H-form DNA and the hairpin–triplex model

SIR—In reporting the occurrence of a novel DNA form, the 'H-form', in supercoiled homopurine–homopyrimidine tracts at low *p*H, Mirkin *et al.*[1] apparently ignored our previous description of such a structure (the 'hairpin–triplex')[2]. We came up with this model when analysing the precise positions where the enzyme S_1-nuclease was able to digest a cloned homopurine–homopyrimidine element, normally lying upstream from the human thyroglobulin gene.

The proposed structure, virtually identical to the one depicted in Fig. 3 of ref. 1, was suggested to us by the work of Lee *et al.*[3] who showed that $(TC)_n \cdot (GA)_n$ duplexes could form triple-helical complexes at low *p*H. Careful examination of data available at that time concerning the digestion of other homopurine–homopyrimidine sequences with S_1-nuclease, as for example the one located in the human α_2–α_1 globin intergenic region[4], showed that they also fitted into the proposed model.

We therefore argued[2] that our hairpin–triplex structure represented "an alternative to the [then favoured] slippage-mechanism hypothesis[5] as long as the distance between the repeats still allows the formation of a double-stranded hairpin[2]. As well as setting the facts in their true light, we consider that mention of our data in the context of the work of Mirkin *et al.* is worthwhile, as both point to the same model while stemming from different methodological approaches.

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FRANK-KAMENETSKII REPLIES — Although our *Nature* paper[1] did not cite the paper by Christophe *et al.*[2], its two predecesors[3,4] both did. In ref. 3, where we formulated our final model of the H-form, we wrote[3]: "To explain the bimodal cleavage pattern Christophe *et al.*... also invoked the triple helix." We also properly cited the paper by Lee *et al.* which Christophe mentions in his letter.

We disagree that the structure claimed in ref. 2 is "virtually identical to the one depicted in Fig. 3 of Mirkin *et al.*". The Christophe *et al.* structure is virtually identical the structure proposed by Lee *et al.* (see Fig. 5 of ref. 5), which we knew before starting the whole business. Indeed, we wrote in the introduction to our very first paper on the subject[6]: "Slippage loops ....., a left-handed helical structure ... triple and quarter helices ... have been discussed in the literature." The principal difference between the structure of Lee *et al.* and Christophe *et al.* on the one hand, and our structure on the other, is the nature of the hairpin. According to the former it is double-stranded, whereas according to the latter it is single-stranded.

Christophe *et al.*[2] invoked the 'hairpin–triplex' structure to explain the bimodal pattern of cleavage of their homopurine–homopyrimidine tract by S_1-endonuclease. The two sites of cleavage are more than 100 base pairs apart and they considered that this 'spacer' region forms a double-stranded hairpin. On the basis of our recent findings[2], another interpretation of their data seems more plausible. We have found that the two sites of cleavage are actually H-palindromes (underscored in the figure).

^{46}GGAAGGAAGGAAAGAAGGAAGAAAGAAAAG

^{155}AAAGGAAGAAAGGAAAGAAGGAAGGAGGAAGGA

We therefore believe that these two H-palindromes, under superhelical stress and at acid *p*H, form two separate H-forms and these are the S_1-hypersensitive sites. These H-palindromes are, at least, very similar to those collected in Table 1 of our *Nature* paper[1]. The interpretation of the S_1 cleavage pattern in terms of the model of Christophe *et al.* seems doubtful for several reasons, which are beyond the scope of this short reply. The above discussion clearly shows that these different models entail different interpretations of the same experimental data.

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Species selection and the role of the individual

SIR—In opposing the punctuational model of evolution and species selection[1] and in his reply to Eldredge and Gould[2], Maynard Smith has seriously misrepresented my writings on the subject, making my position appear far more radical than it has ever been.

In promoting the concept of species selection, I have never denied that selection at the level of the individual plays an important role in speciation. In 1979, in addressing quantum speciation, I wrote[3], "It is quite likely that in the punctational model natural selection will continue to be viewed as the dominant guiding process of generation-by-generation change". And in 1982, I wrote (in italics for emphasis)[4]: "The punctational model is essentially a description of temporal and spatial patterns, not of population genetic mechanisms, and it is compatible with the possibility that virtually all of the evolution that occurs during divergents speciation is achieved by conventional natural selection among individuals". None of my other writings has been intended to express any other view. Thus, Maynard Smith is mistaken in his claim that the raw material of species selection, as I have defined the process[3–5], relies strictly on "non-adaptive punctational changes that occur when new species arise"[1].

The definition of the word random, as applied to speciation, seems to be at the root of the misunderstanding. Maynard Smith[2] has quoted out of context a statement of mine that refers to "a strong random element" in speciation. Randomness here does not refer to non-adaptive genetic drift or haphazard mutation, as he seems to have concluded. Again, for historical accuracy, I quote one of my previous statements[4] (omitting the references):

"The random element in speciation to a considerable degree decouples macroevolution from microevolution. The meaning of "random element" has frequently been misunderstood. Although there is often a bias in the direction of speciation within the higher taxon — a morphogenetic or environmental tendancy for certain changes to occur rather than others — the direction that the next event will take in any segment of phylogeny nonetheless remains highly unpredictable: a pair of dice may be loaded, but each one still has six sides. Where, when, and in what subenvironment the next speciation event will occur within a lineage is always highly uncertain. Mann has discussed this kind of randomness in the operation of geologic processes. Species selection can operate even without the direction of a speciation event being entirely random. The only requirement is that speciation generate a variety of species upon which selection can operate. As characterized by Mayr, speciation amounts to experimentation by which evolution continually probes the environment. The origin of a particular kind of species at a particular time and place is no guarantee that this kind of species will fare well in a broader environmental context."

It is also important to recognize that selection at the level of the species is not predicted upon the punctuational model. Species selection simply looms larger in this model than in a gradualistic framework, which grants gradual evolution a larger role in the determination of macroevolutionary trends. In fact, although he

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