Recombinant DNA Research: Beyond the NIH Guidelines

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The guidelines (*1*) on recombinant DNA research issued by the director of the National Institutes of Health (NIH) last June represent a compromise between two fears, (i) that of conceivably dangerous new biological entities and (ii) that of excessive regulation of the search for new knowledge. These were the fears that led to the Asilomar conference of February 1975. This international conclave of about 150 molecular biologists, in the presence of members of the press and four attorneys, evolved a consensus on a concept of balance between the estimated risk of conceivable experiments and the estimated efficacy of proposed levels of containment.

The Asilomar consensus became the foundation for the NIH guidelines, with appropriate modification on a number of disputed points. The NIH director made clear in publishing the guidelines that they are a step in a decision process requiring continual monitoring and modification as knowledge grows.

In their present form, the guidelines provide a framework for continuance of recombinant DNA research under regulatory surveillance. They affirm and implement the view that the research is potentially of enormous benefit, but conceivably also may involve hazards difficult to assess. The guidelines do not have the force of law nor even of formal regulations. Their effectiveness depends on their NIH auspices, since it represents the weight of a major federal funding agency that also has carried out a formal assessment. Other federal agencies are accepting the NIH lead, and an interagency committee has been formed to oversee executive implementation. The guidelines will exert heavy pressure for conformity on U.S. academic science and moderate pressure on U.S. industrial circles. They will have some influence abroad, and an international framework to facilitate such influence is being organized. However, the guidelines themselves can hardly assure universal compliance nor can they allay all anxiety. In terms of the particular issues they address, they are a good beginning.

Their strategy is to assign responsibility for compliance to individual investigators backed by peer review through sponsoring and supporting agencies. Responsibilities of the investigator are also the "responsibilities of the institution . . . fulfilled on its behalf by the principal investigator." The institution, in addition, is required to establish a biohazards committee of suitable competence to certify to the NIH that research for which support is sought will be carried out in accord with the guidelines.

The NIH study sections that consider applications for support will independently evaluate biohazard and determine whether proposed physical and biological containment are adequate. An NIH Recombinant DNA Molecule Program Advisory Committee will advise top officials of the Department of Health, Education, and Welfare (HEW) and NIH concerning management of biohazards resulting from the broad recombinant DNA program. The NIH staff will insure that all NIH-supported investigators comply with the guidelines and the staff will perform site inspections of containment facilities intended for the potentially most hazardous work.

The surveillance and regulation provided by these arrangements are fairly characterized as moderate, in the sense that some proposals made during the course of consideration of the guidelines were more and some were less stringent than the eventual result [see the statement of the NIH director (*1*)]. In their present form the guidelines may be expected to broaden awareness of potential hazards, to reduce the chances that highly hazardous experiments will be undertaken irresponsibly, and to render less probable damaging effects from any degree of hazard that particular experiments may involve. Their consequence will depend almost entirely on the attitudes and performance of principal investigators, supported by the monitoring influence of other scientists in sponsoring institutions and the NIH. Thus, in balancing the twin fears of the Asilomar Conference the guidelines rely primarily on self-regulation within the involved research commmunity. There is sound rationale for this as an effective holding operation to stave off hasty and inappropriate action or decision. The strategy does not, however, fully cope with all of the issues presented by recombinant DNA research. This requires consideration of the perspectives beyond those of the involved community of investigators and even of the scientific community as a whole.

Such broadening of perspective already has begun. Aspects of the general public interest will be considered under the National Environmental Protection Act now that the NIH has filed an environmental impact statement (*2*) on the guidelines. The interest of one locality has already demanded attention when the Cambridge City Council, in connection with recombinant DNA research at Harvard and the Massachusetts Institute of Technology, asked for a further local moratorium. Other communities in the vicinity of research institutions are evincing similar concerns. These stirrings focus on the matter of biohazard but also raise other issues.

The concerns expressed are not, in fact, exclusively or typically environmental. They range from the technical to the ethical; they rattle skeletons that include Galileo's and even that of Socrates. At the same time they echo some of the implication of Hiroshima. Scientists, despite their demonstrated self-discipline in this case, are regarded in some quarters as being guilty of overweening and arrogant ambition. Experimentally induced genetic liaison among bacteria, mice, and men is said to threaten incalculable and uncontrollable dangers. To some, the practical and ethical consequences of human beings becoming dictators of all evolution, including their own, is found frightening. There is some public resentment that science is thrusting an unprepared and reluctant humanity into a brave new and possibly Orwellian world.

These are serious concerns that are not easily substantiated or allayed. However, a convincingly objective, dispassionate, and comprehensive analysis, without preconception and intended to inform all points of view, may help. I suggest that such an analysis is urgent before any further major policy decisions

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are made about recombinant DNA research.

There are urgent reasons why such a second step is needed even though the first effort is hardly truly in place, and why we should not wait to gain some experience with the guidelines. Given the breadth and magnitude of the issues that are now perceived by a significant number of responsible persons, hindsight suggests that the procedure that produced the guidelines was limited in its context. The guidelines appropriately provide a sound framework for dealing with immediate potential hazards to life and health as perceived primarily by involved investigators. Significant risk is conceded by these investigators, more by some than by others. Whatever the degree of risk, the guidelines were drafted and adopted under conditions that did not give substantial opportunity for widespread "informed consent." Public discussion and participation has, as yet, been minimal despite the intensive involvement of a dedicated few. Moreover, the possible advantage of concentrating and isolating facilities for testing the allegedly more dangerous activities remains a subject of controversy that has not been resolved by the guidelines.

Broader open assessment also is needed of the issues that go beyond human health hazards. These issues, probably wisely, were minimized or specifically excluded in formulating the NIH guidelines. Potential ecological hazards, although touched on, were deemphasized by the very selection of NIH as the lead federal agency. What may be loosely called ethical, social, and political issues were avoided entirely. Substantial concern has been expressed about a series of such questions, concerns that remain to be evaluated on balance against potential benefits. Are there some kinds of knowledge, even though they offer health benefits, for which the price in other values is too high? Is it safe, in the present state of our society, to provide means to intervene in the very essence of human individuality, even to achieve humanitarian ends? Can genetic destiny, whether of human or other species, wisely be governed by human decision? Will genetic engineering widen or close the existing gap between knowledge-rich and knowledge-poor cultures and nations? Will it provide a new club in the hands of terrorists or dictatorial regimes? Will it render still more turbulent the currents of national and international power conflict?

These are the kinds of questions often raised when large increments of knowledge are suddenly thrust upon unprepared minds. Uncertainty and fear, as well as wonder and excitement, accompany the disclosure of the previously unknown. Moreover, every potential increment of individual and social control brings misgivings. The advance guard sights new vistas, and the rear guard senses possible future threats. In an open society the only effective answer is full and patient ventilation. Cover-up, whether fancied or real, whether inadvertent or deliberate, whether political or scientific, only further alarms the public subconscious.

Questions dictated by anxiety about the future are often vague and difficult both to phrase and to answer. They are, nonetheless, dangerous to ignore. In the present instance, there admittedly are legitimate grounds for concern and risks of uncertain dimension to be taken. Moreover, both the risks and benefits are difficult to quantitate, and neither may bear equally on all groups. Discussion of what can be done to reduce uncertainty may not yield universal assurance but it can lessen purely imagined fears. Such fears, otherwise, may come to dominate public reaction and become major determinants in new policy decisions.

It is important, therefore, to broaden and transform the restricted context of the Asilomar conference and the resulting NIH guidelines. The approach should now be dominated not by fears but by fundamental and positive objectives: (i) to continue expansion of the understanding of genetic phenomena; (ii) to minimize foreseeable hazard, whether to health, essential human relations, or biotic environment; (iii) to consider the priorities to be assigned to realization of positive social benefits from growing genetic engineering capability; (iv) to give "due process" to deeply held values whose accommodation may require time and special attention; and (v) to provide opportunity for "informed consent" or other reaction from the several publics that may otherwise see themselves involuntarily placed at risk.

Under what auspices and in what time span should this kind of broad assessment occur? The objective is to inform public understanding and improve further policy decisions that may be necessary. The auspices, therefore, must be chosen to assure complete objectivity and comprehensiveness. On the other hand, the impact of the assessment must be able to feed quickly and efficiently to decision points ranging from the local to the international level. (The greater the danger is estimated to be, the more the solution defies local and demands international action.) In the United States, only the federal government can provide such auspices. Moreover, its responsibility cannot, in this instance, be delegated—either to the National Institutes of Health, or to the National Science Foundation, or to the National Academy of Sciences. None of these can effectively convey the full governmental presence nor can they achieve the necessary full perspective.

The broadest and highest national auspices include the President and the Congress. Moreover, both the executive and legislative branches will have to implement any national and international policy that flows from the analysis—whether it only confirms the NIH guidelines or proposes modification or alternatives. Careful consideration is needed of possible mechanisms, but a joint commission chosen by the President and the Congress, with the Vice President as chairman, would seem eminently suitable. Such a commission should be charged not to conduct the analysis itself but to assure its quality and comprehensiveness. The President's Science Adviser and his staff in the Office of Science and Technology Policy could be the channel for scientific expertise, the Office of Technology Assessment could be the channel for assessment expertise, and the executive agencies and appropriate congressional committees could be the channels for public reaction and other considerations.

Whatever the mechanism, a full assessment should be forthcoming not more than 2 years from the date of initiation and not more than 3 years from the date of the NIH guidelines. In this time-span any serious defects in the NIH guidelines can be detected, yet no line of research under control of the guidelines is likely to have progressed to irreversibly damaging consequences, even if such a possibility proves necessary to entertain. In this time-span, too, suitable legislation can be enacted to establish the mechanism of assessment and, if necessary, to implement policy that may be suggested during the assessment. A much shorter time than 2 years may not yield reliability, and a longer postponement of possible new decisions may not satisfy some current concerns.

Whether this procedure is too elaborate and portentous is debatable. It has been suggested in several authoritative evaluations (*3*) that the sweep and continuing momentum of molecular genetics, even excluding recombinant DNA technology, presage practical consequences as profound as any yet registered in this knowledge-prolific century. Recombinant DNA technology, moreover, lies

close to the heart of the advance of molecular genetics and epitomizes many issues of the envisioned "biological revolution." Earlier and fuller public analysis of the consequences of nuclear fission, insecticides, fossil fuels, or antibiotics might have moderated or avoided some of today's less desirable consequences.

Is there something to be lost by a "high visibility" assessment? This is again debatable. A Washington-based extravaganza in the polarizing light of the mass media certainly is not needed. The procedures adopted must avoid this. The substantive activity is only in small part suitable for Capitol hearing rooms. In large part it belongs in secluded conference rooms and individual studies. Yet somehow the overall process must be observable and eventually widely shared. Will such visibility elevate public unease to hysteria, thereby cutting off the additional insight that is the only sure antidote to uncertainty? Hopefully not, if the analysis is designed and conducted appropriately. Is this kind of issue better resolved in informed inner circles rather than in the view of a general population that some believe does not have sufficient background for sound judgment? Here the bite of the doctrine of "informed consent" and the weight of "sunshine politics" must take precedence over the nervous concerns of the expert and the professional.

There is, therefore, really no choice but to take this new broader second step, even at the risk of some confusion and inconvenience. Recombinant DNA technology and its associated issues need to be opened to full discussion and the widest understanding under appropriate auspices. If the potential hazards of this step prove manageable, public confidence will be elevated, and the traumas of Hiroshima and environmental pollution may be partly compensated. If the hazards of recombinant DNA technology should prove unmanageable but are concealed, the rate of advance of knowledge may be slowed by far more than inconvenience. If the whole process goes well, science, technology, and the world will each breathe more easily, knowing that on this issue they live openly and honorably, each with the other.

References

1. *Federal Register*, vol. 41, No. 131, 7 July 1976, part 2, pp. 27902–943.
2. *Ibid.*, No. 176, 9 September 1976, part 3, pp. 38426–483.
3. For example, *Report of the President's Biomedical Research Panel*, Publication No(05)76-501, Appendix A., Department of Health Education and Welfare (Washington, D.C. 1976), pp. 11–12 and 25-26.

4. This statement has benefited from the comments and discussion of more than a dozen colleagues in Class II of the National Academy of Sciences. I do not name them to avoid any suggestion of their individual or collective endorsement. Their very different points of view, nonetheless, contributed substantially to the final form of the statement and I am grateful to each of them.

The Histocompatibility System in the Warao Indians of Venezuela

Warao exhibit restricted polymorphism in A, B, and C loci, HLA system, and simplicity of the HLA-D locus.

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The Warao are a tribe of Amerindians who inhabit the Delta region of the Orinoco River in northeastern Venezuela. Several smaller groups of Warao have also settled in adjacent areas to the northwest and the southeast of the Delta proper (60° 40′ to 62° 25′W; 8° 25′ to 10° 5′N). The entire tribe does not exceed 16,000 individuals. With its labyrinthian network of waterways and its islands of dense pluvial forests, the Orinoco Delta has offered refuge to its inhabitants from expanding tribes of Arawakan and Cariban affiliations (*1*).

The tribal name is a self-denomination meaning "Boat People." The Warao are small in stature, measuring 160 cm and less (*1–3*). Travelers through their territory have often commented on the strongly developed thorax and arms and weaker lower extremities of these Indians. That the observed somatological characteristics of the Boat People are the result of environmental adaptation was confirmed by Gardner (*4*), who found that scores for the leg strength of the Warao were significantly below the scores obtained for other Indians.

According to reliable demographic information, the Warao are experiencing a population explosion. The women show a high rate of fertility, averaging 5.4 live births per woman of all ages. The average reaches 8.5 for women with completed reproductive age. The average number of surviving offspring per woman is 3.7, a number that increases for women over 40 years of age to 5.6, or 69 percent of live births (*3*). This figure is very high for tribal populations, where it is not uncommon to find average values below four surviving offspring per woman past reproductive age (*5*).

From the time they were discovered, the Warao have had only sporadic contact with Europeans. Until the 1930's, they did occasionally venture out of the Delta to trade overseas with Trinidad or upstream with Angostura (Ciudad Bolívar). For centuries, however, their basic livelihood depended upon swamp scavenging and riverine and coastal resources, as well as on the systematic exploitation of *Mauritia* sago. It is only recently that horticulture was introduced among them. Nowadays, the Warao plant fields of ocumo, bananas, and maize. Some manioc is also grown and rice serves as a cash crop (*1, 3, 6*).

The Warao are grouped into several independent subtribes. Each subtribe consists of several bands of 25 to 60 individuals that live in one or more villages. The bands of a subtribe form marriage alliances, assist each other in the acquisition of food, and converge for ritual gatherings. Marriage between secondary cousins is preferred but, in the

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