevant biological information derived from animal tests. I am not opposed to the use of mathematical models. However, they are currently based on too limited data, and I would prefer their use in conjunction with the weight of biological evidence.

The letter by Fröhlich and Hess raises a question fundamental to any such systematic approach. I agree that, if each of the factors were independent variables, the sum total might be meaningless. However, the factors are probably not independent. They, in fact, generally correlate in their direction of severity and their "sum" reflects the weight of evidence for estimation of carcinogenic potential in an untested species. I do not necessarily believe the factors should be given equal weight, as most are in my article, or that the figures I have assigned have any intrinsic value. They are largely arbitrary. However, I believe it is the *cumulative* evidence that must be evaluated in carcinogenesis risk assessment, and the system I proposed is merely an example of an approach that could be considered.

ROBERT A. SQUIRE
Division of Comparative Medicine,
School of Medicine,
Johns Hopkins University,
Baltimore, Maryland 21205

Erratum: In the issue of 9 August 1968 (p. 541), *Science* printed the Nobel lecture of Hans A. Bethe on "Energy production in stars." Eddington had at one time hypothesized that stellar energy arises from complete annihilation of matter. The energy to be set free by such a process, if it could occur, would be enough to supply the sun's radiation for 15,000 billion years. In the lecture, this number was erroneously given as 1500 billion years.