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LETTERS

NIH R&D Priorities

I must object to the way Jeffrey Mervis, in his 3 June News & Comment article (p. 1395), portrays my views about the 6 May memorandum on fiscal year (FY) 1996 research and development priorities signed by John Gibbons and Leon Panetta. In an interview with Mervis specifically related to the memorandum, I strongly supported the effort to lay out principles, goals, and priorities for development of FY 1996 agency budgets. I also told Mervis that I agreed with the specific principles and priorities that were selected and said that the scientific community would applaud an emphasis on peer review, investment in human resources, and fundamental science. The comments Mervis attributes to me were drawn from a talk I gave on 24 May at a public policy meeting of the American Society for Biochemistry and Molecular Biology; that talk did *not* relate to the memorandum by Gibbons and Panetta, but was aimed at explaining the specific hard choices that have to be made in today's difficult climate as we shape budgets for the National Institutes of Health and distribute funds among the institutes.

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Risks in Using Transgenic Plants?

The recent report by Ann E. Greene and Richard F. Allison, "Recombination between viral RNA and transgenic plant transcripts" (11 Mar., p. 1423), raises safety issues about the field release of transgenic plants. In their Perspective in the same issue (p. 1395), Bryce Falk and George Bruening come to the conclusion that there is probably no greater chance of recombination producing a dangerous new virus than of two viruses jointly infecting a nontransgenic plant. What was not brought out in the Perspective was that recombination is just one of the potential risks of using transgenic crops and that there are ways of minimizing undesirable effects.

The expression of viral sequences in transgenic plants is designed to confer protection against the donor virus and related strains. The major question that arises is, what is the possibility of an interaction between the products of a transgene and an unrelated superinfecting virus? There is a wide range of approaches to this nonconventional protection strategy (*1*) and at least one of them, that of inducing crop plants to express viral coat proteins to give viral protection, will be commercialized soon. The coat protein of many viruses confers the specificity of interaction with the vector (for example, insect, nematode, or fungus) that naturally transmits the virus. This raises the possibility of a transgenically produced coat protein encapsidating the genome of a superinfecting virus, thus changing its vector specificity. There are examples of this heteroencapsidation between related and even unrelated viruses occurring in transgenic plants (*2, 3*).

The argument that these interactions rarely happen in natural joint infections and are thus unlikely in a transgenic situation is open to question on several counts. First, most of these interactions, except for that of heteroencapsidation between related viruses (*4*), have not been sought experimentally, and molecular studies that could reveal such interactions have not been widely applied to field situations. Second, heteroencapsidation or recombination will only take place when a viral genome is exposed, that is, when it is being expressed or replicated. There is strong evidence that this occurs in different cellular compartments for different viruses, but there is no information as to whether the products of transgenes are similarly compartmentalized. Third, the use of transgenic plants will involve their wide-scale deployment, thus increasing the potential for risk (risk = hazard × frequency). This leads to a dilemma as to whether to undertake wide-scale field releases of such transgenic plants—this is the only situation in which current issues can be resolved, but if a problem were to arise, it would then be too late to correct it.

Is there any way that these problems can be bypassed? There is evidence, at least with some viruses, that the region of the coat protein that determines vector specificity is not important for protection against viral infection (*5*). Thus, one can effect biological containment by rendering a protein incapable of vector interactions while maintaining its capacity to afford viral protection. This approach to biological containment could have application to all virus-related transgenes. What is needed is an understanding of interactions that might lead to undesirable properties of a transgene product so that a gene could be refined or tailored to remove "bad" features while

retaining those which yield desired protection. In the absence of information about potential dangers, it would seem prudent to minimize any chance of a risk rather than perform the grand field experiment.

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Falk and Bruening suggest that co-infections are probably universal among viruses capable of infecting a particular host species, and hence transgenic RNAs will not alter the existing possibilities for recombination. They also suggest, on the basis of experimental results, that recombination between virus-derived transgenic RNA and virus RNA does not occur more readily than virus-virus recombination. On these grounds they conclude that the potential for recombination involving a transgenic RNA in a crop is equal to the potential for natural viral recombination.

Although the proposal that co-infections are universal is questionable, it is known that different viruses replicate in discrete subcellular structures with differing locations, that this may be a genus-specific feature, and that co-infections usually involve viruses of different genera. Hence, cellular compartmentalisation may limit contact between different viruses infecting the same plant, but not limit contact between a virus and transgenic RNA. Similarly, different tissue tropisms or epidemiologies that normally separate viruses might not separate these same viruses from contact with transgenic RNA.

The experiments from which Falk and Bruening infer recombination frequencies describe two kinds of interaction, either recombination between a virus and a transgenic RNA derived from that same virus or recombination between RNA species belonging to a single virus. Both kinds of experiment provide data about recombination between RNA molecules originating from the same virus, but not data about recombination between RNA molecules originating from different viruses, including virus-virus recombination. To my knowl-

edge there are no comparable experimental data concerning this phenomenon.

Molecular phylogenetic studies, however, show that genetic recombination that combines genes from different families or genera is a common feature of plant RNA virus evolution and contributes significantly to the generation of new groups (*1*). Although the time scale of this evolution is unclear and may be comparable to the time scale of plant evolution, the survival of these natural recombinants contradicts another of Falk and Bruening's arguments, that new recombinant viruses combining genes from different groups will be noncompetitive and not survive.

The success of natural recombinants also puts a different slant on Falk and Bruening's suggestion that great selective pressures will be required for the survival of rare recombinants. At least two circumstances may have allowed recombinants to survive. First, transmission could sometimes lead to isolation of a single recombinant molecule, its clonal propagation, and its escape from direct competition with parental forms. Alternatively, a new combination of genes may offer sufficient selective advantage.

Some of the recognised recombination events combined coat protein genes from one family and replication genes from another, which gives us a clue as to the nature of a possible selective advantage. Most plant viruses are transmitted from plant to plant by a third organism. A fundamental role of viral coat proteins is to interact with these vectors. Viral replication proteins, on the other hand, interact with the cellular machinery of the plant host. Hence, a recombinant virus may have a new combination of vector specificity and host range and find a new niche. The frequent use of viral coat protein genes in the new technology is, therefore, a cause for real concern.

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Response: Hull argues that nonrecombination interactions (transcapsidation, or heteroencapsidation) are additional risks that should be considered in reference to transgenic plants that express virus coat protein. He suggests, as others have (*1*), possible means of alleviating the potential risks associated with such interactions. Although our Perspective was focused on possible recombination interactions, some comments are warranted. The phenomenon of transcapsidation in transgenic plants must be examined against the background of transcapsidation in multiply infected plants. Transcapsidation interactions between related and even unrelated viruses occur naturally in mixed infections and are likely a natural part of plant virus epidemiology (*2*). Quantitative studies have shown that lower concentrations of virus capsid proteins are produced in transgenic plants than are produced in virus-infected plants. Additional evidence suggests that transcapsidated virus genomic RNAs are less infectious on plants that express viral capsid-protein than are corresponding wild-type viruses. Finally, selective conditions, or virus mutants, or both have so far been required to detect transcapsidation interactions in plants that express capsid protein. Taken together, these data suggest that possible transcapsidation interactions in plants that express transgenic coat protein may represent only a small increment above the background of existing natural transcapsidation interactions. Their significance in possible subsequent vector-mediated virus spread is still very much open to question.

Gibbs states that we have not considered several points relative to virus recombination interactions. He questions whether mixed virus infections are as common as we state and says that we assert that great selective pressure will be required for survival of rare recombinants. As our Perspective made clear, selective pressure is required for detection of recombinants, not for their survival. Mixed infections probably are even more common than currently realized when one considers subliminal infections.

A central concept of our Perspective was that recombination between transgene sequences and virus genomic RNA sequences must be viewed against the background of already occurring recombination between viruses. Gibbs compares possible effects of compartmentalization on recombination between virus genomic RNAs and on recombination between such an RNA and a transgene RNA. Whether, during infections, distinct viruses are more thoroughly compartmentalized from each other than are similar viruses remains to be seen. Compartmentalization of cellular (transgene) and replicating viral RNAs is a topic worthy of investigation. However, barriers that result from compartmentalization and barriers that result from sequence differences will be difficult to distinguish. In general, compartmentalization of virus infections is "leaky," which presumably allows recombination to be "a common feature of plant RNA virus evolution," as stated by Gibbs.

We agree with Gibbs' point about the ongoing evolution of viruses. However, the

fact that evidence for modular recombinants is related to an evolutionary time scale supports our contention that "new viral diseases are usually due to minor variants of already known viruses . . ." (p. 1396). It is against the background of novel virus diseases, caused by minor variants, that the risk of recombinants, derived from diverse transgene and virus genomic sequences, should be considered.

Most of the plant viruses for which we now have an understanding in molecular terms have been associated with specific plant diseases over the entire period of disease documentation. This is contrary to Gibbs' point that a recombinant between distinct viruses is more likely (than a recombinant between genomes of similar viruses or strains) to cause widespread disease. We agree with Gibbs that a significant departure from existing virus types may offer greater possibilities for adverse disease consequences than do minor variations in virus type. However, as we stated in our Perspective, this effect is balanced by the much poorer competitiveness that is likely to be characteristic of most such recombinants, as well as the low frequency of their occurrence. The evolutionary time scale over which new virus types appear is consistent with the great rarity of successful recombinants derived from diverse parents.

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NIST: What's in a Name?

Most people knew that NBS meant the National Bureau of Standards (NBS), not the National Bureau of Science. But then it had been around for almost 90 years before its name was changed to the National Institute of Standards and Technology! So perhaps we should forgive *Science* for misidentifying the acronym NIST in the title and text of Philip H. Abelson's 20 May editorial (p. 1063). But this slip has deeper implications. The mission of NBS was to support the science of measurement, metrology. Many are surprised to learn that this does not mean simply maintaining platinum bars or masses. Today the meter is