THE SALK INSTITUTE

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Dr. F.H.C. Crick
MRC Laboratory of Molecular Biology
Hills Road
Cambridge, England

Dear Francis:

I am writing for a change about science rather than about Dipenidam. Two questions have come up in work on non-enzymatic DNA synthesis, which I feel you will be able to answer much better than anyone here.

In general, if a nucleotide analogue can be incorporated into an oligonucleotide on a polynucleotide template P, then it should be possible to use that analogue as a component of a complementary template P'. There is one obvious reservation, namely that the analogue have sites equivalent to both the 3' and the 5' ends of a standard nucleotide, but everything else should be taken care of by the diad axes of the double helix. Can this obvious notion be made more precise by some stronger (symmetry) argument?

The second question is raised by the difficulty of separating double-stranded structures, once they have been formed. The standard answer is that a cycle of heating and cooling is required--separation occurs at high temperatures and synthesis at low. A totally different approach is to suggest that the double-stranded forms of the earliest "nucleic acid" molecules were much less stable than contemporary nucleic acids, but that the association of monomers or very short oligomers with the original single-stranded "polynucleotides" was as stable as in the contemporary

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system. One requires a structure in which the first few base pairs form nicely, but stereochemical or other constraints make indefinite extension difficult or impossible. Can you comment on how this could most easily be done, and also on the relevance of the symmetry of the double helix to the problem of achieving an appropriate "misfit"?

Yours sincerely,

Leslie E. Orgel