LETTERS

Recombinant DNA: NIH Guidelines

Erwin Chargaff's and Francine R. Simring's letters (4 June, pp. 938 and 940) regarding recombinant DNA research require comment. Analysis of the history leading to, and the substance of, the guidelines for conducting this line of research (*1*) suggest that both of these critics overlooked important facts.

It is relevant to our comments that we were among those who first publicly expressed concern over the potential hazards of recombinant DNA experiments (*2*, *3*); we were members of the organizing committee of the Asilomar Conference (*4*); neither of us is a member of the National Institutes of Health (NIH) Program Advisory Committee on Recombinant DNA, although we have been active commentators on that committee's efforts to develop guidelines; and one of us is, and one is not, pursuing recombinant DNA experiments in our own laboratories.

Chargaff questions the propriety and legitimacy of NIH's role in formulating guidelines for recombinant DNA research. Certainly the principal biomedical research arm of the United States must be concerned with the health of laboratory workers and the public at large. Even if Congress or another governmental agency had intervened early and assumed responsibility in the area of recombinant DNA research, it is not conceivable that policy could properly be formulated without the involvement of NIH and informed members of the scientific community. Acceptance of responsibility in this matter by the past and present directors of NIH was courageous, farseeing, and proper; moreover, the directors and the consultants who labored diligently to produce the guidelines deserve our gratitude.

Contrary to the implications in the letters by Chargaff and Simring, the discussions leading to the guidelines were directed toward eliminating or minimizing real and imagined hazards, rather than balancing benefits and risks. The only certain benefit is increased knowledge of basic biologic processes; the predicted benefits for medicine, agriculture, and industry will follow only upon this increased knowledge. It was concern for the potential risks with recombinant DNA that led a group of scientists involved in this research to call for a voluntary deferral of certain experiments (*3*). The guidelines either proscribe such experiments or require extremely stringent containment measures for them. Indeed, the list of experiments in the proscribed category was extended between 1974 (*3*) and the Asilomar Conference report (*4*) and is even further enlarged in the guidelines (*1*).

Permissible experiments under the guidelines are classified according to the best available estimate of potential risk. Increasing potential risk requires increasingly stringent biological and physical containment measures. Not all recombinant DNA experiments yield "new" organisms; recombination between the DNA's of organisms known to exchange genetic information in nature do not add uniquely man-made species to the biosphere. In these cases, the guidelines follow the general principle that the experiments are to be carried out under previously defined conditions for handling the most hazardous parent of the recombinant. When DNA from species that are not known to exchange genetic material in nature are recombined, additional precautions are required. And it is precisely concerns of the kind raised by Chargaff (for example, the unpredictable consequences of intestinal colonization by organisms carrying potentially harmful genes) that led to such special precautions. Admittedly, the estimates of potential hazard are presently conjectural and controversial. But it is precisely for this reason that the requirements specified in the guidelines are more stringent than most scientists estimate are required for safety.

The adequacy of the containment prescribed for permissible experiments is then the central issue. Estimates of achievable containment levels must be based on available facts. We share with Chargaff the belief that it is unacceptable to harm others. But the recommended procedures are not "smokescreens." The P3 and P4 levels of physical containment are designed specifically as controls on accidental dispersal and human errors; they are defined in detail in the guidelines, and there is documented experience on which to judge the efficacy of these facilities.

With regard to biological containment, the encompassing description of *Escherichia coli* as the "predominant facultative species in the large bowel" in Chargaff's letter is misleading. The guidelines require the use of strain K12 of *E. coli* or disabled derivatives of it. Strain K12 is not a predominant species in the large bowel; indeed, the available evidence indicates that *E. coli* K12 rarely establishes itself as a viable resident in the human gut (*1*). The disabled derivatives of K12 must pass strict tests to establish that they are unable to live in natural environments. Only thereafter can they be certified by the NIH Advisory Com-

mittee for use in experiments requiring high levels of containment. The reports from the April 1976 meeting of the Advisory Committee suggest that the committee will be very cautious in its evaluation and certification of such systems. And, contrary to Chargaff's and Simring's statements, the problem of secondary natural recombination of foreign sequences, either out of the original host and into common enteric organisms, or between the experimental vectors and naturally occurring organisms and vectors, has been central to the discussions leading to definitions of disabled host-vector systems. In fact, the guidelines themselves describe and deal with those problems. They require that data regarding the chance of spread of the foreign DNA (by survival of a host cell or secondary recombination) in particular environments must be supplied; the probability of such spread must be less than 10^{-8} before certain experiments are permitted. Probabilities on the order of 10^{-8} afford a high level of confidence for achieving meaningful containment, considering the small numbers of organisms that could possibly escape as a result of human errors or flaws in physical containment. Thirty years of study of the genetic chemistry of *E. coli* K12 provides confidence that such levels of containment can be achieved. While it is important to investigate alternatives to *E. coli* K12, it is not at all certain that useful and safer organisms exist. Predictions about the existence of rare and fastidious organisms unable to exchange DNA with common organisms inhabiting man or other living things are highly speculative.

If Chargaff and Simring had examined the massive and readily available correspondence, minutes, and documents accumulated over the last 3 years, they would have recognized that precisely those matters they claim were disregarded were discussed in considerable detail. (This documentation has been collected by the Massachusetts Institute of Technology Program in Oral History of Sciences.) The charge that discussions have been "permeated by the assumption that the work will go ahead" or that we can "act now and learn later" is inconsistent with the 1974 moratorium and with the acceptance at Asilomar, and in the guidelines, of the principle that certain experiments should be deferred. The essence of the development of the guidelines by the NIH Advisory Committee was a discussion of alternative containment specifications, including those mentioned by Simring. Simring fails to point out that the letters to the director of NIH from eminent scientists

and laymen ran the full gamut in their views concerning the necessity for more or less stringent control measures. Those same issues as well as others raised at the public hearings held in February 1976 were subsequently reviewed in extraordinary depth by the director and his staff. The director then asked the Advisory Committee to again address certain issues. In April, after long and searching consideration, the Advisory Committee reaffirmed certain earlier recommendations and changed others. [This is discussed in the lengthy commentary accompanying the guidelines (*5*).]

Chargaff and Simring urge a slow approach to experimentation. It should be recognized that a "slow approach" is what was achieved by the voluntary deferral and the Asilomar guidelines. Research on recombinant DNA will proceed at only a fraction of the possible rate because of the need for certified host-vector systems, acquisition of sophisticated physical containment facilities, and the required deferral of a large group of interesting and important experiments. Presently, in addition to a slowdown, there is a far-reaching awareness on the part of investigators of the need for caution, and a largely cooperative atmosphere exists regarding the need for control of this type of experimentation.

Simring's attempt to draw analogies between recombinant DNA and the nuclear energy controversies obscures the facts. The discussions on recombinant DNA have been public since their beginning. The matter has been widely reported by the public press. The publicity permitted all concerned individuals and groups to enter the deliberations. No datum has been classified and no commentary has been withheld from the public. Indeed, most policy has been developed in public sessions. In addition to containment, the unquantifiable problems have been addressed. The problems may be difficult, but they can be dealt with in a rational manner.

Finally, we are deeply disturbed by the distortions, derision, and pessimism that permeate Chargaff's comments. He appears to see science as a curse on our time, and men as feeble. In our view it is knowledge and understanding derived from science and scholarship that lead men to rationality and wisdom.

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2. M. Singer and D. Söll, *Science* **181**, 1114 (1973).
3. P. Berg *et al.*, *ibid.* **185**, 303 (1974).
4. P. Berg, D. Baltimore, S. Brenner, R. O. Roblin, M. F. Singer, *ibid.* **188**, 991 (1975).
5. D. S. Fredrickson, *Decision of the Director, National Institutes of Health, to Release Guidelines for Research on Recombinant DNA Molecules* (National Institutes of Health, Washington, D.C., 1976).

Environmental Impact Statements

In his editorial of 7 May (p. 509), D. W. Schindler criticizes ecologists involved in the legal procedure of environmental impact assessment. To summarize, Schindler says that environmental statements are used as a ploy by politicians to silence "ecofreaks"; that environmental statements are voluminous reports containing reams of uninterpreted descriptive data produced in insufficient time by incompetent scientists using an ancient, descriptive, tired old bag of tricks. He contends that the conclusions and recommendations of this "gray literature" are never scrutinized by the scientific community at large. Further, he asserts that the advancement of the scientific method is in jeopardy and the result will be a declining credibility for environmental science and scientists, a reduction in quality of personnel, and the degradation of our natural resources. To this we politely say, "bunk."

The fundamental basis for impact statement preparation was set forth in the National Environmental Policy Act (NEPA) of 1969. Congress, in enacting that statute, established a clear mandate to all federal agencies to consider and give appropriate weight to environmental factors in decision-making. The "detailed statement" required by section 102(2)(C) of that act serves at least three fundamental purposes. First, it provides assurances to Congress, the President, the Council on Environmental Quality, and the public that the agency has made a good-faith effort to consider the environmental amenities that NEPA is designed to protect. The courts have held that to accomplish that end the statement must "explicate fully its course of inquiry, its analysis, and its reasoning" (*1*). Second, NEPA has been properly characterized by the courts as "an environmental full-disclosure act," that is, it brings environmental issues to the attention of the public. An environmental impact statement, therefore, must be organized and written in language that can be understood by decision-makers and the general public and, at the same time, must contain sufficient technical and scientific data to alert specialists to particular problems within their area of expertise. Third, and perhaps most important, the "detailed statement" requirement of section 102(2)(C) helps ensure the integrity of the agency's decision-making process. It is wrong to presume, as Schindler does, that environmental impact statements are technical, scientific documents.

An environmental impact statement as we present it is a document issued by a federal agency [the Nuclear Regulatory Commission (NRC) or the Energy Research and Development Administration (ERDA)] planning a major action. Basically, these impact statements fall into two categories: (i) generic statements that examine a whole program [such as the liquid metal fast breeder reactor (LMFBR) program] or a concept (such as offshore nuclear power stations); and (ii) site-specific statements that relate to a given facility (such as the Indian Point Nuclear Station or the Clinch River Breeder Reactor). The purpose of the generic statement is to decide if a proposed activity should continue, say, to the point of siting and building a facility of the type described. Such continued action requires a site-specific impact statement. Although generic statements are sometimes voluminous because of the scope of the proposed activity (for example, that of the LMFBR program), site-specific statements are neither voluminous nor primarily descriptive. This kind of statement is an interpretation and analysis of data presented in a voluminous environmental report. In the case of nuclear power stations, the environmental report is prepared by a utility according to NRC specifications. Environmental data collected for a minimum of 1 year (usually much more) have been incorporated into the environmental report. The data collection program and methodologies are clearly spelled out in the utility's environmental report. If more data are required, they are furnished before proceeding with the assessment. Only after this data collection is considered adequate do we receive the environmental report and the assignment to assess the impacts and prepare the statement. An average of 8 months is spent in summarization and analysis of the data by an interdisciplinary team of professional scientists. The amount of money spent is a function of the potential for environmental degradation. The time spent is the amount of time needed to analyze the potential impacts for a specific setting

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