This evidence suggests pairwise associations of the histones in chromatin but says nothing of details, such as whether the F2A1 and F3 pair, which occurs as an $(F2A1)_2(F3)_2$ tetramer in solution, also occurs as a tetramer in chromatin. The most direct evidence for an $(F2A1)_2(F3)_2$ tetramer in chromatin is that a complex formed from tetramers, F2A2-F2B oligomers, and DNA gives the same x-ray pattern as chromatin (Fig. 4, upper two traces). Tetramers and F2A2-F2B oligomers are both required to give the x-ray pattern (Fig. 4, lower two traces), but F1 is not—in keeping with previous observations (*3*, *23*) that removing F1 from chromatin does not affect the x-ray pattern. Further implications of these results are discussed in the accompanying article (*24*).

We are currently studying associations of the histones in chromatin by cross-linking. There are two difficulties that do not arise in experiments on the histones in solution: the amino side chains are involved in salt linkages with the phosphate groups of DNA and are thus less available for chemical modification; and the presence of five rather than two histones complicates identification of products from molecular weights. Preliminary results do show less cross-linking of histones in chromatin than in solution, but cross-linked products up to pentamers are readily observed and call for further investigation.

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Chromatin Structure: A Repeating Unit of Histones and DNA

Chromatin structure is based on a repeating unit of eight histone molecules and about 200 DNA base pairs.

Roger D. Kornberg

Evidence is given in the preceding article (*1*) for oligomers of the histones, both in solution and in chromatin. Here I wish to discuss this and other evidence in relation to the arrangement of histones and DNA in chromatin. In particular, I propose that the structure of chromatin is based on a repeating unit of two each of the four main types of histone and about 200 base pairs of DNA. A chromatin fiber may consist of many such units forming a flexibly jointed chain.

Introduction to Chromatin Structure

Chromatin of eukaryotes contains nearly equal weights of histone and DNA. This corresponds, on the basis of the molecular weights and relative amounts of the five main types of histone, F1, F2A1, F2A2, F2B, and F3, to roughly one of each type of histone per 100 base pairs of DNA with the exception of F1, of which there is half as much. The arrangement of histones and DNA involves repeats of structure. The first evidence of this comes from the work of Wilkins and co-workers (*2*) who obtained x-ray diffraction patterns from whole nuclei of cells showing relatively sharp bands. Chromatin isolated from the nuclei as a nearly pure complex of histone and DNA gives x-ray patterns with the same bands. Further x-ray work (*3–5*) has shown that these bands correspond

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to structure repeating at intervals of about 100 angstroms along the length of the chromatin fiber. Neither histone nor DNA alone gives x-ray patterns with such bands.

A "super-coil" model has been proposed (*6*) to account for the x-ray data on chromatin. It consists of a DNA double helix with "a coating of histone" coiled into a single larger helix of axial repeat distance 120 Å and diameter 100 Å. There are 340 Å of DNA double helix or 100 DNA base pairs per turn of the larger helix, which is a major drawback of the model in view of the following discussion of the true size of repeating unit in chromatin.

A Repeating Unit

The ratios of histone to DNA and x-ray data mentioned above do not indicate how the five types of histone are distributed in chromatin. The simplest case would be that the histones act together and form a unique structure that gives rise to the x-ray pattern; at the other extreme would be the case of different combinations of histones in different regions of chromatin, some one of which gives rise to the x-ray pattern. Evidence from the preceding article (*1*) helps to distinguish among these and the many possible intermediate cases. It was shown that histones F2A1 and F3 of calf thymus occur entirely as an $(F2A1)_2(F3)_2$ tetramer. It was further shown that a complex of tetramers, F2A2-F2B oligomers, and DNA gives the x-ray pattern of chromatin, and that tetramers and F2A2-F2B oligomers are both required, but F1 is not. The following conclusions may be drawn: F2A1 and F3 form a unique structure; F2A1, F3, F2A2, and F2B act together and form with DNA the repeating structure responsible for the x-ray pattern of chromatin; and F1 is either added on or located elsewhere in chromatin. In sum, four of the histones and DNA form a unique repeating structure.

Now suppose that the $(F2A1)_2(F3)_2$ tetramer defines a repeating unit of this structure and that all the DNA in chromatin is involved in the structure. Then, as chromatin contains roughly one each of F2A1, F3, F2A2, and F2B per 100 base pairs of DNA, the repeating unit may contain two of each of these histones and about 200 base pairs of DNA. This coincides in a rather striking way with the results of digestion of chromatin by certain nucleases, in which most of the DNA is cleaved to pieces of about 200 base pairs. The first such observation was made by Hewish and Burgoyne in work on digestion of chromatin in rat liver nuclei by an endogenous nuclease (*7*). In this digestion more than 80 percent of the DNA is cleaved to multiples of from one to six times 200 base pairs. The occurrence of multiples rather than just 200 base pair pieces is presumably due to some cleavage sites being blocked by nonhistone proteins. A more clear-cut result has come from an extension of the work of Hewish and Burgoyne, in which staphylococcal nuclease has been shown to cleave more than 90 percent of the DNA in rat liver nuclei to pieces of about 200 base pairs (*8*). Both the endogenous and staphylococcal nucleases produce a slight heterogeneity in size of the DNA pieces, the dispersion being about $\pm$ 10 percent.

The convergence of work on oligomers of histones and work on cleavage of DNA makes a strong case for a repeating unit containing two each of F2A1, F3, F2A2, and F2B, and about 200 base pairs of DNA. Both kinds of work bear on how much repeating structure there is in chromatin, one kind showing that most of the histone is involved (four of the five types of histone) and the other showing that most of the DNA is involved (more than 90 percent in rat liver). The generality of the results can of course be tested by repeating the work on chromatin from other sources. Short of that, it may be asked whether the relative amounts of the histones and relative amounts of total histone and DNA are independent of source. The relative amounts of the histones have been measured (*9–12*) by extraction from chromatin and fractionation by preparative methods or in polyacrylamide gels. The measurements should be regarded as only approximate, because of possible differential extractability, proteolysis, losses during fractionation, and overlaps of bands in the gels (especially the bands arising from F2A2 and F2B, and minor bands arising from histone modification). The results, expressed as molar ratios of F3, F2A2, and F2B to F2A1, are 0.9, 0.8, and 1.1 in calf thymus (*9*) and nearly the same in other calf tissues (*10*), 0.7, 0.7, and 1.0 in *Drosophila* (*11*), and 0.9, 0.5, and 2.6 in pea bud and other pea tissues (*12*). F2A1 and F3 may in fact be equimolar in all organisms, and F2A2 and F2B roughly equimolar with exceptions.

Despite the approximate nature of these measurements, it may be significant that F2A1 and F3 are more nearly equimolar than F2A2 and F2B. F2A1 and F3, which occur as an $(F2A1)_2(F3)_2$ tetramer in calf thymus, would be expected, on the basis of the conservation of their amino acid sequences during evolution (*13*), to occur as a tetramer in all organisms, and might therefore be expected to occur in equimolar amounts in all organisms. The oligomeric structure of F2A2 and F2B, on the other hand, has not been as well established as for F2A1 and F3, and the amino acid sequences of F2A2 and F2B appear to be less conserved than those of F2A1 and F3 (*1*). The numbers of F2A2 and F2B that I have taken to be in the repeating unit are based on the roughly equimolar amounts of all the histones in calf thymus. These numbers (two each of F2A2 and F2B) may not be exactly right (there may be two of F2A2 and three of F2B in the repeating unit in calf thymus), and they may vary from one organism to another. It is possible to envisage structural roles for F2A2 and F2B compatible with such variation (see below).

Measurements of relative amounts of total histone and DNA are more accurate than measurements of relative amounts of the various histones since amounts of total histone are less sensitive to differential extractability, and so forth. The results, expressed as weight ratios of total histone to DNA, are nearly 1.0 for chromatin from a wide range of sources, for example: 1.15, 0.95, 1.17, 1.08, and 1.10 for rat liver, rat kidney, chicken liver, chicken erythrocytes, and pea bud (*14*); 1.02, 1.04, and 0.86 at three stages in the development of sea urchin embryos (*15*); and 1.05 in the slime mold *Physarum polycephalum* (*16*). This invariance, together with the invariance of amino acid sequences of F2A1 and F3, is the strongest evidence for the generality of a repeating unit of two each of four of the histones and about 200 base pairs of DNA.

F1 is not involved in forming the repeating unit (see above), so it must either be added on to the unit or located in a different region of chromatin. The amount of F1 relative to the other histones suggests that F1 is in fact associated with the unit: the molar ratio of F1 to F2A1 is 0.54 in

calf thymus (*9*), 0.40 in *Drosophila* (*11*), and 0.52 in pea bud (*12*); thus there is one F1 for two each of the other histones, or one F1 for every repeating unit.

The repeating structure formed by DNA and all the histones except F1 gives rise to the x-ray pattern of chromatin (see above). It may be asked whether the quantities of histone and DNA in the repeating unit, inferred from biochemical evidence (see above), are compatible with the size of the repeating unit indicated by the x-ray pattern. The answer may be seen by taking the dimensions of the repeating unit from the x-ray pattern and electron microscopy, together with the proportion of chromatin in the repeating unit from additional x-ray data. The x-ray pattern, as mentioned above, shows bands corresponding to structure repeating along the length of the chromatin fiber at intervals of about 100 Å. Electron micrographs generally show fiber diameters of about 100 Å (*17*). This suggests a repeating unit about 100 Å long in the fiber direction and about 100 Å in diameter. The x-ray pattern disappears when the chromatin concentration is raised above about 45 percent by weight (*3*, *5*); this suggests that the fibers are packed as closely as the structure permits when the concentration is about 45 percent. A unit 100 Å long and 100 Å in diameter which is 45 percent by weight in chromatin upon close-packing contains 2.8×10^5 daltons of chromatin (*18*). This is equivalent to 2.3 each of F2A1, F3, F2A2, and F2B and 230 base pairs of DNA. Thus, the repeating unit inferred from biochemical evidence and the repeating unit that gives rise to the x-ray pattern may be the same (*19*).

Some indication of the unit of packaging of histones and DNA might be expected in studies of events requiring at least partial unpackaging, such as DNA replication. Kriegstein and Hogness (*20*) have suggested that the rate of movement of DNA replication forks in eukaryotes is limited by a process involving the histones. As discontinuous DNA synthesis in *Drosophila* proceeds in steps of about 200 bases (Kriegstein and Hogness show that the single-stranded gaps at replication forks and the fragments of newly synthesized DNA in *Drosophila* are about 200 and 150 bases), the rate-limiting process could well be unpackaging of units of two each of four of the histones and about 200 base pairs of DNA.

The full significance of the repeating unit of histones and DNA may lie in the relation of the units to base sequences in the DNA. It may be asked, for example, whether there is a specific phase relation between the units and base sequences in the DNA. In other words, do the 200 base pair pieces arising from endonuclease digestion of chromatin form a unique set with respect to base sequence or do they overlap in sequence (*21*)?

A Flexibly Jointed Chain of Repeating Units

My views on the arrangement of histones and DNA in the repeating unit are speculative and meant to be taken as a working hypothesis. The basic idea is that a chromatin fiber is a flexibly jointed chain of repeating units. The point is that a jointed structure may be as flexible as the underlying DNA, whereas a continuous structure, such as a helix, is not. The idea arises from the fact that a chromatin fiber is flexible enough to be extensively coiled or folded. Such coiling or folding must occur, for example, in the bands of polytene chromosomes of *Drosophila*, where the ratio of length of DNA to length of DNA-containing structure is an order of magnitude greater than in a chromatin fiber (*22*).

A possible arrangement of histones and DNA in the repeating unit, leading to a jointed structure, is as follows. The $(F2A1)_2(F3)_2$ tetramer forms the core of the repeating unit [this is suggested by the essentially globular nature of the tetramer (*1*), the conservation in amino acid sequence of F2A1 and F3, and the fact that these histones are the last to be removed from chromatin by mild methods of extraction (*23*)]. F2A2 and F2B determine the spacing of tetramers along the length of the chromatin fiber, perhaps as F2A2-F2B dimers, or as an F2A2-F2B polymer running alongside [suggested by x-ray experiments showing that tetramers and F2A2-F2B oligomers act together to form a structure repeating at regular intervals along the length of the fiber (see above)]. Much of the 200 base pairs of DNA in a repeating unit would follow some path on the tetramer, and the remainder of the DNA would connect tetramers along a path defined by F2A2 and F2B. In brief, I suggest that a chromatin fiber consists of tightly packed DNA and associated protein alternating with more extended DNA and associated protein, rather like beads on a string.

Some evidence for such a structure comes from the nuclease digestion work mentioned above. Endonucleases may produce 200 base pair pieces of DNA by cleaving the connecting strand between tetramers. And recent work (*24*) has shown that the 200 base pair piece and associated protein occurs as a discrete complex in solution.

Electron micrographs of chromatin are also compatible with a jointed structure. Chromatin fibers observed after critical point drying have a generally "knobby" appearance (*25*). Spray-mounted and shadow-cast specimens show "nodules" alternating with thin strands, although the nodules are often widely spaced and are absent from some preparations (*26*). Striking examples of micrographs showing alternate thick and thin regions were published (*27*) while this manuscript was in preparation. In these micrographs, which were obtained by formaldehyde fixation and positive or negative staining, the thick regions are quite closely spaced and have a beadlike appearance. These regions were suggested to contain all five histones, in contrast with the arrangement of histones and DNA suggested above (*28*). Of course electron micrographs alone say nothing of the locations of particular molecules. But it may be possible, for example by selective extraction of histones (*23*) and nuclease digestion, to relate some features of the micrographs to particular histones and to DNA.

Summary

Many lines of evidence on chromatin structure have been discussed. The essential facts are:

1) Chromatin contains roughly one of each type of histone per 100 base pairs of DNA, except for histone F1.

2) X-ray patterns reveal a structure repeating along the length of the chromatin fiber. F2A1, F3, F2A2, and F2B are required in this structure, but F1 is not.

3) Two each of F2A1 and F3 combine to form a tetramer.

4) Certain nucleases cleave almost all the DNA in chromatin to pieces of about 200 base pairs.

5) Chromatin fibers are often extensively coiled or folded.

These facts lead to two proposals:

1) Chromatin structure is based on

a repeating unit of two each of F2A1, F3, F2A2, and F2B and about 200 base pairs of DNA.

2) A chromatin fiber consists of many such units forming a flexibly jointed chain.

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Budget and the National Cancer Program

National Cancer Institute funding through grants and contracts for 1972 to 1974 is presented and discussed.

Frank J. Rauscher, Jr.

Since its creation in 1937, the National Cancer Institute (NCI) has been the primary agency through which the federal government has supported cancer research. The National Cancer Act of 1971 gave the NCI responsibility for conducting a much broader National Cancer Program with the goal of bringing cancer under control. The act specifically directs the director of the institute to "plan and develop an expanded, intensified, and coordinated cancer research program encompassing the programs of the National Cancer Institute, related programs of the research institutes, and other Federal and non-Federal programs." This mandate includes support for cancer research in industry and in countries outside the United States.

The purpose of this article is to present accurate information on funding from the NCI for fiscal years 1972, 1973, and 1974, and, in particular, to compare dollars allocated through the grant and contract mechanisms for these years. All figures for 1972 and 1973 are actual obligations, whereas those for 1974 are estimates. Because of the lateness of the present fiscal year and the concomitant firmness of spending plans these estimated 1974 figures, with the possible exception of those for training grants, will vary only slightly.

The National Cancer Act was signed into law by the President in December 1971. In fiscal year 1971, prior to this enactment, the total budget available to the NCI was $233 million. In 1972 this was increased by $145 million to $378 million. In 1973 the Congress authorized $492 million but the NCI was permitted to spend no more than $432 million in accordance with the Administration's overall spending plan. Recently, the President decided to spend

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