A nick-free solution to the DNA winding problem

THE phenomenon of genetic recombination is of great importance and for many decades scientists have attempted to unravel the mechanism of this process. With the elucidation of the structure of DNA, a new era in understanding the mechanism of genetic recombination began.

In 1964, Holliday proposed a general model; according to this model, regions of homologous sequences of two different double-stranded DNA molecules come together and pair up. At the region of pairing, the strands of DNA break the old

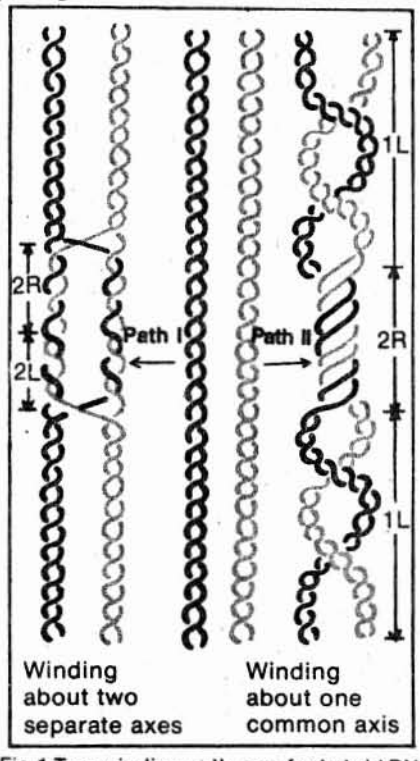

Fig.1 Two winding pathways for hybrid DNA molecules formation. R and L denote right- and left-handed helical segments, respectively, that result from the indicated winding (after Wilson, 1979)

hydrogen bonds and form new ones with the complementary strands of the other molecule to form a heteroduplex. After this, the enzyme, endonuclease, cuts the strands at appropriate points to yield two hybrid DNA molecules. When we attempt to do this with a right-handed double helix of the Watson-Crick type, we encounter a topological problem termed the 'winding problem'. As shown in path I, in Fig. 1 the two strands of the parent DNA molecules come apart and form two regular heteroduplexes with screw axes separated in space. In such a scheme, we inevitably get an equal number of right and left double helical turns for the heteroduplex. But in 1965, Wilkins and his co-workers stated that only right-handed double helical segments are possible in DNA. All the earlier models of recombination involve an endonuclease cut (nick) in one strand of each DNA molecule prior to the formation of the heteroduplex because of the underlying assumption that the heteroduplex is a uniformly right-handed structure.

J.H. Wilson *(Proceedings of the National Academy of Sciences,* USA, **76** 3641) has come up with an interesting solution to the winding problem. The importance of his solution lies in the fact that no nick is needed at the region of heteroduplex formation to form a uniformly right-handed helix. This is shown in path II in Fig. 1. Wilson's model involves two steps (as shown in Fig.2). In the first step, the base pairs of the parent molecules associate by interaction through the minor groove; in the next step the bases switch their partners shifting by 90° to form the heteroduplex. The structure formed is four-stranded (a tetrad), uniformly right-handed (both in duplex and in tetrad) and energetically stable. Incidentally, this four-stranded model is reminiscent of the one proposed by McGavin in 1971—a tetrad associating two right duplexes through the major groove. In Wilson's model, the right helical turns of the heteroduplex are compensated by an equal number of left-handed coils — one parent duplex over another, termed homoduplexes. At the region where the homoduplex and heteroduplex join, the bases are largely unstacked and might be

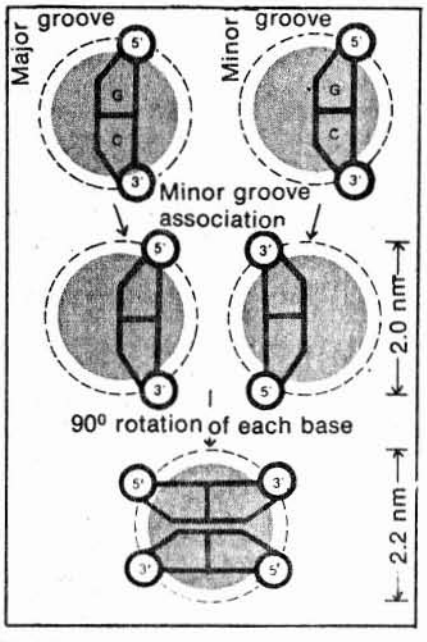

Fig.2. Lateral shift in base pairing. (Top view of the helix axis) Identical base pairs initially associate by the minor groove surfaces. Each base rotates 90° to form two heteroduplex base pairs simultaneously (after Wilson, 1979)

sensitive to nicking; this could provide for the site specificity of the endonuclease action to separate out the two hybrid molecules.

It is important to emphasise that Wilson's model, like all the earlier ones, is primarily concerned with not violating Wilkin's hypothesis that no left-handed helix is possible for DNA. However, Sasishekharan and co-workers *(Proceedings of the National Academy of Sciences,* USA, **75** 4092), by showing that left-handed DNA is possible, place the entire problem in a new perspective. Further, A. Rich has recently reported *(NATO-BMBO-Summer School on Protein-Nucleic Acid Interaction,* Greece, Aug-Sept 1979) the crystallisation of a hexanucleotide C-G-C-G-C-G DNA fragment and he claims that it has left-handed helicity.

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Protein deprivation and immune response

VARIOUS STUDIES have indicated that there is a complex interaction between nutrition and infection. The two major defence mechanisms of a host which operate against infection are immunological activity and phagocytic activity. Any alteration in these mechanisms may be expected to adversely affect resistance to infection. Recently, studies have been undertaken to determine whether nutritional status influences the capacity of the body to elaborate antibodies and whether it impairs the cell-mediated immunological response. Malnourished children who had been given bacterial and viral vaccines were tested for antibody levels. Their ability to produce antibodies was found to be impaired.

A low protein (LP) diet was given to seven-week old rats (each weighing 140 g) to induce protein deficiency (*Nature* **281** 64). Control rats were fed high protein (HP) diet. The LP diet-fed rats lost weight and had lymphoid atrophy but appeared healthy with their intestinal mucosa morphologically normal. Also, there was a diminished number of thoracic duct lymphocytes, including those containing immunoglobin A (IgA) which suggested an impaired mucosal immune response to enteric antigens. This was confirmed in rats immunised orally for cholera. The IgA antitoxin response could be corrected by feeding with HP diet; on refeeding, there was a rapid regeneration of atrophic lymphoid tissue. (In the controls, normal antitoxin containing lymphoblasts were seen.)

This study is relevant to human conditions. Severely malnourished children are seen with depressed immunological