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THE BABOON IN BIOMEDICAL RESEARCH
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This book is dedicated to Professor William H. Stone, who convinced me to explore the possibilities of genetic research with nonhuman primates at a time when I was committed entirely to mouse and marsupial models; and to Professor Henry C. McGill, Jr., who introduced me to the baboon as a model for research on atherosclerosis and convinced me to direct my genetic interests to questions of biomedical relevance to human beings.

It is also dedicated to the baboons which have contributed so much to the advancement of human medicine and which promise to contribute even more in the future; and to the veterinarians, technicians, and caretakers who ensure that the biological and psychological well-being of these marvelous creatures is maintained through superb medical care and enriched environments.

John L. VandeBerg

Preface

Nonhuman primates have played critical roles in biomedical research, and they are among the few animals whose use in research continues to increase. The scientific value of nonhuman primates derives from their close phylogenetic proximity to man and their consequent anatomic, physiologic, and genetic similarities to man. Only nonhuman primates can provide adequate models for many complex physiological and disease processes of humans.

The baboon is a relative newcomer to the repertoire of nonhuman primates used in biomedical research. However, in less than 50 years since its first use in the U.S., it has become one of the most popular laboratory primate species. It is larger than the other widely used monkey species, making it advantageous for many types of experiments and technological developments. It is extraordinarily hardy and highly fecund in captivity. It closely resembles humans in a variety of physiological and disease processes, such as cholesterol metabolism, early stages of atherosclerosis, and alcoholic liver disease. Its chromosomes closely resemble those of humans, and many genes of the two species lie in the same chromosomal order. Among all primates, baboons are the most widely used models for the genetics of susceptibility to complex diseases and they are the first nonhuman primate for which a framework genetic linkage map was established. In addition, the baboon genome is currently being sequenced, and as a result the utility of this species for biomedical research will be dramatically increased. For all of these reasons, the baboon is certain to continue as one of the premier nonhuman species used in medical research.

This book was preceded by two volumes with nearly the same title, published in 1965 and 1967. Those volumes were compendia of papers from symposia, and they recorded the status of knowledge about biomedical research with baboons in the first several years after the species was introduced into laboratory conditions. The texts were descriptive of the basic characterization that had been completed, and they predicted that the baboon would develop a high level of utility in biomedical research.

That prediction has been fulfilled, perhaps beyond the authors' wildest dreams. The present volume was written to provide an overview of many diverse areas of biomedical research to which the baboon has made and continues to make important contributions. Each chapter reviews the recent literature on the topic, discusses work in progress, and presents the authors' vision of research opportunities and likely future contributions of the baboon model to human medicine.

We thank the authors for their care and diligence in preparing the chapters, which exude their enthusiasm for this unique animal model and its diverse roles in biomedical research. Each chapter in this book was reviewed by at least two referees, which in some cases included one or more of the editors. We appreciate the responsiveness of the authors to the criticisms and recommendations of the referees.

We thank April Hopstetter, Director of Technical Publications at the Southwest Foundation for Biomedical Research, for her key role in preparing the text and figures, recommending editorial revisions and working with the authors to implement them, and advising the editors. Without the persistence and hard work of April and her staff, Maria Messenger and Malinda Mann, this book would not have come to fruition.

Finally, we thank the National Institutes of Health for its strong support over the past 50 years of the many research programs that are reviewed in this book. We are particularly appreciative of the National Center for Research Resources and the National Heart, Lung and Blood Institute for supporting the development and maintenance of the national baboon resource maintained at the Southwest National Primate Research Center (SNPRC) located at Southwest Foundation for Biomedical Research (SFBR). That resource has been essential for many of the research programs summarized in this volume. We especially want to acknowledge a program project grant (P01 HL028972), and the base grant of the SNPRC (P51 RR013986). The program project is in its twenty-sixth year and is responsible for the development of the large, six-generation pedigreed baboon colony on which many research programs depend. The SNPRC base grant is in its tenth year and provides support for the infrastructure required to maintain the baboon resource and for pilot studies which, in many cases, have been leveraged into major biomedical research projects involving baboons. It also supported the preparation of this volume.

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Introduction

John L. VandeBerg

1 Early History of the Baboon in Biomedical Research

The baboon is a relative newcomer to the constellation of primate species used to model the human condition. In the United States, the baboon had its beginning as a research animal in April of 1956 while Dr. Nicholas T. Werthessen, an investigator at the Southwest Foundation for Biomedical Research (SFBR), was visiting a collaborator, Dr. Russell L. Holman, at Louisiana State University School of Medicine. The incident that gave rise to this new primate model was described in an article entitled "The Ape Trade" published in the December 1, 1958, issue of *Time Magazine* (1958).

> Dr. Russell L. Holman and a visitor were putting their heads together at Louisiana State University School of Medicine, pondering problems of heart-and-artery disease, when an assistant offered Holman a gory gift – an aorta, nearly 2 ft. long, full of diseased areas. . .. The aorta had come from a 16-year-old female baboon [that had been maintained at New Orleans' Audubon Park Zoo]. [The importance of] this discovery, made in April of 1956. . . lay in the fact that previously (except for rare cases in monkeys and expensive great apes) no animal had been known to develop arterial disease like a human being's, despite ingenious laboratory tricks.

This serendipitous observation of "spontaneous" atherosclerosis-like lesions in a 16-year-old baboon stimulated the two investigators to examine the baboon as a potential experimental animal for the study of atherosclerosis. After preliminary studies on imported animals, the two institutions cooperated in sending a team to East Africa in July and August of 1958 to secure baseline data on the animals obtained directly from their natural habitat and to develop a system for obtaining the animals in the future. Dr. Henry McGill and his colleagues at Louisiana State University published the results of the survey of vascular lesions in 1960, and important findings on schistosomiasis in baboons were reported a year later (Strong et al., 1961). The first group of baboons was shipped from Kenya to SFBR in 1960

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to initiate the present colony and to develop procedures for managing and breeding this species in captivity.

On September 1, 1958, Dr. Werthessen and Dr. Holman were awarded a 3-year NIH grant entitled "Initiation and Support of a Colony of Baboons". The grant provided support for baboon trapping and conditioning facilities at Darajani, Kenya, and for the maintenance of a baboon colony in San Antonio, Texas. A temporary facility designed to house six baboons was constructed in 1958 at the old site of SFBR, and construction of large permanent cages at SFBR's present site was initiated under support from NIH and from the Texas Affiliate of the American Heart Association.

Dr. Holman died in May 1960, and Dr. Werthessen resigned his position at SFBR in 1961. In the meantime, the Regional Primate Research Centers Program was being developed by the National Heart Institute (Yaeger, 1968). SFBR was considered several times during the formative period of the Regional Primate Research Centers Program as a potential Center, but was not successful in the competition for a Center grant. At that time, SFBR had limited experience in nonhuman primate management and research, and the baboon (the only primate species held there at that time) was not yet established as a valid model species. Nevertheless, the National Advisory Heart Council at its November 1961 meeting recommended "that the Southwest Foundation baboon colonies at San Antonio, Texas, and Darajani, Kenya, be partially supported by the Heart Institute until the Foundation has had time to demonstrate whether or not the baboon would be useful in medical research" (quoted from Yaeger, 1968).

Dr. Harold Vagtborg assumed Dr. Werthessen's position as Principal Investigator on the initial grant in 1961. It was continued for a fourth year of support, until August 31, 1962. On September 1, 1962, a new NIH grant was awarded for 3 years; it was entitled "The Maintenance and Development of a Baboon Colony for Research Purposes". The scope of work was expanded, and a year later a 2-year supplement was awarded to support documentation of the complete histology of normal baboons. That grant concluded on August 31, 1965. On January 1, 1964, another NIH grant was awarded to support baseline studies in embryology, steroid endocrinology, clinical chemistry, and microbiology (including bacteriology, mycology, parasitology, and virology).

Many SFBR staff and visiting scientists contributed to the development of the baboon as a model species for biomedical research in those early years. Collaborating scientists also pursued their own research interests with the baboon through the SFBR facilities in San Antonio and in East Africa, and investigators at other institutions began using baboons as models in biomedical research programs.

The flurry of research activity with baboons in the late 1950s and early 1960s led SFBR to sponsor "The First International Symposium on the Baboon and Its Use as an Experimental Animal" in 1963 and a second symposium on the same topic in 1965. The proceedings of these conferences were published in books entitled *The Baboon in Medical Research*, Volumes 1 and 2 (Vagtborg, 1965, 1967). For the most part, those volumes presented descriptive baseline data that would later provide the basis for the hypothesis-driven research that is characteristic of the chapters in

this book. Following up on the earlier observations of naturally occurring vascular lesions in baboons (McGill et al., 1960; Strong and McGill, 1965), Volume 2 contains a detailed account by Dr. Henry McGill and his colleagues of the experimental induction of atherosclerosis in baboons fed a diet enriched in cholesterol and fat (McGill et al., 1967). Dr. McGill became the Scientific Director of SFBR in 1973 and was instrumental in further developing the baboon as a model for experimental atherosclerosis. In addition, he initiated the pedigreed colony of baboons, which now spans six generations and is maintained by the Southwest National Primate Research Center (SNPRC) located at SFBR.

On September 1, 1965, SFBR was awarded two NIH grants to support continued work on baboons. "Resources for Study of Biological Profiles on Selected Primates" supported the basic baboon colony and the attendant personnel and facilities, and continued until December 31, 1972. "Study of Biological Profiles of Selected Primates" supported the collection and publication of basic data on the microbiology, immunology, clinical chemistry, hematology, and reproductive physiology of the baboon. That grant terminated on August 31, 1971.

In just 15 years since the observation of atherosclerotic lesions in a baboon from the New Orleans Zoo, the baboon had become a well-characterized and validated primate model for research in a wide variety of medical fields. Today, baboons are second only to macaques, which have been used much longer as research subjects, as models for biomedical research. The SNPRC maintains more than 2,500 baboons, the largest colony in the world.

Dr. Harold Vagtborg, the first President of SFBR, explained in 1961 why he believed the baboon had not been developed as a model species prior to the 1950s (Vagtborg, 1973).

> For years, I had been convinced that one of the greatest deterrents to progress in medical research was the use of the wrong animal in experimentation; I felt the baboon would aid rather than deter such progress. We had already uncovered many biological similarities between this primate and man, among them a 1:3 ratio for many biological processes. A baboon, old at the age of twenty-five, possessed many of the physiological characteristics of a seventy-five-year-old man. Moreover, its seven-month gestation period, unique for an animal old at twenty-five, made it an unusually good subject for the study of embryology. All in all, it was a puzzle to me why so little work has been done with this animal as a model for the human. Over the years, my inquiries in this regard have yielded the following explanation: because of the baboon's ferocious appearance, it was discounted by many potential users as being too difficult to handle. A grimace from the baboon can indeed cause a person to fear he is about to be attacked by a reduced edition of a saber-toothed tiger. This analogy is plausible since the incisors of the baboon typically grow to a length of more than two inches; however, we have successfully handled thousands of baboons over the years, with only one incident of a handler's being bitten. Thus, we can honestly support the belief that, with the right handling techniques, there is very little danger involved with using the baboon in experimentation.

In fact, over the years, we have maintained on the SFBR campus approximately 19,000 baboons, most of which were born there, and our employees have experienced few bite or scratch wounds. In our experience, baboons are actually more tractable to handling than are macaques despite their larger size. In addition, they do

not carry herpes B, a virus of macaques, which can be lethal to humans after transmission from bites or scratches. Many other advantages of baboons as the primate model of choice for particular applications are cited in this book.

2 General Characteristics of Baboons

2.1 Taxonomy

The Old World monkeys (Catarhini) used most extensively in biomedical research are baboons (genus *Papio*) and macaques (genus *Macaca*). Baboons and macaques are closely related as indicated by the fossil record, their identical karyotypes, and their ability to produce viable hybrids. Common baboons belong to a single polytypic species, which by the taxonomic rules of priority in assigning species names is appropriately designated as *Papio hamadryas* (s.l.) (VandeBerg and Cheng, 1986; Williams-Blangero et al., 1990). There are five commonly recognized subspecies: sacred baboons (*P. h. hamadryas* Linnaeus, 1758), yellow baboons (*P. h. cynocephalus* Linnaeus, 1766), chacma baboons (*P. h. ursinus* Kerr, 1792), red baboons (*P. h. papio* Desmarest, 1820), and olive baboons (*P. h. anubis* Lesson, 1827). Most of the founders of baboons produced in the U.S. were *P. h. anubis* trapped in East Africa, and the remainder were *P. h. cynocephalus*, also trapped in East Africa.

The systematics of baboons and the geographic distributions of the various baboon subspecies have been carefully analyzed and described (Jolly, 1993). More recently, Newman et al. (2004) assessed the phylogeny and systematics of baboons using mitochondrial DNA sequences from each of the five widely recognized subspecies. The analyses established that olive and yellow baboons form a single monophyletic clade. Apparently, these two groups have undergone substantial introgression across a documented hybrid zone that runs southwest to northeast across Tanzania and Kenya, and are admixed in the wild as they have admixed during breeding in the U.S. The mitochondrial DNA analysis suggested that extant baboons originated in southern Africa and that the five subspecies shared a common ancestor approximately 1.8 million years ago (Newman et al., 2004).

2.2 Reproduction, Growth, and Development

Adult female baboons ovulate year round, with an average menstrual cycle of 33 days (Hendrickx, 1971). This characteristic is highly advantageous for many types of research by comparison with the seasonal reproduction of macaques. The state of ovarian activity can be identified readily by observation of the sex skin, which becomes turgescent for 8–10 days prior to ovulation and deturgesces approximately 3 days after ovulation. The ability to know within a day or two the time of ovulation by simple observation makes the acquisition of timed pregnant females much easier and less costly than with macaques. The female is receptive to sexual advances by the male during the period preceding ovulation. The gestation period averages 175

days. Newborn baboons of both sexes weigh, on average, about 750 grams. Infants of both sexes grow at the same rate until 2.5 years of age, at which time they weigh about 6.5 kg. Thereafter, females grow slowly to attain a weight of about 12.5 kg, and males grow more rapidly to attain a weight of about 22 kg at 6–8 years of age (Snow, 1967). Puberty occurs at about age 3.5 years in both males and females, but males typically do not become useful breeders until 5–6 years of age. In captivity, baboons can live to between 20 and 30 years.

3 Content of This Volume

This volume begins with a chapter on the baboon gene map, the first genetic linkage map developed for any nonhuman primate species. This gene map has been used extensively to localize the genes that affect physiological risk factors of human diseases to specific chromosomal regions. It will be invaluable in the future for identifying genes that affect susceptibility to specific physiological characteristics and diseases, including many that are discussed in this volume.

The next several chapters present the results of decades of research on the basic biological characteristics of baboons: behavior, spontaneous pathology, growth and development, reproductive biology, and microbiology.

Most of the remaining chapters summarize the scientific contributions of baboons as models of human diseases or physiological or developmental characteristics. This volume does not include information on husbandry, enrichment, or handling of baboons. In general, information pertaining to these topics is similar for all Old World monkey species. Details have been provided by Kelley and Hall (1995), Butler et al. (1995), and Adams et al. (1995).

In selecting the topics for inclusion in this volume, the editors attempted to be inclusive of models that have been well developed over many years. However, several topics that the editors had hoped to include are not represented and, during the preparation of this volume, some new baboon model systems have begun to emerge.

Of particular importance among longstanding baboon models not represented in this volume is the schistosomiasis model, which has been developed and used for more than 30 years. Fortunately, the baboon as a model of schistosomiasis infection has been reviewed recently by Nyindo and Farah (1999). Schistosomiasis is a debilitating tropical disease that can have a severe negative impact on growth and development of children and on work capacity of adults. An estimated 200 million people worldwide are infected with the parasite *Schistosoma mansoni*, which is responsible for the disease (World Health Organization, 2006). Some wild baboon populations have endemic infections of *S. mansoni*, and captive baboons can easily be infected experimentally. The clinical disease in baboons closely resembles that in humans. The baboon model is currently being used intensively in efforts to develop a vaccine to protect against *S. mansoni* infection (see for example Kanamura et al., 2002; Kariuki et al., 2006a, b; Siddiqui et al., 2005).

Among the conditions for which new baboon models have begun to emerge during the preparation of this volume are obesity and diabetes. The baboon as a model for obesity was recently unveiled by Comuzzie et al. (2005). The focus of

that group's research is on identifying the genetic determinants of obesity using the baboon gene map for genome-wide searches for susceptibility genes. The initial work on obesity has led to the observation that some captive baboons naturally develop insulin resistance, and a subset of those progresses to metabolic syndrome and type 2 diabetes (Bose et al., 2005; Lopez-Alvarenga et al., 2006; Tejero et al., 2006). An intense effort to establish the baboon as a natural model for type 2 diabetes is now underway.

The baboon already has a rich history of contributions as a model for understanding human states of health and disease. Recently, the baboon has been selected by the National Human Genome Research Institute for complete genome sequencing (see http://www.genome.gov/Pages/Research/Sequencing/AHGFinal04272007.pdf and http://www.genome.gov/10002154). The complete whole genome shotgun sequencing of the baboon genome will be completed during 2009, with all resulting sequencing reads deposited immediately in the appropriate databases of the National Center for Biotechnology Information (NCBI). The assembly and annotation of the complete baboon genomic sequence will follow quickly after the completion of the sequencing phase. The availability of the sequence is certain to greatly accelerate the pace of scientific discovery derived from biomedical research using baboon models.

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The Development and Status of the Baboon Genetic Linkage Map

Jeffrey Rogers, Michael C. Mahaney, and Laura A. Cox

1 Introduction

The genetic linkage map of the baboon (*Papio hamadryas* s.l.) genome was the first linkage map developed for any nonhuman primate (Rogers et al., 2000). It has proven to be a valuable resource for numerous genetic studies using this species. The linkage map enables detailed analysis of locus order and recombination distances within baboon chromosomes, and hence provides the best information to date for studies that compare chromosome structure of baboons to that of other species. A number of investigators have used the baboon linkage map to locate, within specific chromosomal regions, functionally significant genes (quantitative trait loci, or QTLs) that influence phenotypic variation related to human disease. The success over the past several years in mapping QTLs in baboons suggests that this approach to the genetic analysis of complex phenotypes will continue to provide meaningful results. In this chapter we review the initial construction of the linkage map, the types of genetic polymorphisms used, and some of the results obtained. We also present our perspective concerning future directions in linkage analysis using baboons and other nonhuman primates.

2 Early Linkage Studies in Macaques and Baboons

The analysis of genetic linkage and linkage mapping in nonhuman primates has a long history, but for most of that history this line of research has been quite limited in scale and impact. The first published study of genetic linkage in nonhuman primates employed data concerning polymorphisms in carbonic anhydrase genes among pig-tailed macaques, *Macaca nemestrina* (DeSimone et al., 1973). Most of the primate linkage studies that followed involved the pedigree analysis of individual variation in immune responses and the inheritance of the ability to generate specific antibody reactions (Dorf et al., 1975; Maurer et al., 1979). These studies were, for the most part, performed with rhesus macaques (*Macaca mulatta*),

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and primarily involved genes linked to the MHC gene cluster. However, without physical mapping data, it was not possible to assign linkage groups to specific rhesus macaque chromosomes. Later, investigators expanded the breadth of the loci analyzed by investigating polymorphisms in isozymes and other blood proteins (Ferrell et al., 1985). The study by Ferrell and colleagues included long-tailed or crab-eating macaques, *Macaca fascicularis*, as well as *Macaca mulatta*. Several years later, Hackleman et al. (1993) showed that two blood group markers (*G* and *Q*) are linked in rhesus monkeys. We also note that during the 1980s, while some investigators were beginning to use linkage analysis to explore comparative gene mapping in primates, other researchers used somatic cell hybrid methods to generate a different type of information related to the same overall goal of comparative gene mapping (e.g., Creau-Goldberg et al., 1981; Ma, 1984). This included somatic cell hybrid and cytogenetic studies of baboons (e.g., Creau-Goldberg et al., 1982; Thiessen and Lalley, 1986).

The first studies of genetic linkage in baboons analyzed protein polymorphisms in the pedigreed colony maintained at the Southwest Foundation for Biomedical Research (van Oorschot and VandeBerg, 1991; VandeBerg et al., 1991). Working with the same pedigreed baboons, Kammerer et al. (1992) examined the linkage between the C3 and LDLR loci, and between the genes for APOA1 and APOA4. Kammerer and colleagues found strong evidence of linkage heterogeneity among baboon families, such that some baboon sires showed tight linkage ($\theta < 0.05$) between C3 and LDLR, while other breeding males showed little or no evidence of linkage, and strongly excluded the possibility of tight linkage. Linkage heterogeneity had been documented in other mammals, but this was the first such observation in a nonhuman primate.

3 Initial Studies of Microsatellite Polymorphisms in Nonhuman Primates

Genetic linkage analysis in nonhuman primates was quite limited during the 1980s because the types of genetic polymorphisms known at the time, primarily protein or isozyme variants and blood group or other immunological markers, suffered from low levels of heterozygosity. Most of these systems consisted of just two alleles. The number of different loci that could be tested in a given nonhuman primate species was also quite small (for a review of protein polymorphisms in baboons, see VandeBerg, 1992).

During the 1990s, investigators began studying polymorphisms in the single-copy DNA sequences of nonhuman primates through the use of restriction fragment length polymorphism (RFLP) methods (e.g., Rogers and Kidd, 1993). However, those markers also exhibited generally low heterozygosity and thus were not adequately informative for effective linkage mapping (see Rogers, 2000 for a review of RFLPs in baboons).

The ability of researchers to detect and assay highly polymorphic (and hence highly informative) genetic loci in nonhuman primates increased dramatically with

the discovery of microsatellite variation (Litt and Luty, 1989; Weber and May, 1989). Microsatellites were first identified in human DNA sequences (Litt and Luty, 1989; Weber and May, 1989), but soon researchers began testing for these highly informative markers in various nonhuman primate species. Morin and Woodruff (1992) described a set of human microsatellite loci that were polymorphic in chimpanzees. Inoue and Takenaka (1993) cloned and characterized polymorphic microsatellites from Japanese macaques (*Macaca fuscata*), and also showed that those markers were polymorphic in baboons. Other investigators also described useful DNA polymorphisms in primates, with the majority of these analyses involving either chimpanzees (e.g., Deka et al., 1994) or macaques (e.g., Kayser et al., 1995).

After the initial studies by Inoue and Takenaka (1993), the next analyses of microsatellite polymorphisms in baboons used polymerase chain reaction (PCR) primers designed to assay human microsatellites to amplify homologous loci in individual baboons (Rogers et al., 1995). Previous investigators had used this strategy to identify DNA polymorphisms in chimpanzees (e.g., Morin and Woodruff, 1992). However, studies of baboons were the first to perform genetic linkage analyses in nonhuman primates using microsatellites (Rogers et al., 1995). Screening of human microsatellites from specific chromosomes or segments within chromosomes allowed investigators to identify the loci that were likely to be closely linked in the Old World monkeys. Prior studies had compared the karyotypes of baboons and macaques to that of humans (Cambefort et al., 1976; Finaz et al., 1978; Dutrillaux et al., 1979), and thus suggested which chromosomal regions were likely to show similar order among microsatellites across species. Perelygin et al. (1996) used this approach to construct a map that covered much of the baboon homolog of human chromosome 18.

4 Development of the Baboon Whole Genome Linkage Map

The development of the baboon linkage map was significantly accelerated as the result of collaboration among scientists at the SFBR and Sequana Therapeutics, Inc., a biotechnology company located in La Jolla, CA. The collaboration was established in 1993 with the goal of investigating the genetic control of individual variation in bone density among SFBR baboons. One major component of the project was the completion of a genetic linkage map for the baboon genome that would cover all 20 baboon autosomes and exhibit average spacing among loci of less than 10 cM. The resulting map would be able to support the whole-genome linkage analyses designed to search for quantitative trait loci that influence bone density among baboons.

The identification of several hundred human microsatellites that were polymorphic in the SFBR baboon pedigrees and were suitable for effective genotyping in that species was accomplished jointly by Sequana and SFBR (Morin et al., 1998). The genotyping of 331 loci in 694 pedigreed animals was performed by Sequana, and the statistical analyses required to both test the pattern of inheritance of these

markers and construct the initial linkage map were performed by investigators (especially Dr. M. Mahaney) at SFBR.

The initial linkage map (Rogers et al., 2000) covered the 20 baboon autosomes, but did not include the X-chromosome. A total of 293 microsatellite loci, including six microsatellites cloned from the baboon genome by Sequana scientists and 287 human microsatellites that were found to be highly polymorphic in baboons, were placed in unique order along baboon chromosomes.

5 Current Status of the Baboon Linkage Map

Since the termination of the Sequana-SFBR collaboration in 1998, investigators at SFBR have continued to genotype additional baboons, to identify new informative microsatellite loci, to add those new loci to the baboon map, and to improve the quality of the map results through additional statistical analyses of the existing data. As of this writing, 290 additional baboons drawn from the same extended pedigrees originally used for mapping have been genotyped for the full linkage map. In addition, new microsatellite polymorphisms have been identified and incorporated into the growing map.

Figure 1.1 presents the current map. The current sex-averaged baboon linkage map covers 2354 cM, with average spacing of 8.9 cM, and uses data from 984 baboons. An initial map of the baboon X-chromosome consisting of 12 loci is also now available, with more loci to be added (J. Rogers, unpublished data). Additional details concerning the current baboon linkage map, including specific information about each mapped locus (e.g., heterozygosity, sizes of observed alleles, PCR amplification conditions, and other information) are available on the website of the Southwest National Primate Research Center (www.snprc.org).

Among the 20 baboon autosomal chromosomes, the order of loci is conserved between humans and baboons within chromosome 9. The other 11 baboon autosomes show differences in locus order from that found in the human genome, indicating the locations of chromosomal translocations or inversions that occurred in either the baboon or human evolutionary lineage, after the separation of those lineages about 25 million years ago. The current map supports the conclusions of the original map concerning chromosome fission and fusion. In baboons, the homologs of human chromosomes 7 and 21 form a single chromosome. The same is true for the baboon homologs of human chromosomes 14 and 15, and for human chromosomes 20 and 22. The updated map also shows, as did the original map, that human chromosome 2 is divided into two separate chromosomes in baboons, as it is in all nonhuman primates that have been examined to date.

Figure 1.1 shows that the differences between human and baboon linkage maps consist of these chromosome fissions and fusions, as well as simple inversions, complex (multiple) inversions, and occasionally a single locus that maps to different locations in the two species. These differences point toward a partial history of primate chromosome evolution, but the determination of which chromosomal change

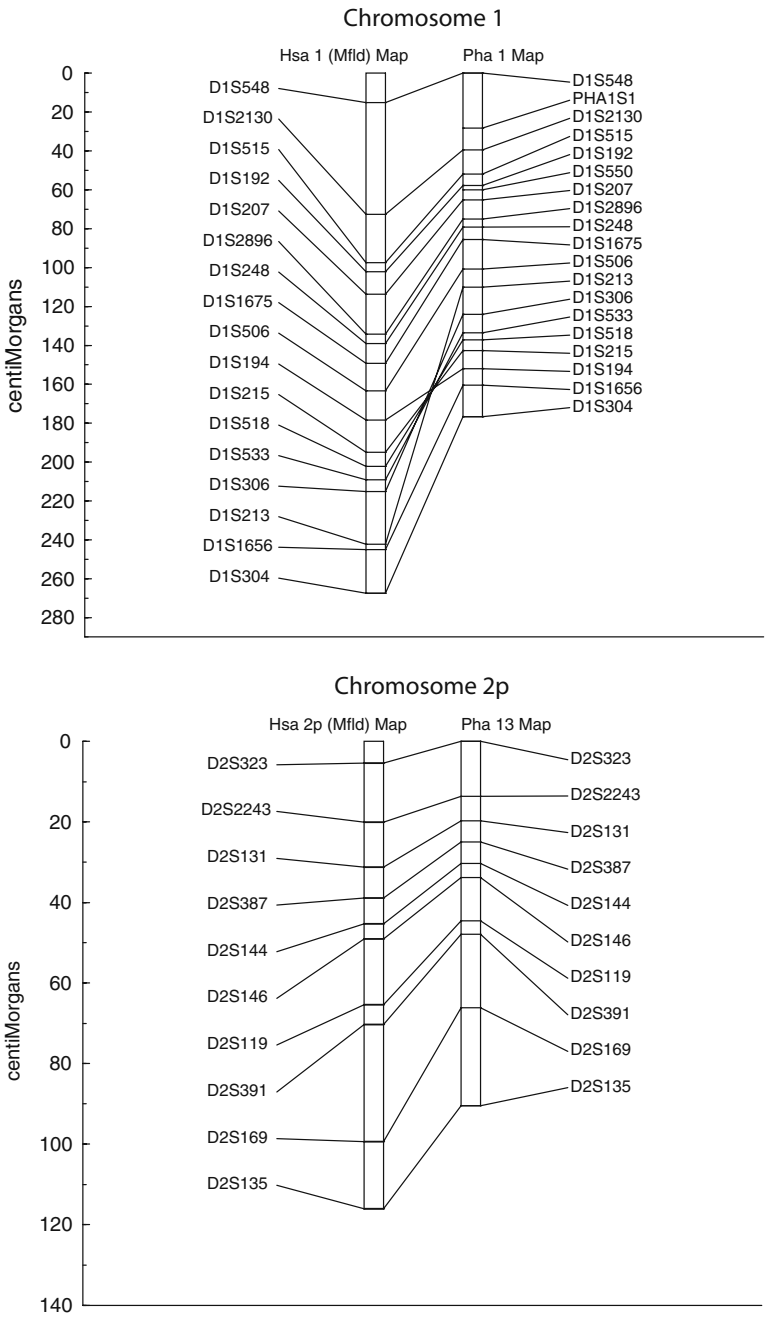


Fig. 1.1 Comparisons of human (Hsa) and baboon (Pha) chromosome maps. For each chromosome, genetic polymorphisms that are mapped in baboon are shown at *right*, and whenever possible the location of the homologous marker in the human genome is shown at *left*.

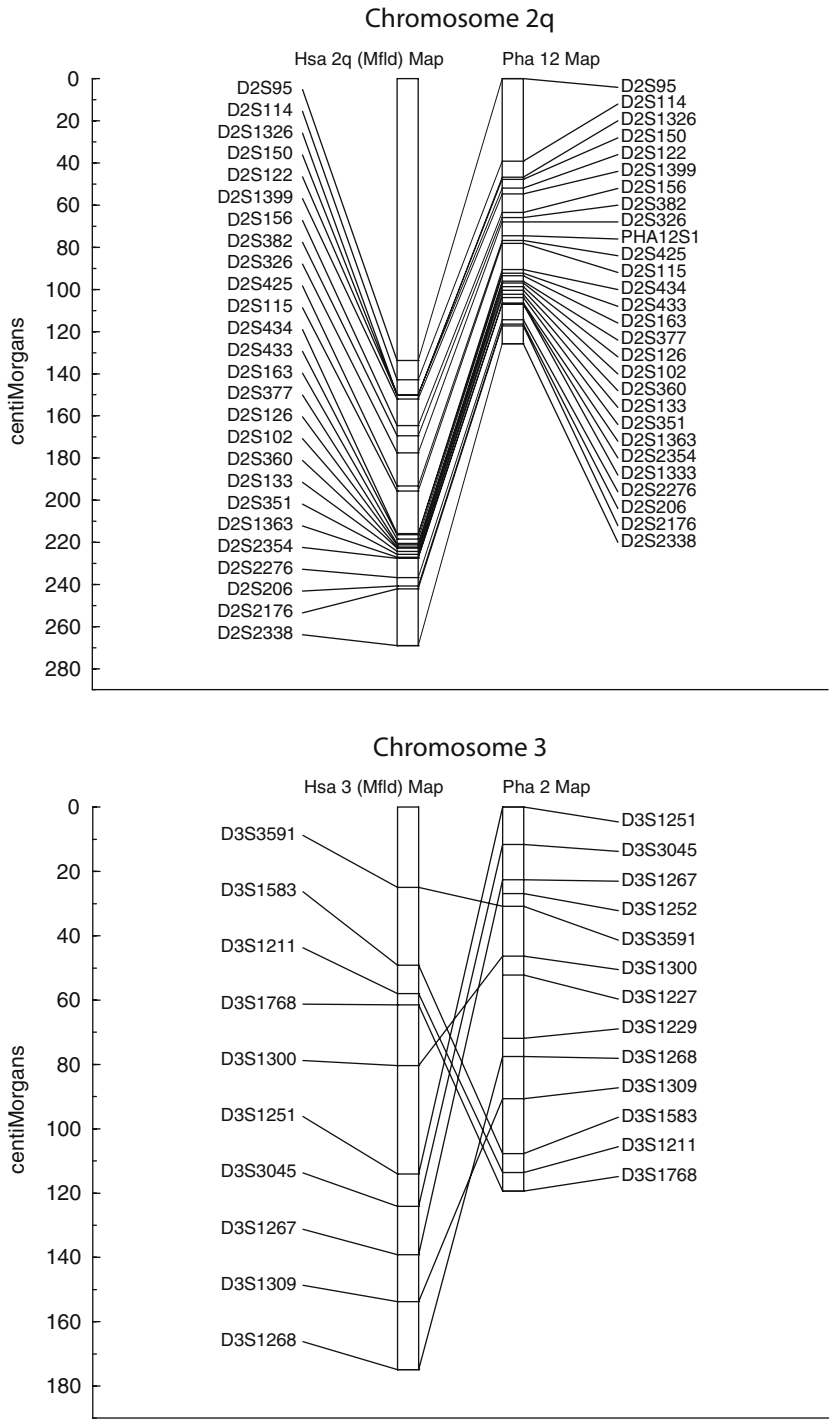
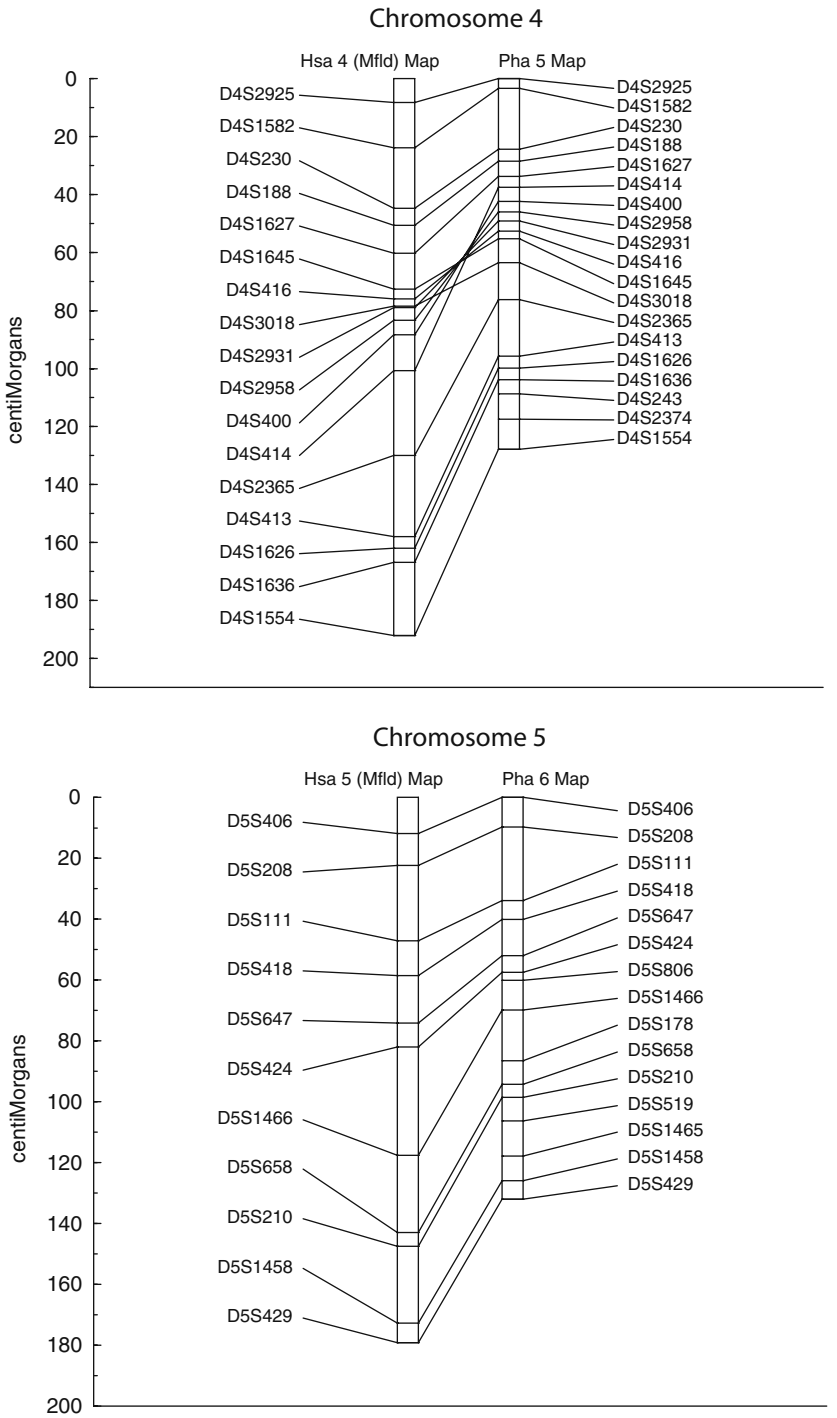


Fig. 1.1 (continued).



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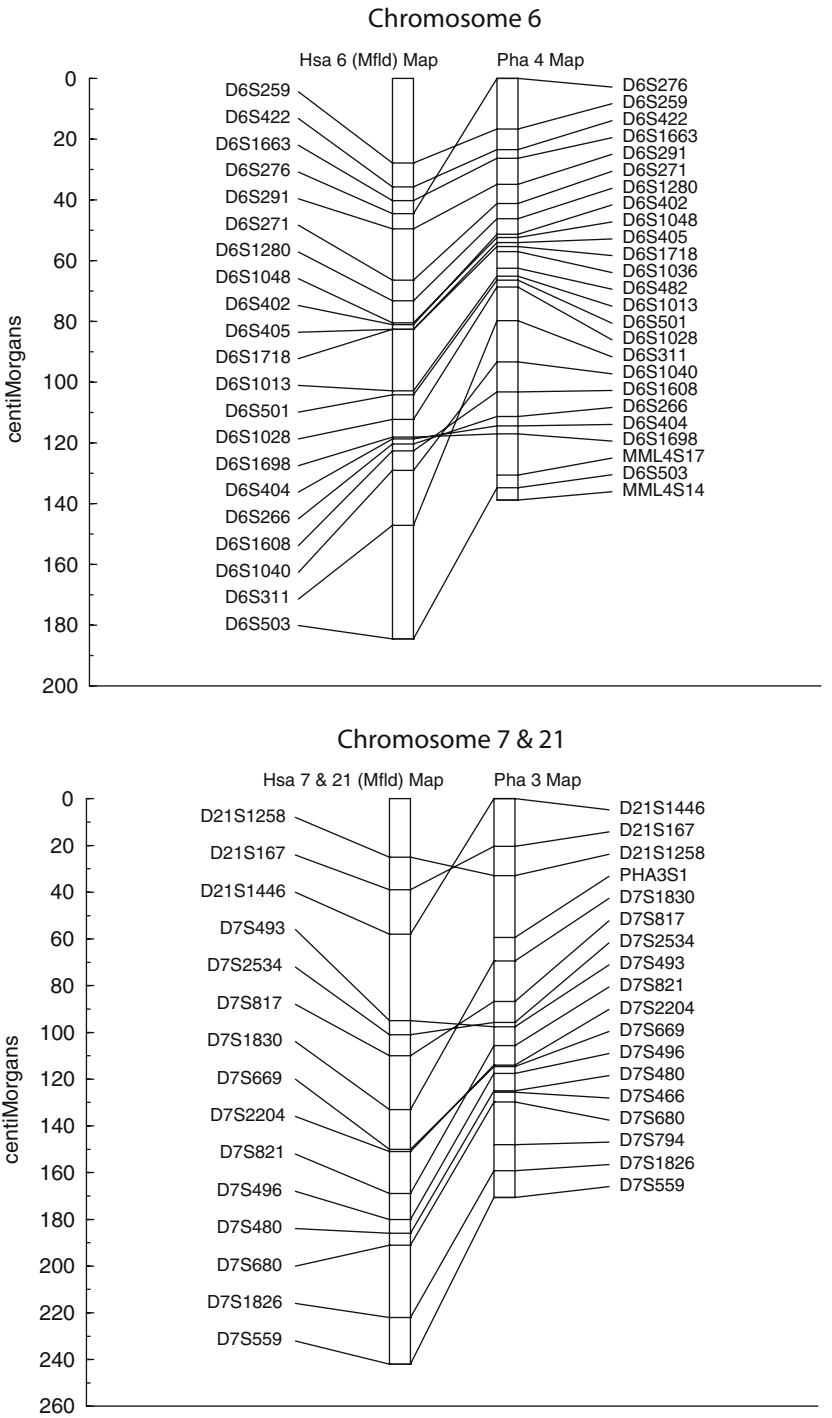

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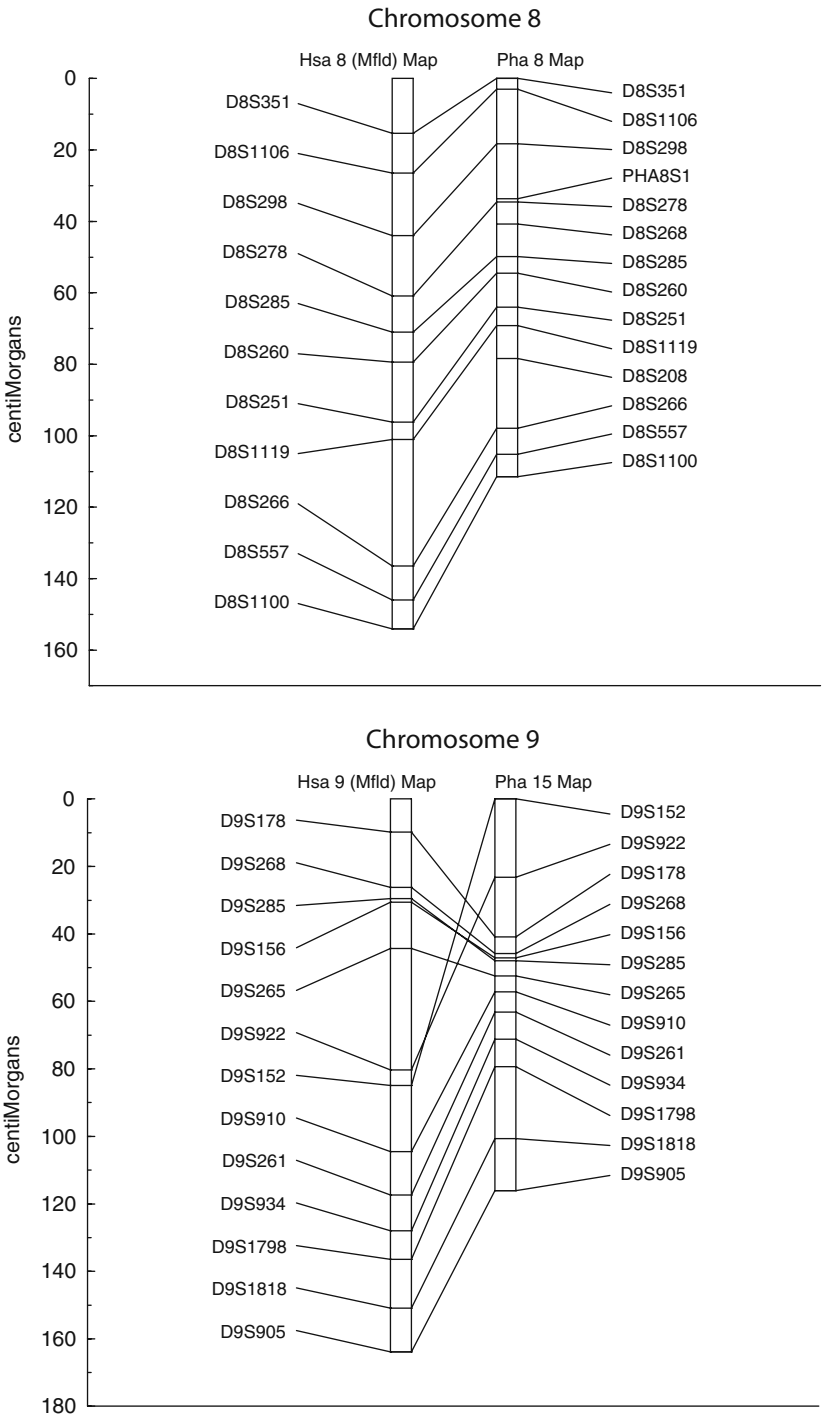

Fig. 1.1 (continued).