the latter, maternal transmission predominates over paternal, and a model has been proposed for testing this (Fine *J. med. Genet.* **14**, 399; 1977). The lesson to be learnt is that the fact that a disease is transmitted in Mendelian fashion does not exclude predominant environmental influences; nor does the presence of a transmissible factor mean that inheritance is not genetically determined. These findings may help in elucidating the mode of inheritance in some other human familial conditions, such as Leber's optic atrophy, where geneticists have for many years been puzzled by apparent inconsistencies with known modes of inheritance. □

Twists and turns of DNA

from Stephen Neidle

It has been realised for some while that the DNA associated with a chromatin repeating unit (the nucleosome), has to be folded to about a seventh of its normal length in order to be accommodated within the known dimensions of this particle. As yet we are some way from having anywhere near an experimental answer to this organisational problem through a high-resolution X-ray crystallographic analysis; it is to be hoped that the quality of the nucleosome crystals reported by the MRC Cambridge group, will in time be sufficiently improved for this goal to be attained (see Finch *et al. Nature* **269**, 29; 1977).

In the absence of such data, several hypothetical models have been suggested for the stereochemistry of DNA folding. The initial 'kinked-helix' model, that of Crick and Klug (*Nature* **255**, 530; 1975), involves short stretches (20 base pairs long) of standard B-DNA double helix. The base pairs at each twentieth position are partially unstacked, with a concomitant alteration in the conformation of the sugar-phosphate backbone, so that these straight lengths become bent, at roughly right angles to each other. The small negative twist produced in the double helix by this kinking, enables it to be formed in a toroid suitable for being wound around the histone core of the nucleosome. A modified kink model has been proposed by Sobell *et al.* (*Proc. natn. Acad. Sci. U.S.A.* **73**, 3068; 1976), which has been extrapolated from their crystallographic studies on dinucleoside phosphate–drug intercalation complexes; kinking, this time every 10 base pairs, is accomplished by conformational changes somewhat different from those proposed by Crick and Klug.

The other, contrasting, approach to this problem may be qualitatively visualised by simply taking hold of a molecular model of DNA—it is apparent that the double helix has sufficient inherent flexibility for smooth, continuous bending along its axis to be possible. Such an alternative has been recently described by Levitt (*Proc. natn. Acad. Sci. U.S.A.* **75**, 640; 1978), and independently by Sussman and Trifonov (*Proc. natn. Acad. Sci. U.S.A.* **75**, 103; 1978). In both models, DNA is smoothly bent into a 45–50 Å radius superhelix, which is of the right dimensions to wind around the histone core. Sussman and Trifonov established a (computer-generated) molecular model corresponding to this degree of deformation by the step-wise procedure of first giving a (13 base pair) stretch of classical B-DNA a small negative twist, followed by a bending-type transformation; the less-than-perfect stereochemistry obtained at this stage was then improved by a least-squares method involving fitting standard molecular geometries to the fragments. Their resultant 'smoothly-deformed' DNA does not differ appreciably from the B-DNA except that some of the sugar-phosphate torsion angles systematically vary as one progresses along the double-helical chain. Levitt has employed his previously developed techniques of empirical energy calculations. He has taken a 20 base-pair length of B-DNA, and allowed each of the 820 atoms involved to shift to an energy-minimum position, before deforming it into a supercoiled configuration which like that of Sussman and Trifonov, is both stereochemically and energetically plausible. However, the two suggested superhelical DNA structures are remarkably different from each other, at the detailed molecular level (their superhelical parameters, as one might expect, are broadly comparable). Whereas the Sussman and Trifonov deformed DNA still resembles the classical B form in many important aspects, that of Levitt clearly does not, apart from still being a 10-fold double helix. Particularly striking in the latter are the now markedly non-planar base pairs, with a 31° angle between each base. The sugar-phosphate conformation again shows a periodicity dependent upon the residue's position in the chain, which seems, for some variables, to be sequence dependent.

In the same paper, Levitt has also provided more details on his energy-minimum form of straight DNA (initially mentioned by Finch *et al.*) which he considers to be more representative of DNA in solution than the familiar B type structure, whose detailed character is suggested to be a consequence of crystal packing forces. In contrast to the 10-fold helix, his calculations suggest a non-integral number of base pairs (about $10\frac{1}{2}$) per turn. These base pairs have a markedly propellor-like character (as in his supercoiled DNA), and thus the individual bases become no longer almost perpendicular to the helix axis.

Direct experimental verification of any of these models is unavailable at present, although a recent ^{31}P nuclear magnetic resonance study of DNA in chromatin (Kallenbach *et al. Nature* **272**, 134; 1978) suggests that all the backbone units of the nucleic acid are roughly equivalent—this favours a smoothly deformed, as opposed to a kinked model of supercoiling. However, whatever hypothesis is ultimately found to be closest to physical reality, the usefulness of these model-building exercises is undeniable in that they demonstrate that DNA can no longer be considered to be a relatively rigid structure. □

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Differentiation dissected

by Peter Newmark

In the reasonable belief that determination of cell lineage is a prerequisite to the understanding of differentiation attempts are being made to dissect, as finely as possible, the separate steps and decision points in various systems. A selection of these systems was presented at a recent conference on the 'Genetic Control of Cell Differentiation and Malignancy', held early this month at Titisee.*

Of particular interest and complexity is the immune system, in which the stages of differentiation are often defined by the appearance of stage-specific surface markers. These are identified by antibodies, whose production has been revolutionised by the availability of hybridoma cell lines producing monoclonal antibody. Yet higher yields come from the ascites fluid of animals with tumours derived from injected hybridoma cells. C. Milstein (MRC Cambridge) described

*Held on 6–8 April, 1978. A Dr Karl Thomae GmBH International Titisee Conference.

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