The DNA of the African green monkey contains three components that are distinguishable by the kinetics of reassociation. The rapidly reassociating component represents about 20% of the total DNA and is composed almost entirely of a sequence (AGMr(HindIII)-1) which is repeated 6.8 × 10^6 times. The majority of the AGMr(HindIII)-1 sequences are organized in long tandem repeats of a segment of 172 base pairs in length. However, a fraction of the AGMr(HindIII)-1 sequences is interspersed with another 37% of the genome. The structure of the chromatin containing the AGMr(HindIII)-1 sequence is indistinguishable from that containing total DNA. Furthermore, there is nothing inherent in the nucleotide sequence of AGMr(HindIII)-1 which specifies a unique location for nucleosomes.

The genomes of the African green monkey and a derived cell line, BSC-1, both contain a class of highly repeated DNA sequence: digestion of total DNA with the restriction enzyme, Endo R-HindIII, yields a series of discrete DNA fragments (1). The larger fragments appear to be integral multiples of the smallest fragment of 172 base pairs, designated AGMr(HindIII)-1 (2). In partial digests of total DNA with Endo R-HindIII, fragments up to 29 times the monomer length have been observed (3), suggesting that these sequences can occur in long tandem arrays. Upon complete digestion of total DNA with Endo R-HindIII, only monomers, dimers, and a trace amount of trimers are observed; approximately 8% of the DNA is released into both monomers and dimers, in a ratio of 7:1, respectively (2). The AGMr(HindIII)-1 sequences contained within the monomer band have been isolated and the complete nucleotide sequence specifying the most abundant nucleotide residue at each position has been reported (2). Sequence analysis revealed that the many repeats of this complex unit are not all identical but represent a set of closely related segments. The sequence is not internally repetitive although it does contain clusters of pyrimidines and purines.

Earlier studies identified a fraction of the African green monkey DNA, called Component a, as a buoyant density shoulder of the main band DNA (4). Subsequent studies have demonstrated that Component a is composed almost entirely of AGMr(HindIII)-1 sequences, since digestion of Component a DNA with Endo R-HindIII results in a nearly quantitative conversion of the DNA into AGMr(HindIII)-1 and -2 (3).

Cytological studies have localized AGMr(HindIII)-1 to heterochromatic regions of interphase cells (5). Both centromeric and noncentromeric regions of metaphase chromosomes contain sequences homologous to AGMr(HindIII)-1 (6). AGMr(HindIII)-1 sequences do not appear to be transcribed (7).

In the present study, the organization of the class of AGMr(HindIII)-1 sequences within the total DNA and chromatin have been examined. Studies of eukaryotic genome organization have used two major approaches: analysis of the genomic DNA sequence arrangement and analysis of the structure and arrangement of chromatin. The DNA of a wide variety of eukaryotes has been shown to consist of different classes of DNA sequence. The number and nature of these classes for a given species depends on the experimental technique used. The eukaryotic genome can be divided into several repetition frequency classes of DNA sequence, distinguished by reassociation kinetics, ranging from presumed single copy to highly repetitive sequences (8). Highly repeated, complex sequence classes of DNA can be interspersed in a regular fashion with lower repetition frequency classes of DNA (9). Alternatively, analysis of total DNA on buoyant density gradients often reveals one or more satellites of the main band DNA (4, 10). In many cases, these satellite DNA sequences consist of simple, short sequences organized in long tandem arrays (11, 12). Finally, restriction enzyme analysis of total genomic DNA can reveal regularities in the spacing of restriction enzyme sites (1, 13), indicating the presence of tandem arrays of highly repeated, complex sequences within the genome. Characterization of the relationship between these classes of DNA sequences as defined by the various techniques requires a defined DNA sequence.

At present, chromatin organization cannot be related to the underlying DNA sequence arrangement of the genome. The chromatin of eukaryotes is organized in a linear array of structural subunits, called nucleosomes (14-24). Studies from a number of laboratories have demonstrated that all DNA sequence classes can be packaged into nucleosomes (25-29). The present paper describes studies on the arrangement of a defined DNA segment (AGMr(HindIII)-1) in both the total DNA and chromatin of the BSC-1 genome.

EXPERIMENTAL PROCEDURES

Cell Culture—BSC-1 cells were maintained in Eagle's medium supplemented with 10% fetal calf serum (Flow Labs), 0.15% glutamine, 250 units/ml of penicillin, and 250 µg/ml of streptomycin in 150-mm Petri dishes in a humidified 5% CO₂ incubator at 37°C. Twenty-four hours prior to harvesting of cells, 0.5 µCi/ml of [³H]thymidine (NET-0272; 40-60 Ci/mmol) in 15 ml of fresh medium were added to the cell monolayer. Cells were harvested by removing medium, washing the cell monolayer once with Dulbecco's phosphate-buffered saline (without Mg²⁺ or Ca²⁺), and detaching the cells in the same medium but supplemented with 10 mM EDTA at room temperature for 10 to...
15 min. SV40 DNA was prepared from purified strain 776 virions by Dr. L. Rosenthal, Georgetown University.

**Enzymatic Digestion—** BSC-1 DNA was digested with 2 units of Endo R-HindIII (New England Biolabs)/μg of DNA for 12 h at 37°C in 1 mM Tris, pH 7.5, 7 mM MgCl₂, and 6 mM magnesium.

Treatment of nuclei with staphylococcal nuclease (Worthington) was according to the procedure of Sollner-Webb and Felsenfeld (19). Nuclei were suspended in 1 mM Tris, pH 8.0, 0.1 mM CaCl₂, 0.3 mM sucrose, and treated with staphylococcal nuclease at a concentration of 160 units/mg of DNA at 37°C. Kinetic data of digestion were monitored in each experiment by determining the percentage of the DNA digested as a function of time. The rate of digestion was adjusted to result in 20% acid solubilization of DNA; the extents for individual experiments are indicated in the legends to the figures. The reaction was terminated by the addition of a 10-fold excess of EDTA and chilling of the sample.

Preparation of Nucleosomal DNA—Trimmed nucleosomal core particles were prepared from BSC-1 nuclei according to the procedure of Whitlock and Simpson (30). Analysis of purified core DNA in denaturing gels revealed no internal single strand scission (data not shown).

Core particle, monomer, dimer, and trimer nucleosomes were prepared according to the method of Varshavsky et al. (22). Nucleosomal core particles were separated on low ionic strength gels; nucleosomal DNA was purified from these particles by cutting out gel fragments containing the bands of interest, grinding the gel fragments in a buffer containing 2% sodium dodecyl sulfate, 1% mercaptoethanol, 10% glycerol, 90 mM Tris, pH 8.0, with a Dounce homogenizer, and stirring the suspension overnight at room temperature to allow passive diffusion of the DNA. Gel particles were removed by low speed centrifugation. The DNA was further purified as indicated above for total DNA. Analysis of the purified DNA fragments in denaturing 7% urea gels revealed no internal single-stranded breaks (data not shown).

Radioactive Labeling of DNA Fragments—DNA fragments were labeled by nick translation with deoxyribonucleoside [³²P]diphosphates (34). Each reaction contained two radiolabeled precursors (New England Nuclear Corp., specific activity 250 Ci/mmole) and was incubated at 37°C for 2 h. Following re-extraction and precipitation as above, DNA was resolved in 1.5 mM NaCl, 0.15 mM sodium citrate, 1 mM EDTA, and dialyzed against the same buffer.

**Absorption of Total DNA, AGMr(HindIII)-1, and AGMr(HindIII)-1-depleted DNA—** Total DNA from BSC-1 cells was prepared by the method of Eden et al. (30). Briefly, BSC-1 cells were suspended in 100 mM NaCl, 50 mM EDTA, 50 mM Tris, pH 8.0. Sodium dodecyl sulfate was added to a final concentration of 0.3%.

**Purification of Total DNA, AGMr(HindIII)-1, and AGMr(HindIII)-1-depleted DNA—** Total DNA from BSC-1 cells was prepared by the method of Eden et al. (30). Briefly, BSC-1 cells were suspended in 100 mM NaCl, 50 mM EDTA, 50 mM Tris, pH 8.0. Sodium dodecyl sulfate was added to a final concentration of 0.3%. Cells were lysed at room temperature for 20 min, following which the lysate was treated with 200 μg/ml of proteinase K (EM Biochemicals) for 2 h at 37°C. DNA was extracted once with buffer-saturated phenol, containing 0.1% 8-hydroxyquinoline, once with equal volumes of phenol and isoamyl alcohol/chloroform (1:24), and wound out of solution following precipitation with 0.3 M sodium acetate, pH 6.0, and 2.5 volumes of ethanol. DNA was dissolved in 10 mM NaCl, 20 mM EDTA, 50 mM Tris, pH 8.0, dialyzed against the same buffer, and treated with 50 μg/ml of RNase A for 1 h at 37°C, followed by 100 μg/ml of proteinase K for 2 h at 37°C. Following re-extraction and precipitation as above, DNA was recovered in 1.5 mM NaCl, 0.15 mM sodium citrate, 1 mM EDTA, and dialyzed against the same buffer.

**Nuclear Isolation—** BSC-1 nuclei were isolated according to the procedure of Sollner-Webb and Felsenfeld (19). Nuclei were collected by centrifugation for 10 min at 2000 rpm. Nuclei were resuspended in 10 ml/plate of Buffer H + 0.1% Triton by agitation on a Vortex mixer at low speed for 15 to 30 s. The nuclei were then pelleted, resuspended in 5 ml/plate Buffer H + 0.1% Triton, and subjected to 1.6 M sucrose by the addition of 0.3 ml/plate of 0.5 M sucrose in Buffer H. A maximum of 20 ml of nuclear suspension was layered onto 15 ml of 2.0 M sucrose in Buffer H in SW 27 tubes. Nuclei were pelleted through the 2.0 M sucrose cushion by centrifugation for 1 h at 20,000 rpm. Sucrose solutions were removed from the nuclear pellet by aspiration. The nuclear pellet was suspended in 0.25 M sucrose, 1 mM Tris, pH 7.8, and washed once by centrifugation for 15 min at 4000 rpm. Nuclei were suspended to a DNA concentration of approximately 1 mg/ml, as estimated from the A₅₀₀ of an aliquot of nuclei lysed in 2 ml NaCl, 5 mM urea. Nuclei prepared by this technique support the linear incorporation of [³²P]UTP into trichloroacetic acid-precipitable material for at least 1 h. These assays were kindly performed by Doctors J. Christiansen and K. Mullinix, National Institutes of Health.

**Arrangement of Repeated DNA in Monkey Genome and Chromatin**

It should be noted that DNA fragments of length greater than 50 150,000 base pairs were not analyzed in this study.

**K. Mullinix, manuscript in preparation.**

**D. S. Singer, unpublished observations.**
Arrangement of Repeated DNA in Monkey Genome and Chromatin

stranded DNA was eluted from the columns at 98°C. Radioactivity in the hydroxyapatite column fractions was measured in 0.08 M phosphate buffer in Aquasol in a refrigerated Beckman LS scintillation spectrometer. Reactions rates were determined from computerized analysis of the data (36).

**Kinetic Components**

Fractionation of AGMr(HindIII)-1 was accomplished by electrophoresis on 3-mm preparative 5% polyacrylamide slab gels (acylamide:bis, 30:1.5) in 0.04 M Tris, pH 7.8, 0.02 M sodium acetate, and 0.002 M NaEDTA. Electrophoresis of gels was for 1 h at 100 V prior to the application of sample, and separation of fragments for 5 to 6 h at 175 V. DNA bands were visualized by staining with 0.04% methylene blue in 0.01 M Tris, pH 8.0.

Separation of nucleosomal particles was according to the method of Varshavsky et al. (22).

Analytical slab gel electrophoresis of DNA fragments was in 5% polyacrylamide gels in Tris/borate buffer (37). Electrophoresis was for 4 to 5 h at 120 V. Gels were stained in 0.5 mg/ml of ethidium bromide for 1 h and visualized with short-wave UV light.

Denaturing gels for determining DNA single-stranded lengths were in 7 M urea run in Tris/borate buffer (38).

**Filter Hybridization**—Following electrophoresis and staining of analytical polyacrylamide gels, DNA bands were transferred to nitrocellulose filters by the following modification of the technique of Southern (39): elution of DNA fragments was in 3 M NaCl, 0.3 M sodium citrate for 48 h. Nitrocellulose filters of both 0.45 µm (S & S RAP) and 0.2 µm (S & S RAR) were used. It was noted that Schleicher and Schuell nitrocellulose filters efficiently retained small fragments of DNA (as small as about 30 base pairs) and the 0.25-µm filters were more efficient than 0.45-µm filters for this purpose.

Hybridization of 32P-labeled DNA to filters was according to the method of Botchan et al. (40), except that 100 µg/ml of Escherichia coli tRNA was added to the hybridization solution. Between 3 to 5 × 10^10 cpm of probe were used in each reaction. Following hybridization and drying, filters were exposed to x-ray film (Kodak, X-omat) in the presence of intensifying screens at -70°C for 5 to 7 days.

**Analytic Sucrose Gradients**—Separation of DNA fragments of discrete lengths for use in interspersion analysis was on isokinetic alkaline sucrose gradients (15 to 94.5% sucrose) (41) using sea urchin DNA fragments of known length as internal markers (kindly provided by Dr. F. Eden, NIH). Centrifugation was in an SW 40 rotor at 39,000 rpm at 20°C for 15 to 20 h. Following centrifugation, gradients were fractionated in 0.4-ml aliquots which were neutralized with NaH2PO4 and dialyzed against 1.5 mM NaCl, 0.15 mM sodium citrate, 1 mM EDTA. DNA fragments used in the interspersion analysis were analyzed on alkaline sucrose gradients to determine exact lengths of single strands.

**Interspersion Analysis of AGMr(HindIII)-1 DNA**—Interspersion analysis was performed according to the method described by Britten and Davidson (4). In vivo labeled BSC-1 DNA fragments (1.2 × 10^3 µg/ml/3000 cpm) of varying lengths were hybridized to an excess (2.5 µg/ml) of short, unlabeled driver DNA to a Cot 8 × 10^-3 in 0.12 M phosphate buffer at 60°C. Sheared driver DNA had an average length of 250 to 400 base pairs, as determined by gel electrophoresis. Samples were analyzed on hydroxyapatite columns; to reduce the possibility of shearing of long DNA fragments, no air pressure was applied to the columns.

**RESULTS**

**DNA Sequence Arrangement**

Kinetic Components of the BSC-1 Genome—The kinetic data of reassociation of total genomic DNA from BSC-1 cells reveal three major kinetic components. The most slowly reassociating component represents about 60% of the total DNA and is presumed to contain DNA sequences present in a single copy in the genome. The moderately rapid and rapidly reassociating fractions, which contain families of repeated DNA sequences, represent about 14.9% and 20.8%, respectively. The kinetic parameters of the three components are summarized in Table I.

Concentration of AGMr(HindIII)-1 DNA in the Total Genome—The concentration of AGMr(HindIII)-1 DNA in the total genome was determined by analysis of the kinetics of reassociation of 32P-labeled AGMr(HindIII)-1 tracer with an excess of randomly sheared, total BSC-1 DNA (Fig. 1). AGMr(HindIII)-1 is calculated to be 19.3% of the total DNA from the relative rates of reassociation of the tracer with pure AGMr(HindIII)-1 and with total DNA (Table II). Reassociation of the 32P-labeled AGMr(HindIII)-1 tracer with total DNA occurs over the same range of Cot as does reassociation of the major rapidly reassociating component of the total DNA (Table I). Therefore, AGMr(HindIII)-1 DNA clearly derives from this component. Furthermore, the rapidly reassociating component of the total DNA is composed almost entirely of AGMr(HindIII)-1 sequences, since 20.8% of the total DNA is in this component (Table I) and AGMr(HindIII)-1 DNA represents 19.3% of the total DNA. The kinetic parameters of the reassociation studies with the 32P-labeled AGMr(HindIII)-1 DNA tracer are summarized in Table II.

**Genome Size**—From these data, an estimate of the total genome size of BSC-1 cells can be made by two independent methods. Comparing the rate of reassociation of slowly reassociating DNA sequences (presumed to be single copy) of the BSC-1 genome with that of a known standard, in this case sea urchin DNA (K = 1.25 × 10^-3; 8.3 × 10^9 base pairs per haploid genome (42)), the size of the BSC-1 genome is estimated to be 6.1 × 10^9 base pairs per haploid genome (Table III).

| Component | Fraction of genome | DNA content | Relative rate of reassociation
|------------|--------------------|-------------|----------------------|
| Rapid      | 0.208              | 7.4 × 10^-3 | 1.4 × 10^2           |
| Moderate   | 0.149              | 1.9 × 10^0  | 5.3 × 10^-1          |
| Slow       | 0.560              | 7.9 × 10^1  | 1.3 × 10^-3          |

a K is the rate constant of the reassociation reaction for a given component.

b The rates of reassociation of each of the kinetic components are compared to the slow component.

**FIG. 1.** Kinetics of hybridization of 32P-labeled AGMr (HindIII)-1 DNA in the presence of an excess of various DNA fractions. AGMr (HindIII)-1 (C), total DNA (D), AGMr (HindIII)-1-depleted DNA (E), and core particle DNA (F) fragments were all prepared as described under "Experimental Procedures." A 2,500 to 10,000-fold excess of each DNA preparation (driver) was reassociated separately with 32P-labeled AGMr (HindIII)-1 DNA tracer. The specific radioactivity of the 32P-labeled AGMr (HindIII)-1 DNA tracer was 1.8 × 10^12 cpm/µg. Kinetic parameters are summarized in Tables II and IV. All DNA driver samples were labeled with tritium and their self-reassociation was measured in parallel; these data are summarized in Table IV.
TABLE II
Reassociation of 32P-labeled AGMr(HindIII)-1 DNA with Total BSC-1 DNA and AGMr(HindIII)-1

| DNA                  | C0.5 [M] | K [M\(^{-1}\)s\(^{-1}\)] | Relative rate of reassociation \(^a\) |
|----------------------|---------|--------------------------|-------------------------------------|
| AGMr(HindIII)-1      | 5.1 x 10\(^{-4}\) | 1980                    | 1.0                                 |
| Total BSC-1          | 2.0 x 10\(^{-6}\) | 0.32                    | 0.193                               |

\(^a\) K is the rate constant of the reassociation reaction.

\(^b\) The reassociation of the 32P-labeled AGMr(HindIII)-1 DNA was compared relative to its reassociation with AGMr(HindIII)-1 DNA. This is a measure of the concentration of AGMr(HindIII)-1 sequences in the total BSC-1 DNA.

**Reiteration Frequency of AGMr(HindIII)-1**—It is also possible to calculate the reiteration frequency of the AGMr(HindIII)-1 sequence in the genome by independent methods. The various calculations are summarized in Table III.

The rate of reassociation of a highly repeated DNA component relative to that of single copy DNA has been widely used as a measure of reiteration frequency. In this case, the relative rates indicate a reiteration frequency of 1.07 x 10\(^{-6}\) copies/haploid genome for sequences homologous to AGMr(HindIII)-1. This value is in reasonable agreement with earlier estimates (44). However, it is also possible to calculate the reiteration frequency directly from the known fragment length of AGMr(HindIII)-1 (172 base pairs), the fraction of the genome which it represents (0.193) and the estimated genome size (6.1 x 10\(^9\) base pairs/haploid genome). In this case, the reiteration frequency is estimated to be 6.8 x 10\(^{-9}\). This is a frequency seven times greater than that determined by kinetic parameters alone. Even if the lower genome size estimate is used in the calculation, a reiteration frequency of 3.7 x 10\(^{-9}\) is obtained. Possible sources of the discrepancies in the two methods of analysis will be discussed later.

**Interspersion of AGMr(HindIII)-1 with Unrelated Sequences in the Genome**—The organization of sequences homologous to AGMr(HindIII)-1 within the total genome was investigated by the interspersion analysis as first described by Davidson (9). Previous studies have demonstrated that at least a part of the family of AGMr(HindIII)-1 sequences is arranged in long tandem repeats (2, 3). The results shown in Fig. 2 clearly demonstrate that in addition a fraction of the AGMr(HindIII)-1 sequences are interspersed with other unrelated sequences in the BSC-1 genome. With increasing tracer lengths of up to 2200 nucleotides, an increasing proportion of the labeled tracer is retained on hydroxyapatite following hybridization at a Cot of 3 x 10\(^{-2}\). This indicates that sequences homologous to AGMr(HindIII)-1 are spaced at 2200 nucleotide intervals. The curve intersects the ordinate at a value of 15%, indicating that about 15% of the total genome is homologous to AGMr(HindIII)-1. This value is in reasonable agreement with the results obtained by reassociation kinetics. Above a tracer length of 2200 nucleotides, the proportion of the tracer which is hybridized remains constant at 52%; it is calculated that AGMr(HindIII)-1 sequences are interspersed with another 37% (52 - 15%) of the total BSC-1 genome. Furthermore, these data indicate that there is no other detectable interspersion of sequences homologous to AGMr-

**TABLE III**
Estimates of BSC-1 genome size and reiteration frequency of sequences homologous to AGMr(HindIII)-1

| Method          | Genome size (except AGMr(HindIII)-1) | Reiteration frequency of AGMr(HindIII)-1 |
|-----------------|--------------------------------------|----------------------------------------|
| I               | 6.1 x 10\(^9\) base pairs/haploid genome | 1.0 x 10\(^{-6}\) copies/haploid genome |
| II              | 3.3 x 10\(^9\) base pairs/haploid genome | 1.1 x 10\(^{-6}\) copies/haploid genome |
| III             | 1.1 x 10\(^9\) base pairs/haploid genome | 1.1 x 10\(^{-6}\) copies/haploid genome |
| IV              | 3.7 x 10\(^9\) base pairs/haploid genome | 1.1 x 10\(^{-6}\) copies/haploid genome |
| V               | 6.8 x 10\(^9\) base pairs/haploid genome | 1.1 x 10\(^{-6}\) copies/haploid genome |

**Method I**
The genome size of BSC-1 DNA was calculated from the relative rates of reassociation of the slow kinetic component (Table I) and the rate of reassociation of a sea urchin DNA standard determined under identical conditions. The rate constant determined for sea urchin single copy DNA (8.3 x 10\(^{-9}\) base pairs/haploid genome (42)) is 1.25 x 10\(^{-11}\) M\(^{-1}\) s\(^{-1}\) for DNA fragments of 450 nucleotides. This rate constant was corrected to the rate predicted for fragments 250 nucleotides according to the relationship K corrected = K predicted/2 (43). The corrected rate is 3.9 x 10\(^{-11}\) M\(^{-1}\) s\(^{-1}\). The BSC-1 genome size is then calculated to be:

\[(8.3 \times 10^9 \text{ base pairs/haploid genome}) \times \left(3.9 \times 10^{-11} \text{ M}^{-1} \text{s}^{-1}\right) = 6.1 \times 10^9 \text{ base pairs/haploid genome}\]

**Method II**
The genome size of BSC-1 DNA was calculated as in Method I, except that the reassociation rate constant of purified AGMr(HindIII)-1 was used as the standard. The length of the AGMr(HindIII)-1 DNA fragment is 172 base pairs, the rate constant was corrected to the rate predicted for fragments 250 nucleotides. The corrected rate is 2387 M\(^{-1}\) s\(^{-1}\). The BSC-1 genome size is then calculated to be:

\[(172 \text{ base pairs}) \times (2387 \text{ M}^{-1} \text{s}^{-1}) = 3.3 \times 10^9 \text{ base pairs/haploid genome}\]

**Method III**
The reiteration frequency of sequences homologous to AGMr(HindIII)-1 was calculated from the relative rate of reassociation of the slow and rapid components of the total BSC-1 DNA:

\[K_{\text{rapid}} = \frac{1.4 \times 10^9 \text{ M}^{-1} \text{s}^{-1}}{1.3 \times 10^{-4} \text{ M}^{-1} \text{s}^{-1}} = 1.1 \times 10^9\]

**Method IV**
The reiteration frequency of sequences homologous to AGMr(HindIII)-1 was calculated from the known fragment length of AGMr(HindIII)-1 of 172 base pairs, its representation within the genome of 0.193 (Table III) and an estimated genome size of 3.3 x 10\(^9\) base pairs (Method II). The latter two figures were both obtained by using the rate of reassociation of purified AGMr(HindIII)-1 as a kinetic standard. The calculation is then:

\[(3.3 \times 10^9 \text{ base pairs/haploid genome}) \times (0.193) = 3.7 \times 10^9\]

**Method V**
The reiteration frequency of sequences homologous to AGMr(HindIII)-1 was calculated as in Method IV, only using the genome size of 6.1 x 10\(^9\) base pairs/haploid genome derived from a sea urchin standard (Method I).
(HindIII)-1 at intervals greater than 2200 nucleotides.

The data do not exclude the possibility that each 2200-base
pair interval contains several AGMr(HindIII)-1 sequences in
tandem, or alternatively, less than a complete copy of
AGMr(HindIII)-1. However, if it is assumed that only a single
complete copy of AGMr(HindIII)-1 occurs within every 2200-
base pair interval, then the number of AGMr(HindIII)-1
sequences interspersed with unrelated sequences can be cal-
culated as follows. Each 2200-base pair interval will contain
172 base pairs of AGMr(HindIII)-1 and 2028 base pairs of
unrelated sequences. Altogether, these interspersed unrelated
sequences comprise 37% of the total BSC-1 genome. Using the
estimated genome size of $6.1 \times 10^9$ base pairs/haploid genome
(Table III, Method I), there are $(6.1 \times 10^9) \times (0.37)/2028 =
1.1 \times 10^6$, or 16.2% of the total number of
sequences homologous to AGMr(HindIII)-1 (Table III,
Method V).

The presence of AGMr(HindIII)-1 sequences in nucleoso-
al core particle, monomer, and dimer was demon-
strated by hybridization of $^{32}$P-labeled AGMr(HindIII)-1 to
d these DNA fragments. Purified nucleosomal DNA fragments
corresponding to core particle, monomer, and dimer were
separated by electrophoresis in a polyacrylamide gel, trans-
ferr ed to a nitrocellulose filter, and hybridized with $^{32}$P-labeled
AGMr(HindIII)-1 DNA. The results (Fig. 3, right panel)
indicate that AGMr(HindIII)-1 sequences occur in all three
nucleosomal classes. Furthermore, the size distribution of
DNA fragments containing AGMr(HindIII)-1 sequences in
each nucleosomal DNA class is indistinguishable from that of
the total nucleosomal DNA. Therefore, the highly repeated
DNA fraction of the BSC-1 genome is packaged into nucleo-
somes with the same average repeat length as the total DNA.

**Extent of Packaging of AGMr(HindIII)-1 into Nucleo-
somes**—It is not known whether all DNA sequence classes are
packaged in chromatin such that they are equally susceptible
to staphylococcal nucleosome digestion. To examine this question
for the AGMr(HindIII)-1 DNA sequence class, the concentra-
tions of AGMr(HindIII)-1 sequences in both total DNA and

![Fig. 2. Interspersion analysis of sequences homologous to AGMr
(HindIII)-1. $^3$H-Labeled DNA was purified from BSC-1 cells. Frag-
ments of different lengths were obtained as described in the text. The
lengths of the fragments were measured on analytical alkaline sucrose
gradients with internal markers. $[^3]$H DNA fragments ($1.2 \times 10^{-2}$ mg/
ml, 1000 cpm) were reannealed in the presence of 2.6 mg/ml of unla-
bele d, sheared total BSC-1 DNA (average length 250 to 400 base
pairs). Hybridization reactions were in 0.12 M phosphate buffer at
60°C to a $C_1 = 3 \times 10^{-7}$.

![Fig. 3. Nucleosomal repeat lengths of total and AGMr (HindIII)-1
chromatin. Left panel, ethidium bromide-stained gel of nucleosomal
DNA fragments. Purified nuclei were treated with staphylococcal
nuclease until 20% of the DNA was acid-soluble. Nucleosomal DNA
fragments were purified from the corresponding particles after iso-
lation according to the method of Varshavsky et al. (22). Length
markers were Endo R-HindIII-generated fragments of SV40 DNA
((A) and total BSC-1 DNA (F). (B) trimer DNA, (C) dimer DNA, (D)
monomer DNA, (E) core particle DNA. Right panel, Autoradiogram
of hybridization of nucleosomal DNA fragments on nitrocellulose
filters with $^{32}$P-labeled AGMr (HindIII)-1. Following gel electropho-
resis of nucleosomal DNA fragments, the DNA bands were trans-
ferr ed to a nitrocellulose filter and hybridized as detailed in the text.
Length markers were Endo R-HindIII generated fragments of total
BSC-1 DNA (D). (A) dimer DNA, (B) monomer DNA, (C) core
particle DNA.**

**Arrangement of AGMr(HindIII)-1 DNA Sequences in BSC-
1 Chromatin**

The organization of the family of AGMr(HindIII)-1 se-
quencies in chromatin has been investigated and compared
with the organization of total chromatin. Digestion of BSC-1
nuclei with staphylococcal nuclease releases deoxyribonucle-
oprotein complexes corresponding to nucleosomal core parti-
cles, monomers, and multimers. The length for BSC-1
nucleosomes was determined by comparing the electropho-
retic mobilities of DNA fragments purified from nucleosomal
core particles, monomers, dimers, and trimers, respectively,
with the electrophoretic mobilities of standards of known
length in polyacrylamide gels (Fig. 3, left panel). The length
of core particle DNA was estimated to be 145 base pairs, and
the monomer, dimer, and trimer nucleosomal DNA lengths
were 185, 370, and 560 base pairs, respectively. Analysis of the
length of the DNA fragments using denaturing gels gave the
same estimated sizes (data not shown). Therefore, the ap-
proximate nucleosomal repeat length for bulk chromatin in
BSC-1 DNA is 185 base pairs, consistent with lengths reported
by others (24, 45).

The presence of AGMr(HindIII)-1 sequences in nucleoso-
al core particle, monomer, and dimer DNA was demon-
strated by hybridization of $^{32}$P-labeled AGMr(HindIII)-1 to
d these DNA fragments. Purified nucleosomal DNA fragments
corresponding to core particle, monomer, and dimer were
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indicate that AGMr(HindIII)-1 sequences occur in all three
nucleosomal classes. Furthermore, the size distribution of
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each nucleosomal DNA class is indistinguishable from that of
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for the AGMr(HindIII)-1 DNA sequence class, the concentra-
tions of AGMr(HindIII)-1 sequences in both total DNA and
core particle DNA were determined by measuring the kinetics of reassociation of $^{32}$P-labeled AGMr(HindIII)-1 in the presence of these DNA fractions. The reassociation kinetics of $^{32}$P-labeled AGMr(HindIII)-1 with pure AGMr(HindIII)-1 DNA was used as a standard to determine the concentration of AGMr(HindIII)-1 sequences in each DNA fraction. The reassociation of pure AGMr(HindIII)-1 with the tracer proceeded with a rate of 1980 m$^{-1}$ s$^{-1}$; BSC-1 DNA which had been depleted of AGMr(HindIII)-1 sequences (see "Experimental Procedures") showed no detectable hybridization to the $^{32}$P-labeled tracer over the range of Cot tested (Fig. 1, Table IV). Total DNA and nucleosomal core particle DNA reannealed with the AGMr(HindIII)-1 tracer at rate of 382 and 458 m$^{-1}$ s$^{-1}$, respectively (Fig. 1). These results demonstrate that the representation of AGMr(HindIII)-1 sequences in the nucleosomal core particle DNA fraction is indistinguishable from its representation in the total genomic DNA.

In a variety of tissues, nucleosomes containing actively transcribed DNA sequences appear to be differentially sensitive to the action of DNase I (32, 46). To test the possibility that nucleosomes containing different DNA sequence classes are differentially sensitive to DNase I, the concentration of AGMr(HindIII)-1 sequences in DNA that resisted digestion of BSC-1 nuclei with DNase I was determined. BSC-1 nuclei were treated with DNase I under conditions which solubilized 20% of the total DNA (in control experiments, it was shown that the rates of digestion of AGMr(HindIII)-1 and total DNA by DNase I are equal; data not shown). The resistant DNA was then purified and the concentration of AGMr(HindIII)-1 sequences determined by the kinetics of reassociation with a $^{32}$P-labeled AGMr(HindIII)-1 DNA. In two separate experiments, the rate of reassociation of the tracer in the presence of the DNase I-resistant DNA was indistinguishable from its rate of reassociation with total DNA (Fig. 4, Table IV). Therefore, nucleosomes containing the highly reiterated DNA class of the BSC-1 genome are not differentially sensitive to the action of DNase I.

**Spatial Relationship between Nucleosomes and Protected DNA Sequences**—The results presented thus far indicate that the organization of the highly reiterated DNA fraction of AGMr(HindIII)-1 sequences in nucleosomes is grossly indistinguishable from that of the total DNA. Therefore, this sequence can be used to investigate a more general question, namely, does a given DNA sequence uniquely define the position which a nucleosome occupies on that sequence? Two extreme possibilities can be considered: 1) the arrangement of nucleosomes is nonrandom such that a particular region of the AGMr(HindIII)-1 sequence tends to be associated with the same regions of the nucleosomal core, or 2) the arrangement of nucleosomes on the family of AGMr(HindIII)-1 sequences is completely random with respect to sequence. These alternatives can be distinguished experimentally as follows. Staphylococcal nuclease digestion of BSC-1 nuclei will solubilize the internucleosomal DNA linker, leaving core particle DNA intact. If the same region of the AGMr(HindIII)-1 sequence is always associated with the core particle, the resulting core particle DNA fragments of AGMr(HindIII)-1 will be in register with respect to the AGMr(HindIII)-1 sequence. Thus, reannealed core particle DNA will only form AGMr(HindIII)-1 duplexes 145 base pairs in length. On the other hand, if the arrangement of nucleosomes is random with respect to sequence, nucleosome digestion will release a series of fragments of AGMr(HindIII)-1 which are circularly permuted with respect to the AGMr(HindIII)-1 sequence. In this case, reassociated core particle DNA duplexes will be concatamers of the AGMr(HindIII)-1 sequences.

Thus, the fragment lengths of core particle DNA prepared

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**TABLE IV**

Reassociation rates of $^{32}$P-labeled AGMr(HindIII)-1 in the presence of various fractions of chromosomal DNA

| Driver DNA | $^{32}$P-AGMr(HindIII)-1 tracer | $^{32}$P-BSC-1 DNA driver |
|------------|---------------------------------|--------------------------|
| **Experiment I** | $C_{d/2}$ | $K$ | RMS$^a$ | $C_{d/2}$ | $K$ | RMS$^a$ |
| AGMr(HindIII)-1 | $5.1 \times 10^{-4}$ | 1980 | 0.019 | $6.0 \times 10^{-4}$ | 1680 | 0.012 |
| Core particle | $2.2 \times 10^{-3}$ | 458 | 0.35 | $7.2 \times 10^{-3}$ | 138 | 0.015 |
| DNase I-resistant | $2.0 \times 10^{-3}$ | 512 | 0.063 | $8.0 \times 10^{-3}$ | 123 | 0.014 |
| **Experiment II** | | | | $1.0 \times 10^{-2}$ | 19 | 0.19 |
| Total | $6.3 \times 10^{-3}$ | 159 | 0.046 | | | |
| DNase I-resistant | $9.9 \times 10^{-4}$ | 101 | 0.046 | | | |

$^a$ Root mean square deviation of the curves from the data points. The indicated values were derived from computerized analysis of the data (36).
Arrangement of Repeated DNA in Monkey Genome and Chromatin

FIG. 5. Mobility in polyacrylamide gels of AGMr(HindIII)-1 DNA sequences following reannealing of core particle DNA. DNA was purified from core particles prepared according to the method of Varshavsky et al. (22). Five micrograms of core particle DNA were denatured by boiling in the same buffer used for Endo R-HindIII digestion supplemented with 100 mM NaCl and reannealed by slowly cooling the sample. Following electrophoresis of the samples on a 5% polyacrylamide gel, DNA was transferred to a nitrocellulose filter and hybridized with 3 x 10^6 cpm of 32P-labeled AGMr (HindIII)-1 DNA, as detailed under “Experimental Procedures.” Experiment I. A, B, reannealed core particle DNA (2.5 μg); C, native core particle DNA (2.5 μg); D, Total BSC-1 DNA (3 μg) digested with 35 units of Endo R-HindIII. Experiment II. A, total BSC-1 DNA (3 μg) digested with 35 units of Endo R-HindIII; B, Native core particle DNA (2.5 μg); C, reannealed core particle DNA (2.5 μg); D, reannealed core particle DNA (2.5 μg) digested with 31 units of Endo R-HindIII; E, AGMr (HindIII)-1 DNA (2.5 μg); F, reannealed AGMr (HindIII)-1 DNA (2.5 μg); G, reannealed AGMr (HindIII)-1 DNA (2.5 μg) digested with 31 units of Endo R-HindIII; H, reannealed, BSC-1 DNA 200 to 400 base pairs (2.5 μg); I, reannealed BSC-1 DNA, 200 to 400 base pairs (2.5 μg) digested with 31 units of Endo R-HindIII. Arrows indicate regions of each gel in which concatamers of AGMr (HindIII) were observed in Experiment I A, B, and Experiment II C, D.

AGMr(HindIII)-1 does not result in concatamer formation (Fig. 5b). This result was expected from the known nucleotide sequence of AGMr(HindIII)-1 (2).

The observation that direct digestion of mononucleosomal DNA (185 base pairs) with Endo R-HindIII generates a smear of DNA fragments smaller than 185 base pairs which contain AGMr(HindIII)-1 sequences but no discrete band (data not shown) is consistent with the conclusion that the arrangement of nucleosomes on AGMr(HindIII)-1 DNA is random with respect to sequence.

It is impossible to exclude the possibility that randomization of nucleosomes on the AGMr(HindIII)-1 sequence occurred during the isolation procedures. However, attempts were made to minimize this possibility. All isolation procedures were carried out in low ionic strength buffers, and similar results were obtained when core particle DNA was prepared by two different methods.

DISCUSSION

The Arrangement of AGMr(HindIII)-1 in the BSC-1 Genome

The arrangement of a highly repeated DNA sequence, AGMr(HindIII)-1, in the BSC-1 genome was studied by two approaches. The analyses both of the reassociation kinetics of the total DNA and of the products of restriction enzyme digestion provide a description of the organization of a well defined family of sequences within the genome, and also reveal the limitations of each approach.

Sequences Homologous to AGMr(HindIII)-1 Are Interspersed in the Genome—Analysis of the total BSC-1 DNA by reassociation kinetics reveals the presence of three distinct kinetic components: a rapidly reassociating fraction, a mod-
erately rapidly reassociating fraction, and a slowly reassociating fraction. The rapidly reassociating fraction constitutes 91.8% of the total genomic DNA and is composed almost entirely of AGMr(HindIII)-1 sequences. The DNA sequences homologous to AGMr(HindIII)-1 are organized in two distinct fashions within the genome. Earlier studies have demonstrated that AGMr(HindIII)-1 sequences occur in long tandem arrays of up to 250 times the monomer length (2, 3, 45). From the present studies, it is clear that some of sequences homologous to AGMr(HindIII)-1 are also interspersed with unrelated sequences. Assuming a single, complete copy of AGMr(HindIII)-1 in each interval, roughly 16% of the class of AGMr(HindIII)-1 sequences are interspersed with another 37% of the total genome at intervals of 2200 base pairs. (It is important to point out that the present data do not provide information about the number of copies of AGMr(HindIII)-1 in each interval).

Highly repeated DNA sequences are found in nearly all eukaryotic genomes (47). Typically, highly repeated DNA sequences which occur in long tandem arrays consist of millions of copies of short repeat units of 6 to 20 base pairs and often can be isolated as buoyant density satellites of the main band DNA (10). Such satellite sequences do not appear to be interspersed with unrelated DNA sequences (48). Another class of highly repeated DNA sequences which are interspersed with unrelated DNA sequences has been described in a variety of eukaryotes (49). These sequences are more complex, based on repeat units of 150 to 450 base pairs, and do not appear to occur in long tandem arrays. The BSC-1 genome represents the first example in which homologous, highly repeated DNA segments are shown to be organized in both fashions.

The observation that a fraction of the sequences homologous to AGMr(HindIII)-1 is interspersed throughout the genome may be relevant to an apparent discrepancy between results obtained by restriction enzyme digestion and those obtained by reassociation kinetics. Complete digestion of total BSC-1 DNA with Endo R-HindIII releases at most 10% of the total DNA into AGMr(HindIII)-1 and -2 and much less into higher multiples (2). However, the estimates of the representation of sequences homologous to AGMr(HindIII)-1 in the total DNA by reassociation kinetics with either the 32P-labeled AGMr(HindIII)-1 DNA tracer in a total DNA-driven reaction or in a self-reassociation reaction are 19.5% and 20.8%, respectively. This 2-fold difference, which is highly reproducible, is unlikely to be due to incomplete digestion of the total DNA by Endo R-HindIII, since SV 40 DNA added to the reaction mixture is completely digested under these conditions. Furthermore, higher enzyme concentrations do not increase the amount of AGMr(HindIII)-1 generated. These apparent quantitative differences can now be understood to result in part from the interspersion of sequences homologous to AGMr(HindIII)-1 within the genome. Interspersed sequences homologous to AGMr(HindIII)-1 would not necessarily be released by digestion with Endo R-HindIII unless such an interspersed sequence contained two adjacent Endo R-HindIII sites. There are some data to suggest that the interspersed sequences homologous to AGMr(HindIII)-1 retain at least one Endo R-HindIII recognition site.

It should be noted that in the present work, the DNA studied was derived from an established cell line derived from the kidney of African Green monkey. This raises the possibility that the observed DNA sequence organization of the BSC-1 cell line is different from that of the monkey. Preliminary observation of the patterns of reassociation and Endo R-HindIII digestion of monkey liver DNA indicate a similar organization to BSC-1 DNA.

**Genome Size of BSC-1 DNA**—The slowly reassociating fraction of the BSC-1 DNA, constituting 60% of the total DNA, presumably contains those sequences which occur as single copies within the genome. From the rate of reassociation of the single copy sequences, it is possible to estimate the total genome size of BSC-1 DNA. Previous estimates of genome size in a number of eukaryotes have been based on the reassociation rate of the single copy fraction relative to the rate of reassociation of randomly sheared DNA from a genome whose size has been measured independently, such as *E. coli*. The genome sizes of sea urchin and mouse have been obtained in this way. In the same manner, and using the determined sea urchin genome size as a standard, the data presented here indicate that the BSC-1 genome size is 6.1 X 10^9 base pairs per haploid genome. Independently, it is also possible to calculate the genome size of BSC-1 DNA relative to the size of AGMr(HindIII)-1 DNA (192 base pairs). In this case, the estimated size is 3.3 X 10^9 base pairs/haploid genome. Although the discrepancy in calculated genome size may be within experimental error, it may also derive from differences in the preparation of the DNA fragments used as standards. The genome size of the sea urchin was based on the reassociation rate of randomly sheared DNA, whereas the reassociation kinetics of purified AGMr(HindIII)-1 DNA used DNA segments that had been specifically cleaved by Endo R-HindIII. Since the exact effect on the reassociation kinetics of using short DNA fragments containing aligned sequences is not known, it seems more appropriate to base the estimate of genome size on a standard prepared in the same way as the total BSC-1 DNA, i.e. the sea urchin standard.

**Reiteration Frequency of AGMr(HindIII)-1**—The reiteration frequency of highly repeated DNA has been estimated by comparing the relative reassociation rates of very rapidly and slowly reassociating components. Calculating the reiteration frequency of the very rapidly reassociating fraction in the BSC-1 genome in this manner yields a value of 1.1 X 10^6 copies. It has been demonstrated that this kinetic fraction consists almost entirely of sequences homologous to AGMr(HindIII)-1. On the other hand, from the established values for AGMr(HindIII)-1 of 172 base pairs for the fragment length, of 19.3% for the representation in the genome, and an assumed genome size of 6.1 X 10^9, it is calculated that sequences homologous to AGMr(HindIII)-1 occur 6.8 X 10^6 times/haploid genome. The large discrepancy between the two methods of calculation is probably the result of an underestimate of the reassociation rate of highly repeated DNA fragments of short sequence in a population of randomly sheared DNA fragments.

The moderately rapidly reassociating component of BSC-1 DNA reassociates 4.2 X 10^4 times faster than the slow component. Nothing is known about the organization within the genome or the number of different sequence classes contained within this kinetic component.

**Organization of Sequences Homologous to AGMr(HindIII)-1 in Chromatin**

The experiments reported here indicate that the organization of AGMr(HindIII)-1 DNA sequence into chromatin is

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5. Rosenberg, unpublished observations.

6. D. Singer, unpublished observation.

T. McCutchan, M. Rosenberg, and M. Singer, manuscript in preparation.
not dependent solely on either the DNA nucleotide sequence or the reiteration frequency of the sequence. The repeat length of nucleosomal DNA sequences homologous to AGMr(HindIII)-1 is indistinguishable from that of total DNA, that is, approximately 185 base pairs. The extent of packaging of sequences homologous to AGMr(HindIII)-1 into core particles is also the same as that of total DNA. Probing the internal structure of the nucleosome with DNase I revealed no differences in sensitivity to this enzyme between bulk DNA and DNA homologous to AGMr(HindIII)-1.

The present data are consistent with those recently reported by Gottesfeld and Melton (50) who demonstrated that nucleosomes containing mouse satellite DNA are not phased with respect to the underlying DNA sequence. However, Musich and co-workers (45) reported that nucleosomes containing Component α DNA sequences are indeed phased with respect to sequence. The reasons for this discrepancy are not known. However, in all cases in the studies reported here, following renaturation of core particle DNA, some sequences homologous to AGMr(HindIII)-1 remained 140 base pairs in length. Some of this material may represent residual single-stranded DNA, but some may derive from a subpopulation of nucleosomes containing AGMr(HindIII)-1 sequences which were in register with the chromatin.

From the present studies, it is not possible to exclude the possibility that a given tandem array of AGMr(HindIII)-1 sequences will always display one specific spatial arrangement of nucleosomes while another tandem array, perhaps on another chromosome, will always display a specific but different spatial arrangement. This seems unlikely in view of the facts that the repeat length of all nucleosomal DNA is 185 base pairs which is longer than the AGMr(HindIII)-1 sequence of 172 base pairs, and that the core particle DNA contains the same proportion of sequences homologous to AGMr(HindIII)-1 as total DNA. These data suggest that chromatin organization does not reflect DNA sequence organization.

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