Evolution of Primate Chromosomes

Man's closest relative may be the gorilla, not the chimpanzee.

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Summary. Human and higher primate chromosomes have been compared by general and regional banding methods, including hybridization in situ. The general banding patterns of the chromosomes of gorilla, chimpanzee, and orangutan, but not gibbon, are similar to those of the human. Preliminary results show that chromosomes with similar banding patterns in different species often carry the same genes. Repetitious DNA's have undergone changes in structure and distribution which are reflected in changes in the regional banding patterns. These studies confirm that the evolutionary distance between the gibbon and the orangutan is relatively great compared to the distance between the orangutan and the other great apes, and suggest that man is more closely related to the gorilla than to the chimpanzee.

The evolution of man continues to be a subject of curiosity, and as new methods have been devised for comparing physical and biological properties of species, these have been applied to comparison of the great apes with man. Recent technical advances in the study of metaphase chromosomes are of particular interest in this respect because the chromosomes carry the genetic information of each individual.

Almost as soon as new techniques made possible the study of human chromosomes, the same techniques were applied to studies of the other primates (*1*). In most of these studies, the cells were arrested in metaphase with Colcemid, and the chromosomes were separated by swelling the cells with a hypotonic solution and then stained with Giemsa or orcein. Such treatment provided information about the relative lengths of chromosomes, the position of each centromere, and the presence of satellites (*2*); therefore, the emphasis was on uniformly, deeply stained chromosomes that had the chromatids well separated. These methods did not produce consistent banding along the chromosomes and they are often referred to as prebanding methods. The studies showed that human (*Homo sapiens*), gorilla (*Gorilla gorilla*), chimpanzee (*Pan troglodytes*), and orangutan (*Pongo pygmaeus*) (*3*) have rather similar karyotypes (*1*). Although the human has 46 chromosomes and each of the other species has 48, all of these species have some chromosomes with the centromere near the middle (metacentric) and some with the centromere close to one end (acrocentric). In contrast, the gibbon (*Hylobates lar*) (*3*) has 44 chromosomes, all metacentric (*1*), supporting the conclusion derived from other studies that the gibbon is a greater evolutionary distance from the great apes than great apes are from one another (*4*).

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Chromosome Banding Methods

The demonstration that bright and dull fluorescent bands can be produced along the length of metaphase chromosomes by a fluorescent dye, quinacrine (*5*), led a number of investigators in the early 1970's to develop methods for delineating chromosome banding patterns. These patterns are unique for every chromosome within a species, and the pattern of a chromosome segment remains unaltered when its location is altered by translocation or inversion (*6*). The chromosomes require a somewhat different method of preparation compared with chromosomes prepared for nonbanding studies. Banding patterns are more distinct if the chromosomes are longer (they could be made longer by reducing the treatment with Colcemid), and if the chromatids are together (this could be brought about by altering the hypotonic treatment).

Banding along the length of the chromosome, or general banding, can be produced by staining with a fluorescent dye, such as quinacrine or acridine orange, or with Giemsa after specific treatment. The Q banding pattern produced by quinacrine is the same as the G banding pattern produced by Giemsa after treatment of the chromosomes with trypsin. A reverse, or R-banding pattern, is produced by either acridine orange or Giemsa after controlled heat treatment. Detailed comparisons of the chromosome banding patterns of various species can be made by using one or more of these methods.

Such studies have enabled investigators to suggest counterparts for each chromosome of the human complement in the gorilla (*7–11*), chimpanzee (*7, 12–17*), pygmy chimpanzee (*18–21*), and orangutan (*7, 22–24*). Very few of the chromosomes, except the X, have exactly the same banding patterns in man and the great apes. For example, the longest chromosome in each species has the same banding pattern but only that of the human has a secondary constriction in the long arm; thus the relative length of the two arms of chromosome 1 in the human is the reverse of that in the gorilla, chimpanzee, and orangutan. As expected, one large human chromosome, No. 2, replaces two acrocentric chromosomes of each of the other species, thus accounting for the reduced number of chromosomes in the human. Somewhat surprisingly, the easiest way to make the chromosomes in various primates look alike, that is, to make the chromosome bands match, requires pericentric inversion. This type of inversion is produced by breaking a chromosome on each side of the centromere and inverting the middle segment before rejoining the broken ends. Dutrillaux and coworkers (*9*) have suggested that human and gorilla, human and chimpanzee, and gorilla and chimpanzee differ by inversions involving six to eight chromosomes, and that nine to ten inversions separate these species from the orangutan (*22*). Pericentric inversions are known in the human population, but they are relatively rare, occurring at a frequency of 1×10^{-4} in the newborn (*25, 26*) (Table 1). On the other hand, reciprocal translocations, involving exchange of DNA between two different chromosomes, usually have not been invoked in explaining the evolution of the chromosomes of the higher primates, although in

studies of the newborn human they occur almost 20 times more frequently than inversions.

Each group of workers reached somewhat different conclusions about the evolutionary changes in the chromosomes of higher primates and, because many of the numbering systems were based on the system used for the human, each group developed a different numbering system. In an effort to simplify communication, workers from several laboratories have jointly proposed standard numbering systems for the karyotypes of gorilla, chimpanzee, and orangutan (*27*). In recognition of the status of each of the higher primates as a separate species, the numbering systems were derived independently from one another and from that of the human, with the arrangement of each karyotype based on chromosome length and arm ratio (*28*). The pygmy chimpanzee has not been treated separately: it has a karyotype almost identical to that of the chimpanzee (*18–21*) and the same numbering system can be used for both. The proposed numbering systems are presented in the Paris Conference (1971) Supplement (1975) (*27*), which contains an illustration of each chromosome stained to show G, Q, and R bands. The report also has a diagram comparing the banding patterns of chromosomes thought to be homologous, that is, carrying the same genes, with one another and with their human counterpart. In this article I discuss mainly the comparative aspects of the primates and man; therefore, only human equivalent numbers will be used (except when indicated) and the reader is referred to the joint report (*27*) for corresponding numbers for each primate.

The joint report (*27*) fails to illustrate the appearance of the Y chromosome of gorilla, chimpanzee, and orangutan stained to show Q and G banding, and the diagram of the gorilla Y chromosome is oversimplified. The Y chromosome shows more variability from species to species than almost any other chromosome, and the banding pattern of the gorilla Y chromosome is more complex than that of the human, which in turn is more complex than that of the chimpanzee or orangutan. The gorilla Y chromosome is longer than that of the human (*29*) and, although it is generally only moderately bright with quinacrine, it differs from the human Y chromosome in having a very dull band in each arm (*11*). The gorilla is the only mammal, other than the human, known to have a brilliant quinacrine-stained region on the Y chromosome (*30*). The chimpanzee has a very small Y chromosome which is not clearly banded by any of the available methods (*7, 12–17*). The Y chromosome of the orangutan is longer than that of the chimpanzee but has no brilliant Q fluorescence (*7, 24*).

Table 1. Chromosomal abnormalities in higher primates.

Type of abnormality	Number per 100 live-born humans	Primate	Abnormality	Reference
Sex chromosome abnormality	0.21	Chimpanzee	XX/XY male	(*80*)
		Orangutan*	Virilized XX	(*22, 23*)
Autosomal trisomy	0.12	Chimpanzee	Extra 22(H21)†	(*81*)
		Gorilla	Extra small satellited chromosome	(*8*)
Translocation	0.21	None		
Inversion	0.01 (*26*)	Orangutan*	Rearrangement of 9(H12)†‡	(*22, 23*)
		Orangutan§	Two copies pericentric inversion of 2(H3)† plus rearrangement of 9(H12)†‡	(*23*)
		Orangutan‖	Rearrangement of 9(12)†	(*24*)
		Gibbon	Pericentric inversion of 7(H?)†	(*32*)

*Same animal. †Primate number with human number in parentheses; see (*82*). ‡The abnormal chromosome could not have been produced by simple inversion, but was derived solely from this chromosome. §Two female offspring of this male orangutan were heterozygous for both rearranged chromosomes. ‖Twelve of 23 animals from Borneo and Sumatra; nine had a single rearranged 9(H12) and three had two copies.

The chromosome banding patterns of the gibbon also have been studied in some detail (*31–34*). Few, if any, of the gibbon chromosomes, other than the X, resemble those of the higher primates, and it has been impossible to determine what changes the chromosomes have undergone in the evolutionary divergence of gibbon and man.

Mapping the Genes

Do chromosomes that have similar banding patterns carry the same genes? A few reports indicate that they often do. Mouse-chimpanzee somatic cell hybrids selectively lose chimpanzee chromosomes, so that genes can be assigned to chimpanzee chromosomes by correlating chimpanzee enzyme activity with chimpanzee chromosomes remaining in specific hybrid lines, the same method now being used so successfully to map human genes (*35, 36*). In this way genes have been assigned to the chimpanzee chromosomes corresponding to human chromosome Nos. 1, 2, 11, 12, 17, 21, and the X (*37–39*) (Table 2). These are the same chromosomes to which the corresponding genes have been mapped in the human (*35, 36*). However, such a correlation between species cannot always be demonstrated. Human chromosome No. 6 has a virtually identical counterpart (by banding pattern) in the chimpanzee, gorilla, and orangutan (*27*), but superoxide dismutase-2 (SOD-2), which has been mapped to the human chromosome No. 6, is not located on the corresponding chimpanzee chromosome (*38*). Similarly, in a study of Chinese hamster–gorilla somatic cell hybrids, inosine triphosphatase was localized in the equivalent of human chromosome No. 14 (*40–42*), although there is evidence that the gene is not located on this chromosome in the human (*43*).

Somatic cell hybrids have also been used to map genes in more distantly related primates. Enolase-1 and phosphoglucomutase-1, which are located on the short arm of human chromosome 1, have been shown to be on chromosome 1 of the baboon (*Papio papio*) and chromosome 4 of the African green monkey (*Cercopithecus aethiops*). Peptidase-C, which is located on the long arm of human chromosome No. 1, has been mapped to chromosome 13 of the African green monkey. In each case the general banding pattern of the relevant chromosome is very similar to that of human chromosome No. 1. Despite the occurrence of a chromosome fission (or two fusions) and an inversion, the relationship between chromosome banding pattern and gene location has been maintained for perhaps 50 million years (*44*).

In a different method of mapping that is especially appropriate for genes present in multiple copies, radioactively labeled RNA is hybridized to the DNA of the fixed metaphase chromosome on a slide; this is known as hybridization in situ. In this way the genes coding for 5*S* RNA have been mapped to the distal end of the long arm of human chromosome No. 1 (*45, 46*) and to the corresponding region of No. 1 in the chimpanzee, pygmy chimpanzee, mountain gorilla, and orangutan (*46*). Similar studies show that the genes of 18*S* and 28*S* RNA are located in the secondary constriction regions of the acrocentric chromosomes (*20, 47*).

Chromosome Abnormalities

Chromosome analysis can be used not only to examine normal chromosomes, but to detect chromosome abnormalities. A number of these have been reported in higher primates, including sex chromosome abnormalities, autosomal trisomies, and pericentric inversions (Table 1). It is difficult to estimate the incidence of such abnormalities because only a relatively small number of animals have been studied and because animals that have abnormalities are more likely to be reported than those that do not. It is also possible that animals with an unbalanced karyotype may not live long enough to be studied, particularly in the wild.

One type of rearranged chromosome corresponding to the human No. 12 was present in half the orangutans studied (*22–24*). In a few animals only the rearranged chromosome 12 was present (*24*). Since orangutans from both Borneo and Sumatra were included in the studies, both forms of chromosome 12 appear to have existed in the orangutan population before the two groups of animals were isolated geographically, perhaps 8000 years ago (*24*). The nature of the rearrangement is not clear because, although the rearranged chromosome 12 could not have been produced by a simple inversion, it does not involve translocation of material from a different chromosome. One suggestion is that it was produced by an inversion within an inversion (*24*). One of the orangutans has, in addition to a copy of the abnormal No. 12, two copies of a chromosome 3 which differ from the usual No. 3 by a pericentric inversion (*23*).

The finding of inversions, but not reciprocal translocations, in this small sample of higher primates is especially interesting in view of the suggestion that the karyotypes of these species differ from one another by a series of inversions, but not translocations. Inversions have been reported in other primates, such as the gibbon (*32*) and some New World monkeys (*48, 49*). In the squirrel monkey inversions distinguish the species from different geographical locations (*48*), lending support to chromosomal inversion as a mechanism for evolutionary divergence in primates. Inversions have been invoked not only in the evolution of primates (*50*), but also in that of the cats (Felidae) (*51*) and some species of rats (*Rattus*) (*52*).

An inversion may be fixed in a population if it provides a selective advantage to the individuals carrying the altered chromosome. Inversion leads to a reduction in the frequency of crossing over, or exchange of homologous segments of chromosomes, during meiosis, thus isolating a group of alleles. An inversion that includes a combination of alleles that is especially favorable would provide a selective advantage. In addition, Bodmer (*53*) has suggested that inversion might lead to a superior arrangement of the genes themselves, for example, by bringing together genes whose products interact with one another. The change in gene location produced by an inversion could also lead to a change in function of some of the genes. There is some evidence in the human for such a position effect; the incidence of individuals who have a chromosome rearrangement with no apparent loss of chromosomal material is five times greater in mentally retarded populations than among the newborn (*54*).

Table 2. Location of genes on primate chromosomes.

Chromosome*	Chimpanzee genes	Gorilla genes (*83*)
1	Enolase (ENO) (*38*) Phosphoglucomutase-1 (PGM_1) (*38*) Peptidase C (PepC) (*38*) *5S* RNA (*46*)	Ribosomal RNA (*75*) *5S* RNA (*46*)
2	Malate dehydrogenase-1 (MDH-1) (*38*)	
3		
4		
5		
6	†	
7		
8		
9		
10		
11	Lactate dehydrogenase A (LDH_A) (*38*) [LDH_A linked to acid phosphatase-2 (ACP-2) (*37*)]	
12	Lactate dehydrogenase B (LDH_B) (*38*) ‡	
13	Ribosomal RNA (*47, 75*)	§
14	Ribosomal RNA (*47, 75*)	Inosine triphosphatase (ITP) (*43*) Nucleoside phosphorylase (NP) (*43*) §
15	§	§
16		
17	Thymidine kinase (TK) (*37–39*) Galactokinase (GALK) (*37–39*) Adenovirus-12-induced gaps (*37*)	
18	Ribosomal RNA (*47, 75*)	
19		
20		
21	Superoxide dismutase-1 (SOD-1) (*38*) Ribosomal RNA (*47, 75*)	Ribosomal RNA (*20, 75*)
22	Ribosomal RNA (*47, 75*)	Ribosomal RNA (*20, 75*)
X	Glucose-6-phosphate dehydrogenase (G6PD) (*38*) [(G6PD linked to phosphoglycerate kinase (PGK) (*37*)]	

*Primate chromosome homologous to this human chromosome. †SOD-2 is not here as it is in the human (*38*). ‡PepB is linked to triosephosphate isomerase (TPI), possibly on number 12 (*37*). §Ribosomal RNA is not here, as it is in the human (*20, 75*).

Regional Banding Methods

In addition to the methods for producing general banding patterns (Q, G, and R) there are a number of staining methods that can be used to study selected regions of chromosomes. These methods are most effective if the chromosomes are identified accurately, usually by sequential staining of the same metaphase cell by a general banding method as well as a regional banding method. Most, if not all, of the regions that are selectively stained contain repetitious DNA. Because these variant regions can be absent from chromosomes without producing an obvious phenotypic effect, it is not surprising that this DNA can evolve more rapidly than DNA which contains unique gene sequences (*55*). Study of such regions might, therefore, provide information about more recent evolutionary relationships. The results obtained by using a variety of regional banding methods are summarized in Table 3.

Some caution must be exercised in interpreting the results of the regional banding methods. These methods detect regions that vary from one individual to

Table 3. References for general banding methods and characteristics of human and primate chromosomes. All numbers refer to the human equivalent; for animal chromosome number see (*27*).

Method	Human (*Homo sapiens*)	Gorilla (*Gorilla gorilla gorilla*)	Chimpanzee (*Pan troglodytes*)	Pygmy chimpanzee (*Pan paniscus*)	Orangutan (*Pongo pygmaeus*)	Gibbon (*Hylobates lar*)
General banding						
Giemsa (G)	(*57*)	(*10, 11*)	(*12, 13, 15, 17*)	(*20, 21*)	(*23, 24*)	(*32, 33*)
Quinacrine (Q)	(*57*)	(*7, 9, 10, 11*)	(*7, 14, 16*)	(*18, 19*)	(*7, 22, 24, 75*)	(*7, 31, 32*)
Reverse (R)	(*57*)	(*8, 9, 11*)	(*12, 14*)	(*19*)	(*22, 23*)	(*31*)
Regional banding						
Q, brilliant	Centromere of 3, 4, 13; satellite or short arm of 13, 14, 15, 21, 22; distal end of Y (*57*)	Centromere of 4; satellite of 2q, 13, 14, 15, 18; short arm of 15, 21, 22; distal end of Y (*9–11, 30*)	Short arm of 13, 14, 18, 21, 22 (*14, 16*)	Same as *troglodytes*, but short arm of 22 very large (*18, 19*)	Absent (*7, 22, 24*)	Absent (*31, 32*)
Q-terminal band	Absent (*57*)	Short arm of 4, 5, 6, 7, 8, 10, 11, 12, 16, 19, 20; long arm of 16, 17, 19, 20, 21, 22 (*9*)	Same as gorilla, plus short arm of 17, but not 4, 5 (*14*)	Same as *troglodytes* (*18, 19*)	Absent (*22*)	Absent (*31, 32*)
C band	2° constriction of 1, 9, 16; short arm of 15; long arm of Y; centromeres (*57, 60*)	2° constriction of 9, 16; short arm of 2q, 13, 14, 15, 18; middle of long arm of Y; centromeres, except 2p; many terminal bands (*11*)	Short arm of 13, 14, 15, 18, 21, 22?; long arm of 15; middle of long arm of 13; many terminal bands (Fig. 1)	Same as *troglodytes*; middle of long arm of 4 (7?) (*21*)	Short arm of 22; centromeres, except 12 (*24, 59*)	Centromeres; larger on two chromosomes, one of which has NOR (*32*)
T band	Short arm of 1, 4, 7, 11, 13?, 14?, 15?, 19; long arm of 8, 9, 17 (*61*)	Same as human, plus short arm of 5 (*9*)	Same as human (*14*)	Same as human (*19*)	Same as human, plus short arm of 2, 3, 11; more on 7; long arm, near centromere, of 8 (*22*)	Mostly terminal, some interstitial (*31*)
5-methylcytosine	C-band region of 1, 9, 15, 16, Y (*63*)	C-band region of 2q, 9, 13, 14, 15, 16, Y (*41*)	Absent (*41*)	Not done	Not done	Not done
G-11	Large amount on 9; short arm of 5, 7, 17, and acrocentrics; long arm of 1, 4, 10, 20, Y (*13*)	Short arm of 2p, 7, 16, and acrocentrics; long arm of 9, 14, 20 (*9*)	Short arm of 1, 7, 16, 18, Y, and acrocentrics; long arm of 2p, 9, 15, 17, 20 (*13, 14*)	Same as *troglodytes* (*19*)	Same as gorilla, plus short arm of 2q, short (not long arm) of 7 (*22*)	No banding (*31*)
Ag band	13, 14, 15, 21, 22 (*74, 75*)	1q, 21, 22 (*75*)	13, 14, 18, 21, 22 (*75*)	Not done	2q, 13, 14, 15, 18, 21, 22, ? (*75*)	One site (*75*)
Hybridization in situ						
Human sat. I	Major site on 9, Y; minor site on 1, 5, 7, 12, 13, 14, 15, 20, 21, 22 (*65, 69*)	Major site on 2p, 9, 13, 14, 15, 16, 18, Y; minor site on 5, 22 (*71*)	Major site on 2q, 7, 9, 15, Y; minor site on 13, 14, 16, 17, 18, 20, 21, 22 (*71*)	Not done	Major site on 2p, 2q, 13, 22, Y; minor site on 11, 14, 15, 18, 21, ?(*71*)	Not done
Human sat. II	Major site on 1, 9, 16, Y; minor site on 14, 15, 17, 21, 22, X (*66, 69*)	Major site on 2p, 9, 13, 14, 15, 16, 18, Y; minor site on 22 (*71*)	Absent (*71*)	Not done	Major site on 2p, 2q, 13, 15, 21, 22, Y; minor site on 10, 14, 18, ? (*71*)	Not done
Human sat. III	Major site on 9, 15, Y; minor site on 1, 5, 13, 14, 20, 21, 22 (*67, 69*)	Major site on 2p, 9, 13, 14, 15, 16, 18, Y; minor site on 1, 5, 22 (*42, 70*)	Major site on 7, 9, 15, Y; minor site on 1, 2q, 13, 14, 16, 17, 18, 20, 21, 22 (*42, 70*)	Not done	Major site on 2p, 2q, 13, 14, 15, 18, Y, ? (*42, 70*)	Absent (*70*)
Human sat. IV	Major site on 9, 15, Y; minor site on 1, 5, 7, 10, 13, 14, 17, 19, 20, 21, 22 (*68, 69*)	Major site on 2p, 9, 13, 14, 15, 16, 18, Y; minor site on 22 (*71*)	Major site on 2q, 7, 9, 15, 17, Y; minor site on 13, 14, 18, 21, 22 (*71*)	Not done	Major site on Y; minor site on 2q, 12, 13, 15, ? (*71*)	Not done
Chimp. sat. A	Multiple site (*70*)	Multiple site (*70*)	Multiple site (*70*)	Not done	Multiple sites (*70*)	Not done
rRNA	13, 14, 15, 21, 22 (*73*)	21, 22* (*20*)	13, 14, 18, 21, 22 (*47*)	Same as *troglodytes* (*20*)	Many sites (*20*)	One site (*33*)

**Gorilla gorilla berengei.*

the next, so that the range of differences observed will depend on the number of animals studied and how representative they are of the population (*56*). A rough estimate of the number of great apes studied by one or another of the banding methods is 65 chimpanzees, 35 orangutans, 15 gorillas, and 7 gibbons. It is not always easy to know if the same animal has been studied by investigators in different laboratories, because many animals have not been identified by name or number. It is also difficult to determine the frequency of chromosomal variants from published figures because, in comparative studies, the illustrations often show one homolog from each chromosome pair together with a chromosome from a different species, thus minimizing detection of differences between homologs of the same species. The amount of variation can be surprisingly great: four gorillas that were studied by Q, C, G, and R banding had variants of half the chromosome complement (*11*).

Brilliant and Terminal Q Bands

Quinacrine staining reveals, in addition to the general Q-banding pattern, brilliant fluorescent areas in a variable number of regions of the human chromosomes (*57*; Table 3). Although the gorilla can have brilliant quinacrine staining on the same chromosomes (except for the centromeric regions of the equivalents of human chromosome Nos. 3 and 13), it differs from the human in several ways. In the gorilla the brilliant region on No. 4 is always present and is larger than in man; the Q-brilliant regions of the acrocentrics are more often located in the satellites than in the short arms of chromosomes 13, 14, and 15, whereas they are probably confined to the short arms of chromosomes 21 and 22; and the Q-brilliant regions on two chromosomes, 2q (*58*) and 18, have no counterpart in the human (*7, 9–11*). In the chimpanzee, brilliant fluorescence is found only in the short-arm regions of the equivalents of all the human acrocentric chromosomes, except No. 15, and in the short arm of No. 18. There are no Q-brilliant satellites and the Y does not show such staining (*14, 16*). Both the orangutan (*7, 22, 24, 59*) and the gibbon (*31, 32*) lack regions with brilliant quinacrine fluorescence. These findings suggest that, of the higher primates, the orangutan and gibbon are the most remote from the human and that the gorilla is closest to the human.

Another type of variation revealed by quinacrine is the presence of bright bands at the distal ends of the arms of many chromosomes in the gorilla and the chimpanzee (Table 3). These bands presumably are composed of repetitious DNA because they can sometimes be stained by the C-banding techniques (Fig. 1). They are not found in the human (*57*), the orangutan (*22, 59*), or the gibbon (*31, 32*).

Various Regional Banding Methods

In the human, staining of the constitutive heterochromatin, or C banding, reveals large blocks of material in the region of the long arm adjacent to the centromere of chromosome Nos. 1, 9, and 16, and of the distal half of the long arm of the Y. The short arm of No. 15 has more of this material than the other chromosomes of the D group. There is also a small amount of C-banding material near the centromere of every chromosome. C banding requires denaturation of the chromosomes, that is, separation of the strands of DNA, followed by partial renaturation. The C-band region may be composed of very repetitive DNA which readily regains its native double-stranded form (*60*), or it may be more resistant to denaturation than is the rest of the chromosome. The gorilla and the chimpanzee have rather similar distributions of C bands (Table 3). A karyotype showing the C bands of the chimpanzee is shown in Fig. 1; this figure shows that homologous chromosomes, for example pair 18, have different appearances if they have different amounts of C-band material. The loss of a C band results in a decrease in length, but this may produce no phenotypic effect if genes of a unique sequence have not been lost. The chimpanzee chromosome No. 14 (human No. 13) is unusual because it has a C band in the middle of the long arm, which probably accounts for the extra band seen with Q or R banding (*14*) as well as its extra length compared to its human counterpart, No. 13 (*17*). There is a small C band in the middle of the long arm of chromosome No. 6 (human No. 7) in this chimpanzee; the pygmy chimpanzee also has a C band in the middle of a large biarmed chromosome (*21*).

The telomeric (T) bands found at the terminal ends of some chromosomes are particularly resistant to heat denaturation (*61*), and they have also been resistant to evolutionary change. Human, gorilla, and chimpanzee have almost identical distributions of T bands (*9, 14, 61*; Table 3). The orangutan has a somewhat different distribution (*22*) and the gibbon has an even more different distribution of T bands (*31*). The T bands are not distributed in the same manner as the terminal Q and C bands and, presumably, represent a different class of DNA.

5-Methylcytosine is a base that makes up 1 percent or less of mammalian DNA. In the mouse and kangaroo rat it is concentrated in the low-density satellite DNA (*62*). Antibodies have been produced that will react with 5-methylcytosine in single-stranded DNA. After irradiation of fixed human chromosomes with ultraviolet light, antibodies to 5-methylcytosine bind to the same regions as the C bands on chromosome Nos. 1, 9, 15, 16, and the Y (*63*). In the gorilla relatively large amounts of antibody are bound to the C-band regions of the chromosomes equivalent to each of these, except No. 1, as well as to 2q, 13, and 14 (*41*). In marked contrast, no intense binding of 5-methylcytosine is observed in the chimpanzee (*41*).

If Giemsa staining is carried out at an increased *p*H (11 or higher), specific (G-11) staining of the C-band region of human chromosome 9 is observed, as well as a small amount of staining adjacent to the centromere of a number of other chromosomes (*13, 64;* Table 3). Such G-11 staining is found in the same region of a number of chromosomes in each of the higher primates (*9, 14, 22*) except the gibbon (*31*). Under some conditions the gorilla has a large concentration on certain chromosomes similar to that on human chromosome No. 9.

Buoyant Density Satellite DNA's

The human has four buoyant density satellite DNA's (*2*): satellites I, II, III, and IV. Together they constitute about 3 percent of the total DNA. Hybridization in situ of radioactively labeled RNA's complementary to each of the human satellite DNA's has been used to study the location of the satellites in the human (*65–69*) and in the great apes (*42, 70, 71*). Gosden and his co-workers (*71*) have found base sequences complementary to all four human satellites, usually in larger amounts than in the human, in the gorilla, chimpanzee, and orangutan. The only exception is that sequences common to human satellite II are absent from the chimpanzee (*71*). Since this satellite is present in the orangutan, it seems probable that satellite II was present in a primate ancestor but either has been lost by the chimpanzee or is present in very small amount in this species. In the human, all four satellites are located in the same regions of the same chromosomes, particularly Nos. 9, 15, and the Y. It is not known how satellites which are pre-

sent in the same chromosome region are arranged with respect to one another. The distribution of the four satellites within each of the other species is also remarkably similar. However, in addition to the fact that the chimpanzee lacks satellite II, the orangutan has few DNA sequences in common with human satellite IV; those present are almost all located in the Y (*71*).

Two buoyant density satellites have been isolated from the chimpanzee, satellites A and B. Satellite A has physical properties very similar to, and a 25 to 30 percent base sequence homology with, human satellite III (*72*). Satellite A anneals to the same chromosomal sites as satellite III (*70*). Chimpanzee satellite B has not been well characterized; it shows some similarities to human satellite I (*72*).

Can the distribution of the satellite DNA's be related to the locations of repetitious DNA which are revealed by the regional banding methods? The data in Table 3 indicate this is true only in some cases. None of these satellite DNA's is concentrated at the telomeric ends of chromosome arms; therefore, none of them correspond to the terminal Q or C bands found in the chimpanzee or gorilla, or to the T bands found in the human and the great apes. None of the satellite DNA's corresponds to the DNA that is brilliantly stained by quinacrine. The orangutan has DNA sequences in common with human satellites I, II, and III, and a small amount of satellite IV, but it has no Q-brilliant regions. Human satellite III may be the DNA that is stained by the G-11 method, because their distributions are similar in human, gorilla, chimpanzee, and orangutan, and both are absent from the gibbon. However, the distribution of satellite I is similar to that of satellite III in the various species, so that either or both of these satellites might be the material stained by Giemsa at high *p*H. Satellite II and 5-methylcytosine-rich regions also appear to be related. In the human their distributions correspond well, although relatively more 5-methylcytosine-rich DNA than satellite II DNA is present on chromosome 16. [In most individuals there is as much 5-methylcytosine-rich DNA on No. 16 as on Nos. 1 and 9 (*63*), but there is only 25 to 30 percent as much satellite II DNA on chromosome No. 16 as on Nos. 1 and 9 (*69*).] In the gorilla, too, the distributions of satellite II and 5-methylcytosine-rich DNA correspond well, except that there is relatively less 5-methylcytosine-rich DNA than satellite II on No. 18 (*41*, *71*). (Because only a single gorilla was studied with the use of antibody binding, in this case the absence of 5-methylcytosine-rich DNA may reflect individual variation.) Neither satellite II nor concentrations of 5-methylcytosine-rich DNA are found in the chimpanzee. The data suggest that satellite II is the only one of the four human satellites that is methylated. It is known that satellite II is present in the orangutan (*71*); the demonstration of 5-methylcytosine-rich regions in this species would provide further evidence that it is satellite II that is methylated.

Ribosomal RNA Genes

The location of 18*S* and 28*S* ribosomal RNA (rRNA) genes can be demonstrated by hybridization in situ with radioactively labeled rRNA. In the human these genes are located in the secondary constriction on the short arm of the five pairs of acrocentric chromosomes, Nos. 13, 14, 15, 21, and 22 (*73*). Each of the higher primates has a somewhat different distribution. The gorilla has rRNA genes on only two small pairs of acrocentrics, corresponding to human chromosomes 21 and 22 (*20*). No rRNA genes are present on the large acrocentric chromosomes of the gorilla, despite the similarity of their banding patterns to those of the human D group and the presence of secondary constrictions. The chimpanzee has rRNA genes on five pairs of chromosomes, including the chromosome corresponding to human chromosome No. 18, but not that corresponding to human No. 15 (*47*). The orangutan has rRNA genes on several pairs of acrocentrics (*20*) and the gibbon has them in a single site on the chromosome pair which has a very large secondary constriction (*33*).

The results obtained by using a silver nitrate (Ag) stain which is specific for rRNA sites are virtually identical to those obtained with labeled rRNA (*74*, *75*). With Ag stain, the sites in the orangutan have been shown to include the six chromosome sites found in the human and in the chimpanzee plus two others (*75*). The only discrepancy between the detection of rRNA genes by means of hybridization in situ and Ag stain is that the latter method detects a prominent rRNA site on the distal arm of gorilla chromosome 1 (*75*). Only a small number of animals were examined by each method and it is possible that studies of other gorillas by means of hybrid-

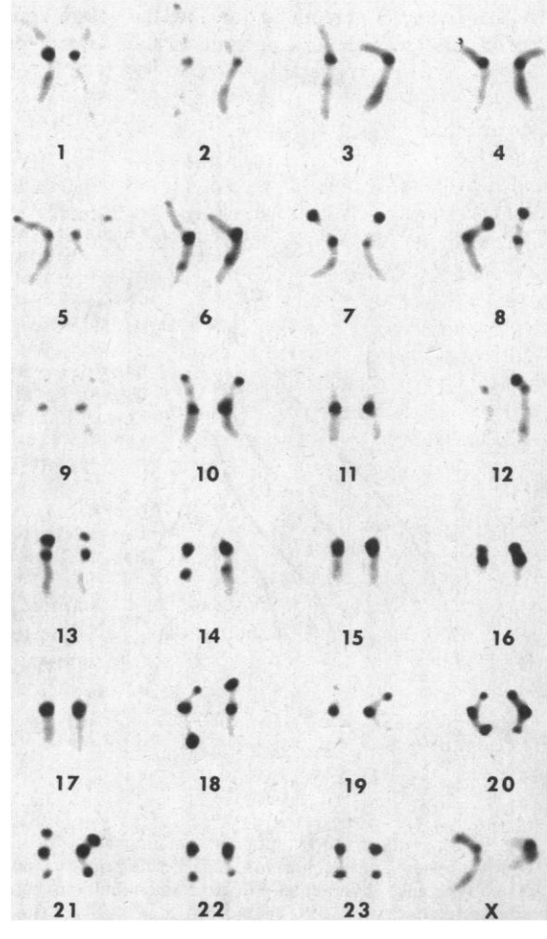

Fig. 1. Chromosomes of a female chimpanzee (*Pan troglodytes*) stained to show C bands. The chromosomes were identified by staining the same cell with quinacrine (not shown); the numbering system is that proposed for the chimpanzee in (*27*). A C band is present at the centromeric region of each chromosome, but those on Nos. 2, 5, 9, 12, and the X are very small. A terminal C band can be seen at the end of some of the chromosome arms (for example, 7, 8, 20); note the difference in appearance of homologs caused by the presence of a C band on only one member of pairs 12 and 18. Interstitial C bands are visible in the long arm adjacent to the centromere of No. 16, and in the middle of the long arm of pairs 6 and 14.

ization in situ would detect such a site. On the other hand, the Ag stain has been carried out only on the lowland gorilla, whereas studies of hybridization in situ have been carried out only on the mountain gorilla; therefore, the results may reflect a different distribution of rRNA genes in these subspecies.

Henderson *et al.* (*20*) calculated that the gorilla has fewer rRNA genes than the human, chimpanzee, or orangutan (270 as opposed to 446, 488, and 422, respectively). When Ag stain is used, the amount of stain at any one site in these species appears to be inversely proportional to the number of sites (*75*); the results suggest that the total number of gene copies is rather similar in each species, if one includes the site on gorilla chromosome No. 1. In the human there is a close correlation between the number of rRNA genes (measured either by grain counts or by the size of the area stained by the Ag method) and the function of these genes as nucleolus organizers (measured by the number of satellite associations) (*76*). The same is true in the gorilla: chromosome Nos. 21 and 22, which have rRNA genes, are involved in a much higher percentage of satellite associations (40 percent for both the lowland and mountain gorilla) than are chromosomes 13, 14, and 15, which lack rRNA genes (9 percent in the lowland gorilla and less than 1 percent in the mountain gorilla) (*20, 75*). It is not clear whether there is a real difference between the gorilla subspecies with respect to the percentage of chromosomes 13, 14, and 15 seen in association. Since these chromosomes lack rRNA, their tendency to associate cannot reflect rRNA gene activity, but may reflect the amount of heterochromatin.

Evolutionary Implications

What have chromosome banding studies, with their quantum jump in the accuracy of chromosome identification, added to our understanding of evolutionary relationships? First they have confirmed the relatively great evolutionary distance between the gibbon and the higher primates. The gibbon does not have any of the acrocentric chromosomes seen in the great apes and man. Inversions, which have been invoked in the evolution of the other species, could lead to the formation of such chromosomes. However, it is not possible to convert the karyotype of the gibbon into that of, for example, the orangutan by a series of simple pericentric inversions, in the way that it is possible to convert the karyotype of the orangutan into that of the gorilla or chimpanzee. This may indicate that the gibbon and the orangutan have been separated for a much longer period of time than have the orangutan and the other higher primates. If inversions were produced over a sufficiently long time interval, a chromosome might be altered by more than one inversion and the origin of such an altered chromosome would be difficult to determine. Such a mechanism has been postulated to account for the appearance of a polymorphic pair of chromosomes in present-day orangutan populations (*24*). Alternatively, the marked differences between the karyotypes of the gibbon and the orangutan may indicate that the chromosomes of the orangutan ancestor did not evolve from those of the gibbon ancestor by inversion, but rather by a different mechanism, such as reciprocal translocation. In that case, the number of translocations would determine how difficult it is to detect the origin of each chromosome segment.

There is evidence that speciation of some primates has been accompanied by reciprocal translocations. For example, comparison of the banding patterns of the chromosomes of the rhesus monkey and the African green monkey show them to differ by a series of centric fusions and reciprocal translocations, not by inversions (*77*). In his review of primate cytogenetics, Egozcue (*50*) points out that the most commonly observed evolutionary changes in primate chromosomes involve centric fusion and pericentric inversion, but that those in various species of *Cercopithecus* involve reciprocal translocations. In addition to the differences in the general banding patterns, the gibbon differs from the higher primates in having a single site of 18*S* and 28*S* rRNA genes (*33, 75*), compared to the multiple sites in the others. Such a redistribution of rRNA sites could also result from a series of reciprocal translocations. Another indication of separation of the gibbon from the great apes is that the gibbon has few, if any, of the DNA sequences the others share with human satellite III DNA (*70*).

The chromosome studies also show that human, gorilla, chimpanzee, and orangutan chromosomes are remarkably similar. Dutrillaux *et al.* (*9*) estimated that 98 to 99 percent of the 500 or so bands observed with the general banding methods are homologous in these four species. However, the studies have reemphasized that the orangutan is more distant from man than are the gorilla and chimpanzee. The orangutan has fewer chromosomes with banding patterns similar to those of the human than does either gorilla or chimpanzee (*27*), and it has no Q-brilliant regions and no terminal Q or C bands (*22, 24*). The orangutan

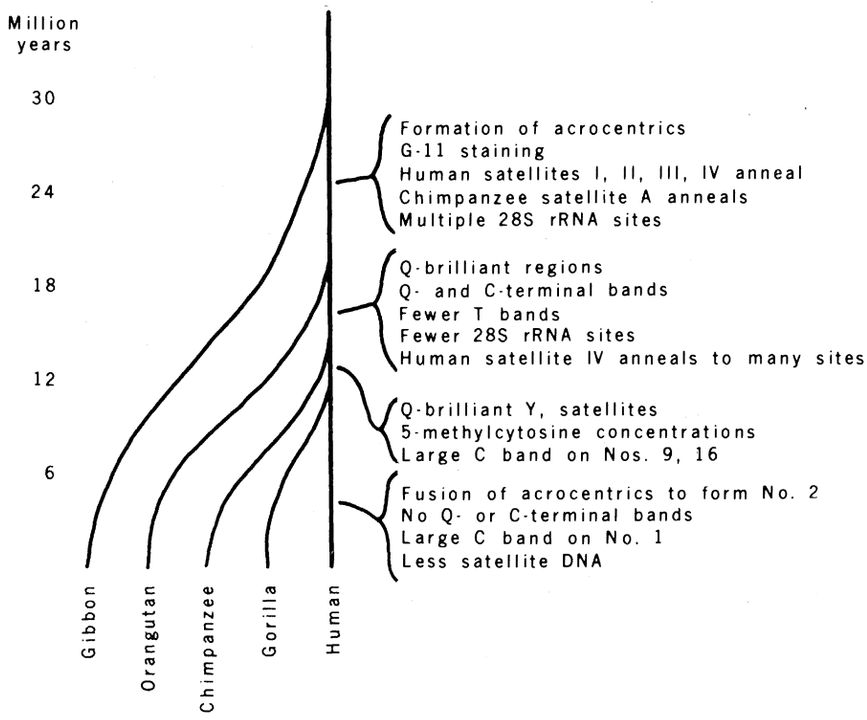

Fig. 2. Diagram of the evolutionary relationships of the higher primates and man based on regional banding of the chromosomes. Pericentric inversions of several chromosomes are associated with each divergence. The time scale (million years) is modified from (*79*). See text for other references.

has a somewhat different distribution of T bands (*22*) and of DNA sequences corresponding to the human satellite IV DNA (*71*), as well as eight rRNA sites compared to a maximum of five in the other species (*20, 75*).

Finally, the studies have shown that the karyotypes of gorilla, chimpanzee, and human are so similar that it is difficult to decide on their relative evolutionary distance. Dutrillaux *et al.* (*9*) suggested that the chimpanzee is more closely related to man than is the gorilla because there are 12 chromosomes they consider to have virtually identical general banding patterns in man and the chimpanzee but only ten in man and the gorilla. Evidence from the more restricted regional banding methods, however, suggests that the gorilla is more closely related to the human than is the chimpanzee. Only the gorilla and man have brilliantly fluorescing regions on chromosome No. 4 and the Y (*30*), a large C band on Nos. 9 and 16 (*11*), and regions with high concentrations of 5-methylcytosine (*41*). The gorilla, but not the chimpanzee, has DNA sequences in common with human satellite II DNA. [However, the orangutan also has DNA sequences in common with human satellite II DNA; therefore, this class of repetitive DNA may be present in very small amount in the chimpanzee (*71*).] Although the chimpanzee resembles the human more closely than the gorilla with respect to the number of 18*S* and 28*S* rRNA sites (*20, 75*), the human distribution of rRNA cannot be derived from that of the chimpanzee as directly as both can be derived from a progenitor with the distribution of rRNA found in the orangutan. King and Wilson (*78*) have reviewed the evidence showing that the proteins of chimpanzee and human are very similar. Further studies of the proteins of the gorilla could provide more information about the relationship of the three species.

Figure 2 is an evolutionary scheme which takes into account the results of the various chromosome banding methods. The proposed order in which the progenitors of the various primate species diverged is: gibbon, orangutan, chimpanzee, gorilla, human. The time interval between the divergence of the gibbon and that of the orangutan is greater than the time interval between the other species. Various evolutionary schemes have been proposed based on chromosome analysis. These agree rather well except for the order of divergence of the gorilla, chimpanzee, and human. Turleau *et al.* (*8*), who constructed a hypothetical R-banded karyotype of a primate progenitor based on the presumptive inversions that separate the primate species, suggest that the progenitor of the chimpanzee and gorilla separated from the progenitor of the human before the progenitors of the chimpanzee and gorilla diverged from one another. Similar schemes have been proposed by other groups (*7, 71*). Dutrillaux *et al.* (*19*), who based their comparisons particularly on the evolution of 2p and 2q in the various primates, including the pygmy chimpanzee, have constructed a scheme in which the gorilla is thought to have diverged before the chimpanzee. A phylogenetic tree based on the extent of reassociation and thermal stability of nonrepeated sequences of DNA from the various species has been proposed by Benveniste and Todaro (*79*); in this scheme, gorilla, chimpanzee, and human are thought to have diverged at approximately the same time. In contrast to these proposals, data derived from the regional banding methods suggest that it is likely that the progenitor of the chimpanzee diverged from the progenitor of the human at an earlier time than did that of the gorilla.

The time scale in Fig. 2 has been modified from that presented by Benveniste and Todaro (*79*). Jones *et al.* (*70*) estimated the maximum age of human satellite III as 25 to 30 million years, that of satellite I as 20 to 25 million years, and that of satellite II as 9 to 12 million years. Sequences common to all three satellites are present in the orangutan, and satellite III, which is the oldest of the three, is not present in the gibbon. Therefore, these three satellites must have arisen during the interval between the divergence of the ancestor of the gibbon and that of the ancestor of the orangutan. In Fig. 2 this interval is about 18 to 30 million years. Although satellite III can be accommodated in this time span, satellite II cannot. That is, either the orangutan would have to have diverged only 12 million years ago, or more likely the age of satellite II would have to be greater than 12 million years.

Comparative studies of the structure and gene content of primate chromosomes are providing detailed information about evolutionary relationships. Correlation of such data with information derived from other disciplines will enrich our understanding of the evolution of man.

Note added in proof: Information on recent gene assignments in primates will be included in the report of the Winnipeg Conference (1977), Fourth International Workshop on Human Gene Mapping. Additional information on nomenclature will be presented in the report of the Stockholm Conference (1977): Standardization in Human Cytogenetics. Birth Defects: Original Article Series, The National Foundation, New York.

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2. The term satellite has been used to describe two different things: (i) the small region or "satellite" on the short arm of an acrocentric chromosome that is separated from the body of the chromosome by a secondary constriction, and (ii) a secondary peak of different average density that appears when the DNA of some organisms is run in a buoyant density gradient, hence "satellite DNA."
3. For convenience in this article the term gorilla will be used to refer to the lowland gorilla, *Gorilla gorilla gorilla*, chimpanzee to *Pan troglodytes*, and gibbon to *Hylobates lar*. In cases in which the mountain gorilla, *Gorilla gorilla berengei*, the pygmy chimpanzee, *Pan paniscus*, or a different gibbon is referred to, this will be indicated specifically.
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27. Paris Conference (1971), Supplement (1975), *Birth Defects: Original Article Series* (The National Foundation, New York, 1975), vol. 11, No. 9. The No. 11 chromosomes of *Pan troglodytes* stained to show R and G bands have been inadvertently inverted in figure 1 of the report. In table 3, the number of the *Gorilla gorilla*

homolog of human chromosome 14 has not been agreed on [see (*40*)] and the corresponding *Pongo pygmaeus* chromosome should read 15, not 16.
28. Measurements have been made on the chromosomes (identified by banding) of the gorilla (*11*) and the chimpanzee (*17*) but not the orangutan.
29. Egozcue *et al.* (*10*) state that the gorilla Y is more metacentric than the human Y owing to a pericentric inversion. Measurement studies show that both arms of the gorilla Y are longer than their human counterparts; the gorilla Y is more metacentric because more material has been added to the short arm of the chromosome than to the long arm (*11*).
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81. H. M. McClure, K. H. Belden, W. A. Pieper, C. B. Jacobson, *Science* **165**, 1010 (1969); R. P. Creagen, S. Chen, F. H. Ruddle, quoted by Ruddle and Creagan (*35*).
82. The joint report (*27*) suggests that the first letter of the generic name and the first two letters of the specific name, for example, HSA for *Homo sapiens*, be used to distinguish chromosomes of various species. This is an awkward nomenclature, and in most circumstances a simple abbreviation which is defined in context is preferable.
83. A number of additional gene assignments, particularly in the gorilla, are listed by D. Warburton and P. L. Pearson [*Cytogenet. Cell Genet.* **16**, 75 (1976)]. Because no supporting data are presented, these have been omitted from Table 2.
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