Regulation of Products from Biotechnology

FRANCES E. SHARPLES

PROPONENTS OF BIOTECHNOLOGY OFTEN ASSERT THAT THE safety of "genetically engineered" organisms has been established because adverse effects have yet to be documented after handling the organisms in contained facilities for a decade. But the past is not necessarily a reliable guide to the future. Although the absence of effects on the health of workers in biotechnology laboratories is admirable, it is not particularly relevant to the question of whether uncontained uses of modified organisms will be equally harmless. For various reasons, the concerns for environmental applications of biotechnology products are fundamentally different from those for laboratory uses.

Environmental Applications Versus Laboratory Uses

First, in environmental applications, it is the myriad of nonhuman species in an ecological community that will be exposed to released organisms. Second, the spectrum of potential effects is not restricted to pathogenicity, although this, too, is certainly a significant concern. Additions of nonindigenous organisms can influence the structure (population size and species diversity) and function (energy and material dynamics) of ecological communities through a variety of mechanisms that sometimes displace or destroy indigenous species. Such events are copiously documented in the literature of ecology (*1*), and experience with the ecological dislocations and economic losses that sometimes result when organisms are introduced into environments where they are not normally found is too abundant to be trivialized or ignored.

Third, the degree of control afforded by experiments conducted in containment differs from that involved in releases in the field. Once released, modified organisms that find suitable habitats may not only reproduce and spread, but can be expected to evolve in ways that are beneficial to their own survival. The evolutionary process can allow modified organisms to escape constraints imposed by debilitating them before their release, so that both physical and biological containment may be nullified outside the laboratory. Fourth, differences of scale become important as the transition from research to commercial products is made. It is one thing for trained experimenters to apply novel organisms to a 0.2-acre field under close supervision. It will be quite another matter to market commercial products for widespread use by applicators whose major qualification for using them is possessing the cash to acquire them. To

(*Sharples, continued on page 1330*)

The author is with the Environmental Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831. She is a member of the Recombinant DNA Advisory Committee of the National Institutes of Health. The Oak Ridge National Laboratory is operated by Martin Marietta Energy Systems, Inc., under contract DE-AC05-840R21400 with the Department of Energy.

Bacterial Domestication: Underlying Assumptions

BERNARD D. DAVIS

OVER THE PAST DECADE THE RECOMBINANT DNA ADVISory Committee (RAC) of the National Institutes of Health (NIH) has outgrown the initial assumption that all recombinant bacteria are dangerous until proved otherwise. Its current restrictions on laboratory research are essentially limited to experiments involving pathogens. Building on this experience, in the recent notice of a coordinated framework for the regulation of biotechnology (*1*), the Food and Drug Administration and the U.S. Department of Agriculture (USDA) announced that they plan to regulate genetically engineered microbes no differently from strains obtained by traditional techniques. The Environmental Protection Agency (EPA), however, adopted a different position; although this was an improvement on its initial, "process-based" proposal (*2*) (which even considered declaring DNA a toxic substance), it still presented highly restrictive and elaborate regulations, accompanied by an extensive exegesis on the hypothetical dangers of engineered organisms.

The conflicting regulations of the different agencies will create administrative problems. However, I will focus here on arguments—most of them presented during the debate over recombinant bacteria a decade ago (*3*)—against some of the underlying scientific assumptions. In addition, I will emphasize that the use of modified microbes is not entirely novel but is an extension of the old process of domestication of wild organisms—including the selection of microbial variants to make bread, wine, antibiotics, or vaccines. Finally, I shall argue that in trying to assess the potential dangers, the experience of ecologists with transplanted higher organisms is less pertinent than are the insights of fields closer to the specific properties of engineered microorganisms: population genetics, bacterial physiology, epidemiology, and the study of pathogenesis.

Not only are the present regulations quixotic, but the problem continues to receive much attention in the news media, and some legislators are proposing more restrictive new laws. Although there have been individual efforts [for example (*4*)] to counter demagogic attacks against this field and the resulting widespread misconceptions, they have been limited. Yet more than the ability of biotechnical industries to engage in field testing is at stake.

Accidental Release Versus Deliberate Introduction

The most basic question in the current debate is how much we are thrashing over issues that have already been settled in the delibera-

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The author is Adele Lehman Professor Emeritus of bacterial physiology, Harvard Medical School, Boston, MA 02115. He is a member of the Recombinant DNA Advisory Committee of the National Institutes of Health.

important substrate (for example, lignin) to a congener with broad environmental tolerances. If intrageneric transfers are to be routinely subject only to lower levels of regulatory review, the flexibility to elevate cases that present special risk factors to higher levels of review should be built into the policy framework. There is, in fact, already such an exception for intrageneric transfers between obligate pathogens, and a mechanism for dealing with other exceptions would be consistent with this approach.

Second, shifts in environmental contexts may be as important as genetic modifications in determining whether the ecological relationships of an engineered organism will be unique relative to those of a parental form. It is not certain before the fact, for example, that beneficial inhabitants of soil ecosystems will not be adversely affected by some property from a leaf-dwelling organism (for example, toxin production) when this property is engineered into soil bacteria. Although such a toxin may certainly not be "new" and certainly may be "natural," its relocation to a new environmental setting could produce unintended negative results on susceptible organisms exposed for the first time. Some provision is needed in the regulatory scheme to ensure that consideration is given to the specific nature of the receiving community and the species in it in assessing risks.

Finally, transfers of regulatory genes and gene deletions are excluded from the definition of "new," which relegates products with such modifications to low levels of review. But the absence of a protein or the amplification of its production could have profound ecological effects in many instances that are neither difficult to imagine nor highly unrealistic, for example, in modifying important biogeochemical processes. In short, the use of a strictly genetic definition to determine whether a particular product should be treated as high or low risk may underestimate ecologically relevant and important factors. Again, flexibility in implementing the policy is needed to take account of exceptions and shift particular cases between review levels when justified.

At this time, all engineered organisms for environmental release should receive at least a minimal level of review to allow screening of the kinds of ecologically relevant exceptions mentioned here. It is too early to create categories of organisms that are completely exempt from review. Although the process of conducting risk assessments for engineered organisms is currently far from routine, as experience is gained, the process will become both more accurate and more efficient. At the moment, only a few new products are entering the regulatory mill. We have the opportunity to compile the knowledge needed to narrow the concerns and streamline the review process before many products need to be regulated. Credible regulatory oversight is essential to ensure public acceptance of biotechnology's products. Evaluations of both the genetic and ecological properties of engineered organisms will foster confidence in their safety and effectiveness.

Ecologists who have voiced their reservations about biotechnology's environmental products have done so for reasons of professional integrity and because of their concern for the environment. We are not Luddites or alarmists, but merely skeptics who wish to consider what the hidden costs of this promising new technology might be.

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tions of the NIH RAC. The root of the new wave of concern is the assumption that large amounts of engineered bacteria deliberately introduced (*5*) to the environment are much more dangerous than small amounts accidentally released from the laboratory. This tacit proposition has seemed self-evident, by extrapolation from toxic chemicals. But the problems are very different. With bacteria it is not the harmful effects of the released material itself, but its capacity to multiply and hence possibly to spread in the environment, that causes concern; the obverse side to this difference from chemicals is that bacteria also have the capacity to die out rapidly. In any concrete case, then, the crucial question is whether the strain will spread or will die out.

We are thus dealing with a problem in natural selection, where success of a novel strain does not depend on its introduction in large numbers. A new gene arises in evolution in a single individual and then, if successful, spreads in the progeny; a single infected person can initiate an epidemic; and a single pair of rabbits started the rabbit plague in Australia. The same will be true of a novel bacterial recombinant created in the laboratory, if it has an evolutionary advantage. To have this advantage and to succeed in nature, however, an organism must not only be able to grow on the nutrients available in the environment, it must also be better adapted than its natural competitors. If it is, then even a small amount escaping from the laboratory or a greenhouse could start the process of spread. Alternatively, if it grows more slowly than its competitors, by even an infinitesimal amount, the release of tons of the organism (whether deliberate or accidental) will have only a temporary and local effect.

The importance of selection is illustrated by an extraordinarily rapid evolutionary shift, taking place within our lifetimes: increase in the prevalence of drug resistance in bacteria, because of the selection pressure exerted by the antibiotics that humans have introduced into the environment. Similarly, the distribution of soil bacteria will change in response to changes in environmental selection pressures (such as nutrients, moisture, *p*H, host plants), and not, except transiently, as a result of the introduction of genetic novelty. The dense and heterogeneous microbial population of the soil (often well over 10^6 organisms per gram) has an enormous

capacity to buffer any introduced genetic change, to provide organisms adapted to an incredible range of environments, and to generate novel forms.

The human gut provides a more familiar example of such buffering. As soon as an infant shifts from a milk diet to solids, the sweet-smelling lactic acid bacteria are replaced by a mixture of enteric bacteria, whose stink suggested to Metchnikov, at the turn of the century, that they were toxic. But his efforts to displace them by administering large amounts of lactobacilli failed to have any lasting effect on the intestinal flora, and the yogurt that he used simply proved to be a palatable nutrient.

To be sure, one type of danger presented by introduced bacteria does depend on scale and must be carefully regulated: the direct toxicity of the cells (without spread) to persons, animals, or plants. But this problem has already been taken into account, within the framework of earlier regulations, for the 14 nonrecombinant microbial species that have been licensed by EPA as pesticides, and for the larger number that have been licensed by USDA—for example, to promote nitrogen fixation in the soil. Moreover, many of these organisms had been modified genetically (by classical techniques). Although these novel strains might conceivably have had unpredictable harmful effects, none has been seen.

Let us consider some specific aspects of the new regulation in the light of this evolutionary perspective.

Intrageneric Versus Intergeneric Recombinants

The EPA will now require approval for recombinants in which a pathogenic species (except for well-authenticated nonpathogenic strains) provides either the cell or DNA that codes for a product. It will exempt recombinants involving nonpathogenic organisms within the same genus. But it will require approval for intergeneric recombinations, whether or not they involve a pathogen.

This reliance on genera arose from the EPA decision to focus on "microorganisms that have been deliberately altered to contain genetic material from dissimilar source organisms, because such organisms are more likely to exhibit new combinations of traits and their behavior is therefore less predictable" (*1*, p. 23,317, column 2). To estimate dissimilarity the agency used genus as the criterion, because (i) "combinations of genetic material from microorganisms from different genera are more likely to result in new traits than combination of genes from microorganisms within the same genus"; (ii) "while genetic exchange occurs naturally and somewhat commonly among many microorganisms, it is more likely to occur in nature within a single genus"; and (iii) "genus designations provide a practical criterion for administrative and regulatory purposes. . . . [It] facilitates the identification of those microorganisms that should be subject to special attention and also that should be considered 'new' under TSCA [the Toxic Substances Control Act]" (*1*, p. 23,317, column 3).

Three reasons for questioning the scientific assumptions underlying this criterion follow.

1) *The meaning of genus in bacteria.* One difficulty is the status of all taxons, including not only genera but even species, in bacteria. In higher organisms the ability to interbreed provides a sharp definition of the boundaries of a species; but with bacteria this criterion is not available. Instead, a species is defined, rather arbitrarily, as a cluster of strains that share a sufficient number of phenotypic traits. The boundaries therefore fluctuate from time to time in the debates between the "splitters" and the "lumpers" among bacterial taxonomists.

The grouping of bacterial species into genera is even more arbitrary, and the resulting assemblages vary enormously in breadth. For example, the genus *Pseudomonas* includes organisms ranging from 60 to 69 percent guanosine plus cytosine in their DNA—a range greater than that of all the vertebrates. In contrast, the organisms of the medically prominent family Enterobacteriaceae all have about the same percentage of guanosine and cytosine, but they have been much more extensively subdivided. Indeed, two of their genera, *Shigella* and *Escherichia*, have a higher degree of homology in DNA sequence than the range of organisms within many species.

Bacterial genera thus provide arbitrary lines of demarcation, far from what should be the real concern of regulations: ability or inability to cause harm.

2) *New traits and the nature of pathogenicity.* EPA's reliance on genera was based on the assumption that recombinants from distant sources are likely to have "new traits." But this concept is excessively vague unless we ask what kinds of new traits should concern us. And here microorganisms are very different from macroorganisms. The latter are closely linked to both our economy and our esthetic satisfactions, so we are acutely aware of any abrupt change in their present distribution, such as the spread of rabbits, starlings, or kudzu vine. In contrast, changes in microbial populations do not even reach our attention except when they have tangible consequences.

One set of consequences of microbial spread, the production of diseases in animals or plants, often involves a genetic change that allows the microbe to overcome widespread host resistance. However, most visible effects of microbes on "the environment" are responses to an environmental change, rather than a consequence of genetic change or a novel introduction. For example, lakes do not become eutrophic because some polluting microbe has been introduced. The responsible anaerobic organisms are already there, and they reach our attention only when an increased level of nutrients supports a population density that exhausts the oxygen. An example of invisible change, the selection for organisms that oxidize hydrocarbons, is detectable in the soil under any gasoline station; yet during the emotional debates of the 1970s some distinguished biologists suggested that bacteria engineered for improved utilization of hydrocarbons might destroy petroleum deposits, or even gasoline in tanks.

By now this particular fantasy seems to have vanished. Yet it is an instructive model, for the present concern of EPA and many ecologists over new traits is addressed to almost equally improbable perturbations of nature, such as a spreading decrease in the fertility of the soil, or disastrous shifts in rainfall. Since we cannot build sensible policy on fear of imaginary monsters, the new traits that merit concern center on pathogenicity. We must therefore consider briefly the nature of this property.

Pathogens are only a tiny fraction of all microbial species. Most of the rest attack only the dead bodies (or the products) of higher organisms. The resulting recycling of organic matter back to inorganic carbon and nitrogen is essential for the continuation of life on the earth. Since this role is much less known than the role of microbes in disease, it is not surprising that the public is receptive to scary scenarios about Andromeda strains.

Pathogenicity is not a trait produced by some single powerful gene, such as that for a potent toxin; it requires the evolution of a special set of properties, involving a number of genes. The component mechanisms include adhesion of the microbe to specific host cells, resistance to host defense mechanisms, formation of toxic products, ability to multiply under the nutritional conditions provided by the host, effective transmission from one individual host to another, and survival until that transmission. Although no one of these confers pathogenicity, a mutation that affects any essential one (such as toxin formation) can eliminate it.

A particularly cogent property, for present purposes, is that mild degrees of pathogenicity are much more common than devastating ones. We are thus assured of an early warning: if a number of hybrids between two particular nonpathogenic species fail to produce even mild harm, it is exceedingly unlikely that the next one will cause a disaster. In contrast, hybrids involving components linked to pathogenicity do present potential hazards and hence require regulation.

3) *Evolutionary distance and genomic balance.* The high level of apprehension in EPA might be justified if its most fundamental assumption were correct: that recombinants from distant organisms are more likely to be dangerous than those from closely related organisms. In fact, however, modern evolutionary theory, linking Darwinian selection with genetics, would predict exactly the opposite. The reason is that a recombinant cannot be dangerous unless it can survive, and such survival, like earlier successes in evolution, depends on a harmonious balance (coadaptation) of the total genome. Hence to be effective any new gene must interact well with the others. But foreign genes from a distant source will not fit well in the recipient genome, so they can be expected to produce noncompetitive (or even nonviable) monstrosities, rather than dangerous monsters.

For this reason we must recognize severe limits to the power of molecular genetics to remake the living world. We can indeed recombine DNA at will, yet we do not have equal power to ensure the survival of any recombinant: the requirements for a balanced genome determine what is viable at all, and then what can survive selection in nature. We can influence natural selection very little, except by changing the environment—as we have done in protecting domesticated organisms, or, unintentionally, in using antibiotics. We can thus expect to use genetic engineering to broaden the range of modified organisms for domestication, but not to create radically new or spreading life forms.

This key principle of genomic balance is applicable to the microbial world as well as to that of higher organisms. It explains why each bacterial gene is generally found associated with a particular cluster of other genes, constituting a species; if, instead, individual bacterial genes contributed to fitness independently, they would be distributed randomly. Bioengineering provides further evidence: in large-scale cultivation of an engineered microbe it is often difficult to prevent outgrowth of derivative strains that have lost the foreign genetic sequences and hence grow faster.

In contrast, closely related microbes can produce effective hybrids, not only in the laboratory but also in nature. For example, reassortment of genes, resulting in altered virulence or altered antigenic specificity, has been shown to occur in animals infected with two strains of reovirus or of herpesvirus. There are strong indications that a similar process underlies the appearance of new epidemic strains of influenza virus. But as EPA pointed out (*1*, p. 23,317, column 2), man-made crosses between closely related microorganisms are unlikely to add significantly to the supply of variation arising in nature.

Contributions of Ecologists to the Controversy

Since the above arguments lead to the conclusion that pathogenicity is of prime importance in assessing dangers from recombinant bacteria, we must ask why EPA has not focused on this principle as NIH RAC has done. One reason is that differences in the history of the two agencies, their mission, and their political vulnerability influence their responsiveness to alarms in the media. But the body of science brought to the attention of EPA by its scientific advisers may be even more pertinent. This agency does not have the broad base of contact that NIH has with the biomedical research community. Heavy reliance by EPA on ecologists has been appropriate for most of its responsibilities, but in its more recent concern with potential microbial spread and harm, ecologists have not been adequately balanced with scientists from fields closer to the problem, such as those in bacterial physiology, epidemiology, infectious disease, plant pathology, and population genetics.

As a result, a 1984 U.S. House of Representatives staff report, "The environmental implications of genetic engineering (*6*)," written with the help of EPA staff and of ecologists funded by EPA, revived an argument that had been prominent in the debate of the 1970s: that we must assume serious risk because we are dealing with "low probability but high consequence." But this argument is now recognized as pseudoquantitative and not really helpful. Other ecologists have offered a historicist speculation: that unanticipated adverse effects will inevitably crop up with these technologies, as with all new technologies. But this view builds on a parallel between genetic engineering and the physical technologies, rather than on a much closer model, with very different predictions: the domestication of wild organisms, resulting in enormous benefits and catastrophes.

The largest source of apprehension among ecologists is the model of the damage created by animals, plants, and microbes transplanted to a new environment. In fact, however, the analogy is weak. All the troublesome transplants have been organisms that were already genetically well adapted, through ages of natural selection, to their native habitat, where their proliferation is held in balance by various ecological factors. In a new environment that lacks these balancing factors they can multiply explosively. With genetic engineering, in contrast, the organism, rather than the environment, is changed; and its adaptation has not had the benefit of prolonged natural selection. Instead, the introduction of foreign DNA, especially from a distant source, is much more likely to impair than to improve the organism's adaptation to its original environment.

This theoretical inference of impairment receives strong empirical support from the effects of even the small genetic changes introduced in domesticated plants and animals. Whereas some domesticated strains have retained the capacity for feral return to the wild, most are clearly at a disadvantage there. Indeed, it is not clear that domestication has improved the ability of any species to thrive in the original environment.

Nevertheless, some distinguished ecologists, impressed by the model of exotic transplants, provided affidavits in support of Rifkin's suit for an injunction against field testing of an engineered ice-minus mutant of *Pseudomonas syringae* (*7*). It would be difficult to imagine a less threatening organism than this one, altered by deletion (which ensures irreversible loss) in a gene contributing to pathogenicity, and indistinguishable phenotypically from strains frequently encountered in nature. Testing was approved by the NIH RAC and was overwhelmingly supported in the suit by scientists from various fields. But because of the testimony of a few ecologists (later recanted by one), Judge Sirica granted the injunction—the resulting cost to the University of California, of hundreds of thousands of dollars, surely chills research on engineered bacteria.

A letter from the Public Affairs Office of the Ecological Society of America (*8*) has added financial to scientific arguments for greater participation of ecologists: "Unfortunately, given the disparity in funding among the various life sciences, the ability to develop new organisms has outstripped the ability to predict the consequences of their release. Research on these consequences and improved communications among researchers in all the relevant biological disciplines are essential before the public will accept the safety of biotechnology" (*8*). Although it is legitimate for ecologists to seek

expanded funding of their field on the basis of interest in the problem of introduced bacteria, it is unfortunate to have this aim linked to a scientific position that in effect leads to interference with the advancement of another field.

This scientific position is further supported by the claim that ecologists can provide reliable assessments of the probability of inadvertent harm from engineered bacteria. But it is difficult to find convincing evidence for this claim. A recent report of a National Research Council committee, analyzing the power and the limitations of ecology in helping to solve practical problems of the environment, emphasized that this science is by nature descriptive and not strongly predictive (*9*). Moreover, this statement referred to the ecology of animals and plants—and bacterial ecology is a less developed field, facing even greater obstacles.

Trying to place the problem of assessment on a firm scientific base, a leading bacterial ecologist has proposed that the probability of environmental harm from a particular strain must be analyzed as the product of six probabilities: release, survival, multiplication, dissemination, transfer, and harm (*10*). This apparently quantitative approach may increase the complexity of the tests that EPA will require and the confidence of the agency in the value of these tests. However, analysis in terms of these six variables could easily lead to much useless work; for unless harm can be demonstrated, examining the other variables is superfluous. More important, it is not clear how this approach can fulfill the promise of providing a reliable prediction of safety: if the concept of harm is open-ended, it is difficult to see how a nonpathogen can be proved to be innocent. In addition, because the natural environment is so heterogeneous and fluctuating, no particular set of "microcosms" that fail to support spread can ensure that still another environment might not provide a more favorable reception.

In seeking a reasonable assessment we must rely heavily on principles from evolutionary biology, microbiology, and epidemiology, instead of requiring expensive testing and delaying useful applications simply because an organism was developed by the technique of DNA recombination. Indeed, the whole science of bacterial genetics might have been aborted if J. Lederberg, F. Jacob, and other pioneers had had a Rifkin in the wings, demanding absolute guarantees of the safety of the mutants that they were producing by classical genetic techniques. The same is true of the development of attenuated vaccines, which were hailed as a medical triumph a few years ago but now evoke legalistic attacks and critical editorials.

Recognizing that the present conflict is serious, a group of ecologists have stated that "progress will . . . only be made if . . . the proponents of the various viewpoints . . . work together to better define the important questions and to answer them" (*11*, p. 112). I agree, and I have tried here to define and to answer a number of such questions. These answers may not allay the apprehensions of these spokespersons in ecology. But meanwhile this disagreement between scientists with different backgrounds is strengthening the influence of nonscientist activists opposed to all genetic engineering. In addition, in the name of protecting the environment, ecologists are delaying efforts to replace current, environmentally damaging chemical pesticides by nontoxic biological pesticides. Finally, the conflict may discourage cooperation of molecular geneticists with ecologists in another, more pressing goal of deep interest to both groups: halting the growing species extinction and conserving the genetic diversity of the biosphere.

Conclusions

On the basis of well-established principles of evolutionary biology and microbiology, I conclude that (i) the deliberate introduction of a novel bacterial strain to the environment is not substantially more dangerous than the accidental release of a smaller number of cells; (ii) distant organisms are less (rather than more) likely to yield dangerous hybrids than more closely related ones; and (iii) the complex attribute of pathogenicity is not likely to emerge from genetic alterations in nonpathogens. If these conclusions are correct, most engineered bacteria need not be regulated more strictly than the bacterial strains that have been tested in the field in the past. The only exceptions would be strains derived from cells, or appropriate genes, of microbes pathogenic for plants or animals. Microbiologists not only recognize the need to handle pathogens with caution: they have long accepted regulations, such as those governing transportation, that reinforce that recognition.

It is remarkable that we can still be arguing, on the basis of analogies rather than firm scientific principles or evidence, about hypothetical disasters from kinds of organisms that are being produced in hundreds or thousands of laboratories without a trace of demonstrable harm. RAC required 6 years to adjust its initially conservative guidelines to the emerging understanding of the scientific realities, while maintaining public confidence. Since the level of public concern is not nearly as great today, EPA should be able to relax its excessive restrictions much more quickly. Even better would be a return to having RAC, or a single successor group, evaluate the problems of danger for all classes of engineered bacteria, since the applicable shared principles outweigh any specialized differences in the nature or use of the specific strains. But the regulations are unlikely to be unified in this way, or to be divested of unproductive restrictions, without broad encouragement from the scientific community—including, hopefully, many ecologists. The agenda has been set for too long by apocalyptic activists. To protect this promising field of research and technological application the scientific community must take initiative in helping the public and decision-makers to distinguish reasonable probabilities from remote fantasies.

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