The indiscriminate use of antibiotics has exerted more pressure on the bacterial population than could be wielded by all research workers in the field put together.

from E. S. Anderson, Colindale

THE NAS statement on plasmid engineering evokes a mixed reaction from me. Whatever its justifiability, I wish it had been presented less pompously. We have been more aware since our first experiments in transferable resistance in 1964 that by introducing an R factor into a pathogen we reinforced this organism's pathogenicity with resistance to drugs that might be effective against the respective disease. In particular, when chloramphenicol resistance was introduced into the typhoid bacillus, we were manufacturing a virulent pathogen resistant to the drug of choice for typhoid fever. And we knew that if we presented such a strain with the opportunity of causing infection we would have been guilty of a grave antisocial offence. But R factors had become important in the enterobacteria and they demanded study. We could not do such work effectively if we shirked the step of introducing them into pathogens. So we transferred them to pathogenic enterobacteria, including *Salmonella typhi*, exercising our routine precautions for avoiding infection with the respective organisms, and for their safe storage. We have studied the typhoid bacillus and related organisms for many years, but no infections have resulted from our work, inside or outside the laboratory; so our protective measures must be reasonably efficient. Moreover, it is fair to say that these manipulations have contributed to the understanding of R factors and other plasmids, including the evolution of an easy method for establishing the plasmid nature of elements concerned with enterobacterial drug resistance, virulence or other properties.

The *in vitro* hybridisation of plasmid DNA with DNAs of widely different, even eukaryotic, origin, adds a new dimension to plasmid studies. Once introduced into the bacterial cell, the hybrid plasmids resume the relationships of their bacterial moiety and multiply with the cell. The eukaryotic regions, however, retain their original coding capacity and initiate the synthesis of the corresponding products.

What is the point of such experiments? First, they demonstrate that DNA-DNA hybridisation need not require extensive regions of base-pair homology. They therefore expose processes that may have important evolutionary significance or medical potential. Second, they may help to clarify the *modus operandi* and the nature of the products of the "Xeno-DNA", if one may coin such a term for the introduced foreign DNA. Normally, such studies are hampered by the relatively slow cell growth and much greater complexity of the respective animals or tissue cultures. In hybrid bacterial-animal plasmids, synthesis and replication are geared to the much higher kinetics of bacterial growth, so that the respective DNA and its products can be isolated in adequate quantities in a short time. This might accelerate the studies of these materials and could add

Alternative experiments?

SECTIONS of genetic material from any source can now be attached to a bacterial plasmid or bacteriophage and so introduced into the bacterial cell where they replicate quickly and can be recovered in relatively large amounts. By-passing the normal biological barriers between species in this way means that completely novel genetic combinations can be created and disseminated.

But it is at present impossible to predict all the properties and ecological consequences of these new genetic arrangements. Not unnaturally this has led to widespread concern over possible biohazards from such research, which has resulted in the National Academy of Sciences appeal. Concern is enhanced because the ubiquitous human enteric bacterium *Escherichia coli*, has been used as the organism in experiments carried out so far.

Anxieties arise on two main counts. (1) It is generally impossible to transpose selectively only those DNA fragments with known functions. Potentially harmful DNA fragments, such as those containing possible oncogenes, may unwittingly be transferred to a new host where their expression may not be properly controlled. (2) The vehicles used (in the work published so far) to transfer foreign DNA fragments to *E. coli* were plasmids that carry genes determining resistance to antibiotics.

The NAS embargo covers two types of experiment (which have already been accomplished by some of the signatories of the statement), namely the transfer of genes determining drug resistance between bacterial strains or species that do not normally carry such resistance, and the fusion of animal virus genes to transmissible systems.

The NAS request is both reasonable and responsible and deserves to be universally respected. It recognises both the difficulty in evaluating real or potential hazards that may be involved in such work, as well as the obvious criticism that these will remain obscure in the absence of experimental study; urgent consideration of the latter is explicitly recommended.

Fears that the proposed limitations to experiments will seriously obstruct research in vital areas of biology seem unfounded. The NAS initiative, by focussing attention on the hazards involved, could well promote rather than hinder work on *in vitro* recombination in animal viral systems, an area believed by many to hold the key to gene therapy in its broadest terms. Similarly, the constraints on experiments with plasmids determining drug resistance need not preclude cautious use of the plasmids for cloning certain DNA fragments. Many experiements in this latter area can also be undertaken with bacteriophage λ which is a safer vector for *in vitro* recombination in that it has strict host specificity and carries no drug resistance determinants; it has the great additional attribute of bringing a wealth of gentic and biochemical experience to the service of studies on the cloned fragment of DNA. Use of phage λ does not, of course, eliminate hazards associated with the incorporation of unknown genes.

In view of the anxieties expressed, the wisdom of using a normal human enteric bacterium as host organism in these experiments might be questioned. Certainly there is no reason to believe that one could not select quite different microbial and viral systems that do not inhabit man or mammals, but the hazards, real or potential, would apply equally well to other ecosystems and thus eventually raise the same problem. To do this, however, would be to forsake the wealth of information and experience with *E. coli* and its viruses accumulated from decades of research. This would be prodigal to say the least.

While welcoming the NAS initiative, one is also appreciative of Anthony Tucker's perspective in his comment "Life Stylists" (*The Guardian*, July 19); equally, if we follow the moderate tone set by the NAS we shall be careful not to oversell the social benefits devolving from recent experiments.

Ken Murray, Edinburgh