ther mutation or recombination—are spawned and sorted, because the pathways and payoffs of the MMR mutator are manifold. Such strains can (i) promote diversification, precipitating adaptive mutations such as resistance to antibiotics; (ii) rapidly accrue multiple independent changes, making an unlikely event (such as successful infection) possible; or (iii) assemble multiple mutations from different chromosomes into one by recombination. Thus, MMR mutators (in particular, the *mutS* mutators) may underpin the compelling evidence showing interchange of DNA among *P. aeruginosa* during chronic infections.

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Response

LeClerc and Cebula propose that mechanisms leading to high mutation frequencies (mainly in the *mutS* gene) that we observed in *P. aeruginosa* strains from CF patients may also explain the hypervariable chromosomal structure observed in different *P. aeruginosa* isolates (*1, 2*). Both adaptive strategies, leading to hypermutator and hyperrecombinant phenotypes in *E. coli* and *Salmonella* MMR-defective strains, have been described (*3*).

We considered the hypothesis of a combined hypermutable and hyperrecombinant phenotype. This possibility is not entirely obvious because MMR deficiency increases the recombination rate only for homeologous sequences, but not for homologous (identical) sequences (*4*), and because most CF patients are infected only with a single *P. aeruginosa* clone (*5*). Therefore, despite the possibility of a high recombination rate, only very similar (or identical) sequences can be shared by *P. aeruginosa* individuals living in a CF lung, and thus the probability of acquiring new or innovative DNA blocks is very low. The problem is that gene sequences in *P. aeruginosa* (including strains from CF patients) are, apparently, less polymorphic than the corresponding macrorestriction patterns, suggesting that DNA rearrangements, insertions, and deletions are the main cause of *P. aeruginosa* chromosomal diversity (*1, 2*).

Bacteria have two main strategies to accelerate evolution to adapt to new environments: mutation and recombination. Mutations may be important when a population is confronted with critical, abrupt, and unspecific changes in the environment, eventually permitting rapid, but not always optimal, adaptation. Recombination may adapt more habitat-specialized populations to comparatively small but more specific fluctuations in the environment. In general, the adaptive biology of bacteria tends to be more mutation-based, because there is a strong risk of exposure of the organism to quite different environments, and because strong environmental changes are more frequent in simpler habitats. The exception is bacteria able to reach high specialization in essentially constant and unique habitats (such as *Helicobacter pylori, Neisseria meningitidis,* or *Streptococcus pneumoniae*) in which recombination becomes the major driving adaptive strategy (*6*).

The position of *P. aeruginosa* in this conceptual frame is paradoxical. *P. aeruginosa* resembles a large-environmental-spectrum organism, but its main adaptive strategy appears to be recombination (*1, 2*). This species has a high metabolic versatility, including the ability to adapt to virtually all aquatic mesophilic habitats (*2*). In the case of the CF lung environment, *P. aeruginosa* has a particularly complex challenge, requiring simultaneous adaptation to dehydration, iron starvation, leukocyte influx, antibacterial peptides, and frequently changing, aggressive, and prolonged antibiotic therapy. In this case, perhaps, its metabolic versatility is not enough to allow a rapid adaptation to this complex habitat. In the absence of innovative related DNA (because the population has a clonal structure), hypermutation may arise as the only available strategy to accelerate adaptation.

A combined strategy using both mutation and recombination (when possible) would have been favored by natural selection. As LeClerc and Cebula suggest, the deficiency in the MMR system provides the potential for the use of both strategies. In the lungs of CF patients, and after a certain (long) period of time, several lineages of MMR mutators are expected to be selected by the hitchhiking effect of different adaptive mutations, thus increasing the genetic divergence. At this point, hyperrecombination between mutationally adapted lineages may occur, and a number of DNA interchanges among *P. aeruginosa* variants ensures the progression toward an optimum in the bacterial adaptation to the lung environment. That would result in a second-order genome diversification: large-scale chromosomal rearrangements have been found in *P. aeruginosa* isolates from CF patients (*1, 7*). This strategy would also tend to minimize the frequency of deleterious mutations acquired by mutators.

We consider that the hypothesis of a combination of hypermutation and hyperrecombination strategies in *P. aeruginosa* cannot be ruled out. On the contrary, it should be tested appropriately; for instance, by studying variations in both nucleotide sequences and large DNA fragments among sequential isolates from single patients. However, we suggest that this combination may occur in this particular environment in a sequential way; that is, genomic rearrangements should be preceded by mutations to be fully effective, because only when a certain degree of variation in the population has been generated by mutation can MMR deficiency have the opportunity to increase variation by increasing the recombination rate.

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Scientists Have Not Been Silent

In his Editorial "Opportunity for agricultural biotechnology" (28 Apr., p. 615), Richard J. Mahoney accuses the scientific community of being "missing in action" on the agricultural biotechnology public debate. Few would disagree that more needs to be heard from agricultural and food scientists in both public and private sectors. They have not been silent, however. In 1996, 11 scientific societies representing some 80,000 scientists united their efforts to articulate the scientific concerns about regulatory policy for agricultural biotechnology. The consortium decried regulation based on process rather than product and declared it "scientifically indefensible to regulate the inherited traits of plants for pest and disease resistance under statutes developed specifically for chemical pesticides applied externally to plants" (*1*). Process-based regulation remains the cornerstone of the Environmental Protection Agency's (EPA) policy.

Repeatedly, in testimonies to Congress,

editorials, and letters, scientists have elaborated on the science and safety of modern biotechnology techniques. Mahoney describes the "disappointment" of industry and government biotechnology supporters at the absence of the greater scientific community in the debate, yet I see little evidence of support for the scientific issues by the biotechnology industry, or, for the most part, by government scientists who, while upholding the Food and Drug Administration's product-based approach, acceded to EPA's emphasis on process. Such divisiveness over fundamental science—indeed, outright support for such nonsense as "genes are pesticides"—has provided opportunity for the recent National Academy of Sciences' panel to call for greater regulatory oversight of agricultural biotechnology and to equivocate about the science. In contrast, the recent report from the House Subcommittee on Basic Research (*3*), under the chairmanship of Representative Nick Smith (R–MI), provides ringing endorsement of the science, warns against the hindrance of suffocating regulations, and points out that there has been no evidence to support the laundry list of fears promulgated by opponents.

Science cannot answer the legitimate social and economic questions embroiled in the controversy about agricultural biotechnology, of which there are several, but it can answer the compelling health and safety questions that are the surrogates for substance in the current controversy. By speaking out, scientists from all quarters can strengthen public policy, add perspective to controversial food issues, and restore public confidence in the truly stunning achievements that science has contributed to agriculture. On the other hand, by appearing to support even greater regulation for a technology that already has more oversight than all traditional foods and plants and an unblemished track record, the biotechnology industry and policy-makers signal their mistrust of biotechnology. What more could the opponents want?

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Response

Nettleton properly points out that a coalition of food scientists was active in challenging certain aspects of biotechnology regulation by the EPA and had testified before Congress on the safety of the technology. However, the vast majority of potentially interested scientists has been largely silent—so that the public stage has been taken over by the constant drumbeat of skilled publicists not troubled by the uncomfortable requirements of rigorous science.

Unfortunately, discussion of regulatory procedures gets buried—if recorded at all—in the *Congressional Record*, whereas the "frankenfood" charges of the biotechnology critics make the 6 o'clock news.

As I said in my Editorial, the scientific community can and should now enter the debate fully and make a significant difference using real science—wherever it leads.

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