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Nucleosome sub-structure during transcription and replication

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We have described (Richards *et al.* 1977) a model for the sub-structure of the core particle (140 base pairs) of the nucleosome repeat in chromatin, based principally on results from neutron and X-ray scattering, together with data from other physico-chemical studies. Like that proposed by others (Weintraub, Worcel & Alberts 1976), a principal feature of the model is that it consists of two identical halves, each containing a heterotypic histone tetramer, which lie face-to-face about a dyad axis of symmetry. In this brief contribution we give more detail to proposals already mentioned (Richards *et al.* 1976, 1977) for the manner in which such a particle *might* linearize to accommodate the action of either the polymerase or replicase enzymes in transcription and replication, respectively.

The model outlined in figure 1 was derived in the following manner. Dilute solutions of nucleosome core particles, purified from lysed chicken erythrocyte nuclei by zonal centrifugation of the staphylococcal nuclease digest (Pardon *et al.* 1977), and 2 M salt-extracted histone tetramers (Wooley *et al.* 1976, 1977; Weintraub, Palter & Van Lente 1975; Campbell & Cotter 1976; Pardon *et al.* 1976) were examined by neutron and X-ray scattering methods. Size and shape of core and tetramer particles was deduced by comparing observed scattering profiles with calculated profiles for models having defined separate domains of scattering density, corresponding to DNA, protein and nucleoprotein, and having the radii of gyration for DNA and protein previously determined (Pardon *et al.* 1975, 1976). Calculations were made using a computer program developed for models in which three coaxial domains for the three scattering densities were shared among a large number (about 700) of small elements of equal volume, such that the coordinates of the centres of each element could be used to calculate the spherically averaged scattering profile using the expression derived by Debye (1915). Models for simple structures such as spheres, ellipsoids and cylinders did not give satisfactory agreement between calculation and observation. When more complicated structures were examined, only the one of type and dimensions shown in figure 1 was able satisfactorily to account for both the neutron and X-ray scattering profiles.

When we consider how the structure might change during transcription and replication we propose the sequence of events shown in figure 2, for which, at the present time, there is little evidence. An intrinsic feature of the model is that the highly basic N-terminal 'tails' of each histone protein bind to DNA by salt linkages (Richards *et al.* 1976; Lilley *et al.* 1976). The attachment could be almost entirely by bonds to one of the sugar-phosphate chains (Pardon & Richards 1973). The first stage in the process (II, figure 2) is the separation of the two half core particles by articulation about the internal linker DNA, maybe by restitution

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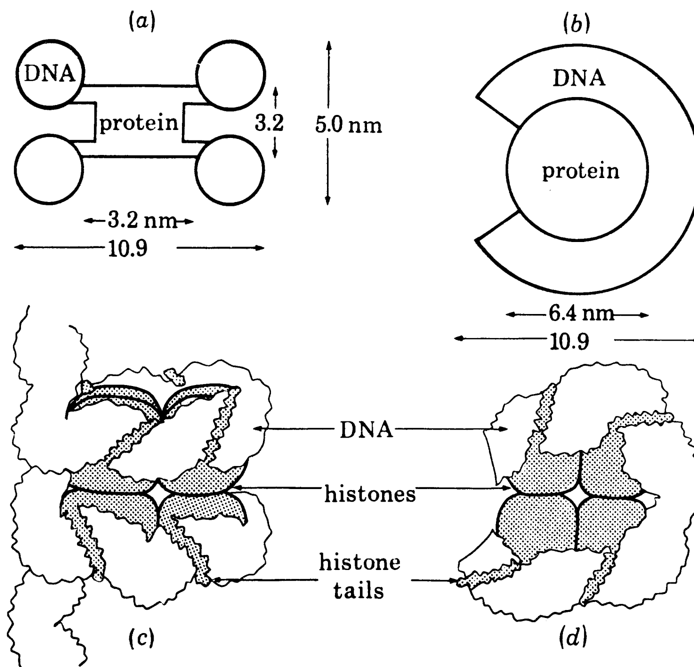

Figure 1. Model for the core particle of the nucleosome. Top: diagram of the domains of DNA (also containing the histone 'tails') and histone, derived from neutron scattering data (Richards *et al.* 1977). (*a*) Longitudinal section parallel to the cylindrical axis of the histone tetramers; (*b*) transverse section in the plane of the half nucleosome core particle. Bottom: schematic views of the core particle based on (*a*) and (*b*); (*c*) from the side, (*d*) along the cylindrical axis of the histone tetramer.

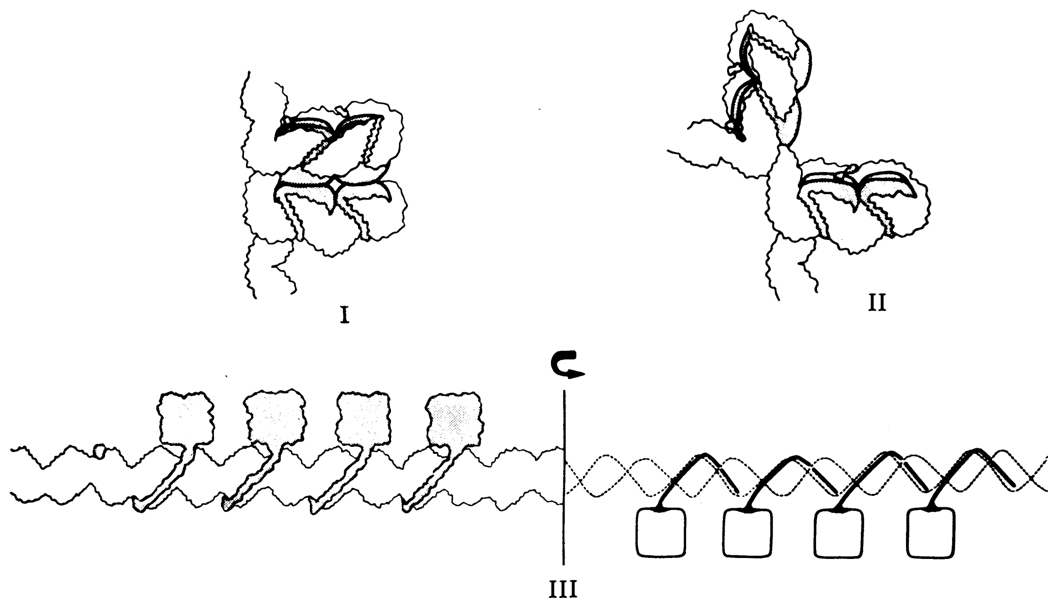

Figure 2. Scheme for the reversible unfolding and folding of the nucleosome core particle. Stage I is the fully folded particle. Stage II is the separation into half core particles. Stage III is the linear form with histones remaining in register on the DNA attached almost entirely to one of the DNA strands, thus permitting local strand separation. After transcription the structure refolds. During replication the linear structure predisposes correct assembly of histones and DNA into new strands and new nucleosomes.

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of linearity of DNA 'kinks' when the interactions between tetramers weaken. When the interactions between each histone in the two tetramers are weakened, passage of the appropriate enzyme is permitted. This breaks the histone–histone interactions but leaves essentially untouched the ionic bonds between the 'tails' and the sugar-phosphate backbone of the DNA. Thus in stage III the DNA duplex is linear with histones remaining attached, in a symmetrical pattern as yet undetermined, predisposing the structure to precise and efficient refolding after strand separation.

Thus, as the polymerase enzyme passes it unfolds the structure, opening and closing the DNA duplex as required for transcription and allowing the refolding to occur under the influence of the histones. During replication, the DNA strands would be separated by the replicase, with the histones remaining attached by the 'tails' while new DNA strands with new histones (Weintraub 1973) are assembled in a manner partly dictated by the undisturbed attachment of the original histones. Such undisturbed attachment of histones to DNA is thus the key to automatic refolding after transcription and to the accurate organization of 'new' DNA and histone with 'old' DNA and histones into 'half new' nucleosomes in replication.

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