Letters

Genetic Engineering in Agriculture

Winston J. Brill's article on "Safety concerns and genetic engineering in agriculture" (25 Jan., p. 381) is a geneticist's evaluation of potential ecological hazards. As ecologists, our evaluation of such hazards is quite different. Brill refers to the likelihood that negative effects will result from environmental uses of genetically engineered plants and microbes in phrases such as "seems very small" and "is extremely unlikely." He calls for basing regulations for the release of genetically engineered organisms "on scientific experience and informed debate of the issues." We have several responses to these assertions. First, the point of risk assessment is to provide sufficient quantitative information about the potential for a negative effect so that the kinds of qualitative and subjective judgments implied in phrases such as "seems very small" are no longer necessary. Drugs and pesticides are not licensed merely because they "seem" harmless and are "unlikely" to cause negative effects. Second, while the probability associated with any of Brill's categories of risk may be small, we can produce examples for each category in which organisms are documented to have done some highly improbable things. Third, we agree with Brill that regulations should be based on scientific experience and informed debate. But it is essential that the multidisciplinary nature of the questions surrounding the environmental safety of genetically engineered organisms be recognized, and that the scientific experience of ecologists and evolutionary biologists be used in concert with that of geneticists, microbiologists, and others to treat these questions.

Brill's conclusions about the safety of genetically engineered plants seem to derive from a two-part argument: (i) that engineered plants are even less likely to cause problems than plant varieties produced by conventional technology; and (ii) that conventionally produced varieties have caused no problems in the past. The first of these assertions is not sound ecology, while the second is incorrect. Scientific study of the evolutionary ecology of weeds (*1–5*) shows that economically and ecologically important weeds originate and spread by diverse mechanisms. Brill's list of the "properties of a weed (efficient seed dispersal, long seed viability, rapid growth in an environment not normally favorable to other plants)" might seem strange to a farmer whose rice field is infested with rice-mimicking barnyard grass (*Echinochloa crusgalli* var *oryzicola*), the most serious weed of cultivated rice in California and worldwide (*4*). This weed sheds its seed under the parent plant, exhibits weak dormancy and synchronous germination, and grows best under the same conditions as rice (*5*). The world's number one agricultural weed, purple nutsedge (*Cyperus rotundus*), thrives under the same conditions as 52 different crops in 92 countries, and propagates almost exclusively by vegetative means, not by seeds (*4*). In fact, "crops" and "weeds" are intimately related categories. Of the world's 18 worst weeds, which collectively cause losses of several billion dollars annually, 11 are themselves grown as crops in several countries (two in the United States) (*4*). Brill's assertion that no commercial variety has caused "serious problems" is further contradicted by the U.S. Department of Agriculture's invocation of the Federal Seed Act. This act, which is intended to control the spread of "noxious weeds," prohibits shipment to some states of particular *commercial* varieties that are themselves considered to be "noxious weeds" in the states in question (*6*). Examples include forage and turf plants and certain *Brassica* species.

Existing weeds are also likely to benefit from many of the same kinds of genetic novelties that genetic engineers are striving to introduce into crop plants—herbicide resistance, insect resistance, stress tolerance, nitrogen fixing ability, and so forth. If genes from one evolutionary lineage are spliced into crop plants in another, it is not necessary to postulate any novel genetic transposition mechanism (although the existence of such cannot yet be ruled out) by which these advantageous new characteristics may find their way into surrounding plants. Hybridization alone provides a sufficient potential conduit for related crops, wild relatives, and existing weeds to acquire genes never before present in their lineages. Many important weeds are congeneric with crops—examples in the United States include *Avena, Hordeum, Helianthus, Solanum-Lycopersicum, Brassica, Raphanus, Daucus*, and *Sorghum*—and in many circumstances hybridize freely with crops (*2–4, 7*). For example, commercial sorghum (*Sorghum bicolor*) seed is sometimes contaminated with seed whose pollen-parent is Johnson grass (*Sorghum halepense*), which gives rise to an aggressive perennial hybrid weed in sorghum fields (*2*). In this sense, genetic engineering may, in particular cases, be *more* likely to produce new or more troublesome weeds than conventional plant breeding, because the new technologies can more readily introduce and spread foreign genes into new lineages whereas selection only rearranges genes already present. Although such cases may be infrequent, they should be avoided.

Brill argues that introduced species have become pests precisely because they are introduced, and that, in contrast, native species that have coevolved in their communities are controlled by competitors, predators, weather, and so forth. He echoes a similar contention by Davis (*8*) that a robust balance of nature obtains, with all ecological niches full; and this balance prevents any native species from escaping control. But "control" in an ecological sense often differs greatly from "control" at economically and environmentally acceptable levels. Since no population increases to infinity, all species can be said to be "controlled" either by other species or by the physical environment. However, many species typically undergo drastic fluctuations in population size (*9*), and the idea that nature has a tight, homeostatic balance is not borne out by field observation and experimentation (*9, 10*). Niches are not always "full," and resources often seem to be available for a new species or genotype. Dramatic population explosions and crashes occur independent of human activities (*11*). Although full explanations are not available, there are even examples in which a small amount of genetic change seems to be the key (*12*). The spread of the apple race of the fruit fly pest *Rhagoletis pomonella* and the explosive expansion of the collared turtle dove, *Streptopelia decaocto*, have both been ascribed to mutations.

Many organisms under consideration for release will be designed to overcome natural limiting factors, such as low nitrogen, low temperature, or predation by insects. Such changes are not minor modifications from an ecological standpoint; rather, they are aimed at the very boundary and definition of the ecological roles of particular species. Outside of human-modified ecosystems there is little precedent for this sort of change, so it is difficult to predict its effects. We know that, when we irrigate the desert, many moisture-limited species suddenly appear; when we remove insect predators, populations of many phytophagous insects are free to multiply to economically harmful levels (*13*). The forces that actually control a species in nature are, however, frequently elusive and can only be detected through intensive field manipulation.

Brill makes a case for the safety of engineered microorganisms largely on the basis of three "principles": (i) "preexisting organisms already have evolved to successfully compete" with any engineered microbes that might be released; (ii) "the extra burden to the organism carrying new genes should decrease its ability to compete and persist"; and (iii) the addition of "characterized recombinant genes" to the genome of an organism "currently considered safe" should cause no problems. It is hard to see how the first two "principles" can be reconciled with the intended effectiveness of genetically engineered organisms in the environment. Such organisms cannot fulfill their intended functions without surviving and competing successfully to some degree. One detects from Brill's description of recombinant organisms that a delicate balance is expected to keep them useful and not harmful. They are to be viable and competitive, but not *too* viable and competitive. Brill's prediction that the new genes a microorganism carries will decrease its ability to survive, on average, is not convincing. Some recombinant forms will persist, even if they are relatively few. Moreover, although many studies show that genes "unneeded" in the current environment slow bacterial population growth, this phenomenon is not universal (*14*).

Brill writes that genetic "characterization" of engineered traits alone permits a firm a priori prediction of the modified organism's performance when it is released into the environment. However, the phenotype of any organism, including its ecological role, is not fully predictable from genotype alone. Pleiotropies, multiple phenotypic effects from the same genetic change, can be ecological as well as physiological or morphological and may include unexpected interactions between species. Stotzky and Babich (*14*) give several examples of "unexpected alterations" in transconjugants that had received well-characterized plasmids. These included "subtle differences in antibiotic resistance, virulence, and biochemistry . . . [that] would probably influence the ecology and population dynamics of these competing cells in natural environments."

Brill makes little mention of the potential of engineered microorganisms to transfer plasmids containing novel genes to other microorganisms in the environment. Although nonconjugative plasmids that are also poorly mobilized by triparental matings are considered to be "safe," low rates of transfer of even safe plasmids to indigenous bacteria do occur (*14*). Furthermore, data on gene transfer come primarily from laboratory studies, and the mediating influences of environmental factors on rates of genetic transfer are poorly understood. In circumstances in which it would be extremely undesirable to have particular engineered genes spread to the indigenous microbiota, a quantitative estimate of the rate of such transfers is far more desirable than a statement that the chance of such an event "seems very small."

We neither doubt the great potential for benefits resulting from the ability to move genes between unrelated species, nor do we believe that most plans for such projects would have severely harmful ecological impacts. We would argue, however, that even traditional breeding has not been ecologically trouble-free, that engineered organisms are analogous to exotic ones to some extent, and that the particular kinds of engineering that are now contemplated are "quite likely," if inadequately regulated, to lead to some instances of ecological harm. The risk of such harm could, however, be greatly reduced by sound prerelease testing.

Brill describes the task of designing relevant tests for determining the safety of recombinant organisms as enormous, if not impossible. Does our current lack of knowledge make it hopeless to attempt to predict possible danger? Past attempts to predict the ecological trajectory of introduced organisms have not been very successful (*15*). But few resources were available to ecologists attempting to predict the outcome; generally there were no preliminary studies nor any sound observational data. Experimental community ecology has made rapid strides in the last 15 years, and techniques of field manipulation are now much more sophisticated. Thoughtful, case-by-case experimental studies of the potential effects of recombinant organisms are necessary to substantially reduce the likelihood of unexpected negative impacts. Progress will, however, only be made if a genuine spirit of interdisciplinary cooperation is adopted, and the proponents of the various viewpoints on the risk of genetically engineered organisms work together to better define the important questions and to answer them.

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Brill's article is a well-prepared, scholarly evaluation of the true benefits and hypothetical hazards of genetic engineering in agriculture. However, since it seems to represent the point of view of the theoretical scientist, a few additional practical points should be included stressing the societal point of view.

1) Brill refers to risks that are "very

small" or "extremely unlikely," instead of saying they are nonexistent from the *practical*, societal point of view. The phrase "very small risks" may be confusing to the general public, because "very small risks" can mean hundreds or thousands of lives lost or injuries inflicted every year, as in the case of alcoholic beverages, cigarettes, or chemicals—all generally accepted products. In modern genetic engineering not a single life has been lost; not a single person has become ill, even though thousands of laboratories carry out recombinant DNA research on the open benches.

2) Brill does not refer to the "early warning principle" which is built into genetic engineering experimentation and which offsets any present need for regulations (*1*). Statistical laws imply that pests which cause great harm could not be inadvertently produced by genetic engineering from innocuous organisms without being preceded by an early warning consisting of the appearance of some weakly harmful constructs. Experimental creation of a well-adapted and dangerous weed would be a formidable task requiring isolation or synthesis, and well-designed placement, of many genes and their regulatory signals. Events like this do not happen inadvertently in laboratories by the random mixing of genes, just as one cannot inadvertently create a television set by a random mixing of electronic components. And should it ever happen, the statistical probability of creating an *imperfect* mix of genes leading to an *imperfect* weed or other pest is obviously much higher, automatically leading to a very early warning.

3) Brill's article implies there are valid reasons for regulations. However, the reasons seem to be only political, and from a logical point of view all regulation of recombinant DNA techniques (often called "guidelines") should be abolished. The argument is simple: (i) the known present and future benefits of genetic engineering are enormous; (ii) the hypothetical inadvertent risks, if any, are more than balanced by the hypothetical inadvertent benefits; and (iii) the overall cost of unnecessary regulations is very high (*2*). Thus, the balance sheet clearly shows that regulations are not justified at present and are against the best interests of society. Regulations cannot be built on hypothetical scenarios, but must always be well justified if they are to become useful and accepted as "necessary evil." I learned that lesson the hard way when serving as a founding member of the Recombinant DNA Advisory Committee (RAC) of the National Institutes of Health.

The purpose of my comments is not to detract in any way from the value of Brill's article, but to supplement it and to emphasize the practical aspects that are important to society.

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References and Notes

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The comments by Colwell *et al.* are appreciated because they outline most of the objections that have been presented recently by scientists who are in opposition to release of genetically engineered organisms. Thus, they provide an opportunity to emphasize the points of common concern about which there is no disagreement and areas about which there are misconceptions or a failure to communicate effectively. In citing specific objections to various points in my article, Colwell *et al.* do not discuss the primary concept that was presented: there is no reason to believe that genetically engineered organisms should be treated differently from conventionally altered organisms with regard to safety evaluation. Colwell *et al.* state that the "particular kinds of genetic engineering now contemplated are 'quite likely,' if inadequately regulated, to lead to some instances of ecological harm." They do not put their concern into perspective. As stated in my article, application of recombinant plants and microorganisms to agriculture may cause problems, but not beyond those we accept and manage in traditional practices. Colwell *et al.* appear to be saying that the ecological harm that is "quite likely" is as significant as the harm caused by the kudzu vine or the gypsy moth (examples cited by those favoring special regulations for released recombinant organisms), but they do not support the suggestion that such harm can occur through release of genetically engineered organisms. Arguments made by Colwell *et al.* can all be applied to traditional agriculture. Unless it can be shown that recombinant organisms have unique properties with respect to safety considerations, then regulations relevant for current agriculture should be satisfactory for future agriculture with organisms modified by genetic engineering.

The first point of Colwell *et al.* is that they represent the ecologist's view and that the article presents the views of geneticists on an ecological issue. One would hope that a scientist who has spent most of his career applying biochemistry and genetics to ecological problems involving nitrogen fixation and who has a number of publications in journals that deal specifically with the environment has a proper perspective in this area. Furthermore, in the preparation of my article, ecologists, agronomists, weed scientists, entomologists, and plant pathologists were consulted and provided helpful reviews of the material. These researchers were in essential agreement with the points made; therefore, one should not assume that ecologists have one point of view and geneticists another with respect to the safety issue.

The analogy that Colwell *et al.* make between genetically engineered organisms and drugs is not valid. Drugs are licensed specifically because there is a high possibility of serious negative effects. In the case of recombinant plants and microorganisms added to fields, there is no reason to believe that a serious negative effect will occur. It is important that we do not ignore the safety record during our decades of international experience with breeding and soil microbe inoculant production and experimentation.

Colwell *et al.* misstate many points that the article presented. They say my article proposed "that conventionally produced varieties have caused no problems in the past." This proposal was not made; rather, examples of problems related to conventional breeding, such as the corn leaf blight, sorghum-related weeds, and toxins in potato, were mentioned. Nor did the article contend that all ecological niches are full, thereby preventing native species from escaping control. In fact, examples of organisms that have escaped control were mentioned. The article showed that this does not represent a problem unique to recombinant organisms. The examples given by Colwell *et al.* of mutations as the primary cause of spread are misleading. The spread is probably associated with man's activities rather than mutations per se. Thus the spread of the fruit fly may have been caused by use of new apple varieties (*1*), and the spread of the collared turtle dove seems to have corresponded with man's agricultural practices (*2*). These two situations are analogous to the spread of antibiotic-resistant bacterial strains as a result of using antibiotics or of herbicide-resistant weeds as a result of using herbicides.

As stated by Colwell *et al.*, it would be desirable to have quantitative values associated with risk, rather than terms such as "unlikely" and "seems very small." At this time, however, one can place no reasonable number on the risks being discussed. Their comparison with quantitation of the negative effects of drugs or pesticides is not helpful. Measuring LD_{50} is quite different from determining the probability of potential damage, in a wide range of environments, of a novel organism, whether produced by a conventional cross or genetic engineering. Even with a traditional breeding cross, can anyone now or in the near future quantitate, from greenhouse experiments, the chance that an undefined problem will occur? Current plant breeding is carried out with no quantitative risk assessment data, but with confidence from long and extensive experience that the risk "seems very small." We know too little about the biochemistry, molecular biology, and genetics of interacting biological systems to quantitate reliably the chance of a problem, especially if field experience with analogous organisms has not revealed a problem. Breeders have always been concerned about unexpected problems, and standard field testing in several locations over several seasons is the accepted way to determine these. Problems have occurred in a few instances, but none has reached the magnitude of those caused by importation of organisms such as the kudzu vine or the gypsy moth.

Will quantitative risk assessment for recombinant organisms be reliable, and is the information to be obtained worth the cost? Such an effort was never required for conventional breeding or microbial inoculant experimentation. Why should it be necessary for genetically engineered organisms? Colwell *et al.* criticize the statement that the task of designing relevant tests to determine the safety of recombinant organisms a priori is enormous. Rather than refute it, however, they say only that ecologists have never had sufficient resources to predict ecological outcomes. They do not suggest a specific program or predict a time scale for how long it might take to build a scientific basis for quantitating risk. Meanwhile, handwringing over recombinant DNA technology without specific plans for feasible and effective risk assessment provides no convincing basis for treating genetically engineered organisms differently from the way we treated earlier products of plant breeding or microbial selection.

To demonstrate how difficult it would be to devise laboratory tests to indicate what will occur in the field, we can take the example of *Rhizobium*, a bacterium that fixes nitrogen on the roots of legumes. *Rhizobium* cultures have been produced commercially for almost a century, and there has been tremendous incentive to devise a laboratory or greenhouse assay to determine which strains are the best under field conditions. Numerous laboratories have put extensive effort into this problem for many decades, but no assay is yet available. Will it be possible in a reasonable time frame to devise tests for organisms less understood than *Rhizobium*? Colwell *et al.* support the view that it is extremely difficult to devise a relevant laboratory or greenhouse test to predict potential danger quantitatively. They state, "The forces that actually control a species in nature are, however, frequently elusive and can only be detected through intensive field manipulation."

Colwell *et al.* suggest that crop plants genetically engineered for desirable properties, such as insect resistance, herbicide resistance, and stress tolerance, have the potential to transfer these traits to related species, thereby creating new or more invasive weeds. This argument can also be made for traditional breeding, in which these properties are routinely added to our crops (and may also be transferred to other plants that can breed with crops). A reason for not being concerned that transfer to other plants will cause a serious problem is the fact that each added gene function generally adds a load to the physiology of the plant. As we develop crops to suit our needs, especially under intensive farming conditions, plants lose their adaptability to grow and flourish in the wild. Very high yielding corn, wheat, or soybeans have not caused weeds to become more invasive to nonagricultural habitats merely because the crops were bred for increased resistances. A recent report (*3*) discusses the potential for generating problem weeds as a result of field testing genetically engineered crop plants, and it comes to the same conclusion as I did in my article.

Colwell *et al.* state that it is a contradiction to develop microorganisms that fulfill certain intended functions yet do not survive or compete to some degree. If a microorganism is to be beneficial it must be maintained for a sufficient period in the soil or on the plant. On the basis of efficacy considerations, but not safety concerns, this issue is the greatest problem for scientists developing useful strains such as *Bacillus thuringiensis* or nitrogen-fixing bacteria. A microorganism cannot be manipulated too dramatically or its effect on the plant will be minimal. On the other hand, it is not necessary that every member of the population of the added microorganism disappear from the site within a short period after the beneficial effect has been obtained. There are many cases in which *Rhizobium* strains were added to fields as long as a decade ago, and still can be found in the soil in small numbers. This is probably true for most of the commercial and experimental soil inoculants added to our environment over the past century. Problems have not occurred. In many cases, the microorganisms were genetically altered. If a foreign gene is added to such organisms, it is difficult to imagine how the chance for a problem will increase.

Colwell *et al.* state that the article made "little mention of the potential of engineered microorganisms to transfer plasmids containing novel genes to other microorganisms in the environment." In fact, it was stated that "microorganisms intentionally and unintentionally added to the environment have naturally exchanged genes with other microorganisms." To elaborate further, however, there is increasing evidence that a tremendous amount of gene transfer occurs naturally, not only among related genera, but also between unrelated microorganisms and even between kingdoms. In rare cases, a new phenotype predominates because of certain selective conditions. This is evolution. What scientists create through genetic engineering is minuscule and ecologically insignificant compared to what occurs continually and randomly in nature.

The negative response of regulatory agencies to requests by academic and commercial researchers who wish to release recombinant organisms for small-scale field testing has been frustrating, but a major benefit is evolving. Disciplines that normally have not been interacting are debating issues of common scientific interest. This can only aid science and the public's perception of science. Meaningful evaluation of the potential for problems associated with the use of recombinant organisms requires a balanced perspective and appreciation of practices that have been used in agriculture for decades or centuries. Field testing is the only way to prove that recombinant organisms are safe, and it is "extremely unlikely" that such tests would cause serious health or environmental problems.

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Reusable Oil Plants?

Philip H. Abelson is correct in observing that "current trends of increased energy efficiency and of [oil] substitution" are encouraging (Editorial, 3 May, p. 531). However, a closer examination reveals information that may temper excessive optimism.

The statistical picture since 1978 (1979 to 1984) shows that coal provided 54 percent, nuclear 20 percent, oil 12 percent, hydro 11 percent, and everything else about 2 percent of the 4 quads of domestic energy production increases. Combined with improving national energy efficiency (measured as a 16 percent decline in total energy needed per constant dollar of gross national product), the trends are in the right direction.

It is also important to note that utilities are directly responsible for reducing total U.S. oil consumption by one-third since 1978, while increasing total electric output. Unlike oil reductions in the transportation sector, in which efficiency improvements for new vehicles are the driving force, utility oil savings have come about because of the addition of new non-oil generation (primarily coal and nuclear, which account for over 60 percent and 25 percent, respectively, of all capacity installed since 1978). There is a dangerous energy wild card here. Unlike the transportation sector, where the guzzlers have been replaced, most of that oil capacity remains in place. There is about 100,000 megawatts electric of oil capacity now unused, comprising virtually all of the excess capacity on the grid. Using only half of this capacity would increase oil imports by over 1 million barrels per day. In the current climate these power plants represent the most likely source of significant new electric power. They involve no capital risk, public controversy, or regulatory uncertainty, as do large coal and nuclear plants. It is highly improbable that this much generation in the form of small-hydro, wind, and wood can be built in the next two decades.

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Erratum: In the article "Hughes Institute poised for growth" by Barbara J. Culliton (News and Comment, 7 June, p. 1178), Raymond Gesteland's name was spelled incorrectly.