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STANFORD UNIVERSITY MEDICAL CENTER

DEPARTMENT OF GENETICS

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Dear Dr. Bernardi:

I was glad to have your letter of July 28th, which asks certain questions about the hazard assessment of cloning in Bacillus subtilis 168. There are, of course, three variables in such experiments: the source of the DNA insert, the plasmid or cloning vector, and the organism -- in this case B. subtilis -- used to propagate the hybrid plasmids.

In view of the many criticisms that have been offered against the use of E. coli, attributed to its close ecological connection with the human species, it is indeed fortunate that a practical cloning system is now available in another bacterial species like B. subtilis. While it is impossible to describe any bacterium as totally harmless under all conceivable conditions, B. subtilis does not depend on its association with animal hosts in its normal life cycle, has no specific adaptations for such association, and has no evident specific pathogenic potential. It can, therefore, be argued to be as nearly harmless as any microorganism that will ever be discovered -- including wine yeast, Penicillium Roquefortii, Lactobacillus acidophilus or many other organisms that are part of a natural diet, but thereby are even more closely associated with man. According to this argument, to the fact that the plasmids grown in B. subtilis are not biologically transmissible. and to the observed instability of the plasmids in the absence of selective pressure, the system that Dr. Ehrlich has developed should be an ideal one from every perspective. These are compelling arguments to support a substantial reduction of hazard in the use of this organism relative to E. coli, particularly if non-sporing strains are used.

I would not agree with a blanket elevation of containment levels for "non-pathogenic soil organism DNA" in B. subtilis, compared to E. coli. This view underestimates the extent to which enteric bacteria, genetically comingled with E. coli, are equally common in soil. Aerobacter and Pseudomonas are particularly in point here. The likelihood of hazard is so low that I

Bernardi, D.G.

would advocate general standards of the same stringency as for E. coli; but of course one should take account of specific circumstances that might elicit more specific concerns. If you are discussing DNA from pathogenic soil organisms, with respect to traits that could plausibly be expected to influence the pathogenicity of B. subtilis, you would of course be dealing with a different situation.

My fear in making these recommendations is that they may give unduly high credit to the hazard that is supposed to be associated with "E. coli," a designation which is in many respects a semantic artifact. It is just an accident that E. coli K-12 has the same taxonomic designation as freshly isolated strains of E. coli that are demonstrably adapted to sustain life in the gut. It is just too bad that mere historical accident requires us to use the common epithet!

In summary: whatever merit one attributes to restrictions on the insertion of DNA from non-pathogenic sources into plasmids grown in E. coli, one should have substantially fewer concerns about the use of the B. subtilis system.

Whatever actions your committee takes, I trust that it will be receptive to important new scientific information that is being developed at a very rapid rate. I believe this already tends to show that the global fears about the biohazard of recombinant DNA experiments have been grossly exaggerated from the inception of this controversy. The most pertinent information is that genetic exchange is a common natural process; and there is already substantial evidence that the experiments in the laboratory do little to add to the natural flow of genetic information in the biosphere on a large scale. The principal distinction between the natural and the laboratory environment is not the production of novel DNA sequences, but rather the selective pressures to which they are exposed.

Yours sincerely,

Joshua Lederberg
Professor of Genetics

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