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Quantitative Genetic Analysis of Third Metacarpal Morphometry in Baboons (*Papio hamadryas*)

Katherine Christine Park
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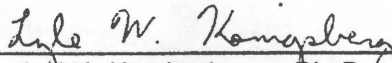
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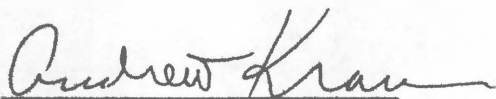
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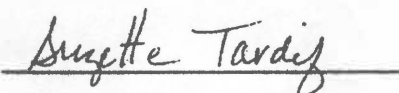
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Lyle W. Konigsberg, Ph.D., Major Professor

We have read this thesis and recommend its acceptance:

Accepted for the Council:

Associate Vice Chancellor
and Dean of The Graduate School

Quantitative Genetic Analysis of

Third Metacarpal Morphometry in Baboons (*Papio hamadryas*)

A Thesis

Presented for the

Master of Arts

Degree

The University of Tennessee, Knoxville

Katherine Christine Park

December 1993

DEDICATION

This thesis is dedicated to the memory of Mary Ann Bass, Ph.D.

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Abstract

Osteoporosis is a very disabling disease in humans, and not until recently with the advent of modern technology has it been researched in a manner beneficial to medical applications. Initially, the use of animals in osteoporosis research served primarily as an avenue for testing and research. Recently the use of nonhuman primates has expanded the research potential for such studies on related individuals more similar to humans. Baboon colonies provide researchers with accessible nonhuman primate populations in which pedigrees can be determined and biomedical studies can be performed. This study is based on 186 hand-wrist radiographs of two baboon subspecies, *Papio hamadryas cynocephalus* and *P.h. anubis*, collected at the Southwest Foundation for Biomedical Research in San Antonio, Texas. The records of the baboons from which the radiographs were taken were arranged into pedigrees. The third metacarpal of each radiograph was digitized on a video analysis system using x,y coordinates at 1.0 mm intervals to establish cortical bone area measurements. Subsequent analysis of these measurements established

first and second moments of area and radii of gyration. Computer analysis using the program "Maxlikh2", similar to Fischer's Fundamental theorem, determined heritability estimates from the measurements along the parameters of the pedigrees for seven quantitative traits. Heritability is a function of degree of genetic inheritance of a complex trait, in this case radii of gyration of cortical bone. Multivariate analysis using variables mean, sex, age, sex/age interaction, and phenotypic variance and yielded heritability and standard error estimates for the quantitative traits kmax, kmin, area, length, subperiosteal-medullary width, kmax\length, and kmin\length. Quantitative traits are significantly heritable. Cortical bone morphology of baboon third metacarpals may provide a methodology for identifying risk factors associated with developing osteoporosis. The study of bone heritability in primates contributes a new application for osteoporosis research. Studies of bone heritability in baboons could lead to the use of such studies as models for human osteoporosis.

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CHAPTER I

INTRODUCTION

Physiological osteopenia (loss of bone) is a common result of the aging process. However, when osteopenia becomes pathological, the loss of bone results in osteoporosis. This pathological loss of bone is not only devastating in human populations, it is also the most prevalent form of disease affecting bone (Dequeker 1989). Dequeker (1989) also refers to osteoporosis as "a silent thief" (p.85), indicating its relationship to bone loss and its initial undetectablility .

The National Institutes of Health (NIH) has defined osteoporosis as an "age-related disorder characterized by decreased bone mass and by increased susceptibility to fractures in the absence of other recogniz-able causes of bone loss'' (NIH Consensus Development Panel 1984: 799). Although this serves as an adequate working definition, it does not provide the medical profession with a method for diagnosis.

The clinical characteristics for diagnosing osteoporosis are fractures detected from radiographs. While fractures induced by osteoporosis are common, the loss of bone mass does not necessarily lead to fracture. Even when bone loss does lead to fracture in the elderly, in the span of a year the chances of subsequent mortality are nearly 20 percent (NIH

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Consensus Development Panel 1984). Without the radiographic evidence of bone fracture, the diagnosis of osteoporosis can be arduous at best. In the absence of trauma to induce fracture, osteoporosis cannot be reliably diagnosed (Raisz 1988). The medical implications of finding a way to determine possible risk factors associated with osteoporosis prior to fracture would be considerable.

Continuing research in osteoporosis reflects the magnitude of concern not only for early detection and diagnosis, but also for reduction in medical costs associated with osteoporosis. The NIH Consensus Development Panel (1984) estimates the annual cost of osteoporosis-related injuries to reach nearly four billion dollars in the United States alone. In elderly individuals, more than 90 percent of all hip fractures will occur in those over the age of 70. Additionally, one third of all females reaching 90 years of age will experience hip fractures, leading to costs exceeding six billion dollars per annum and less than 50 percent chance for full recovery (Resnick and Greenspan 1989). The ecumenical mortality rate of elderly patients experiencing hip fractures is more than 15 percent (Magaziner 1989). Peck et al. (1988: 275) recognize the impact of osteo-porosis in the United States alone: "The frequency of osteo-porosis and osteoporosis-related fractures is expected to increase, because the most susceptible population--the elderly--is expanding." An increase in the elderly population eventuates an increase in medical costs associated with

osteoporotic disorders.

Of all the bones in the body, long bones have a tubular shape and are relatively easy to assess and examine in radiographic form. Of the long bones in the body, some of the smallest are the metacarpals, or the bones which form the palm, articulating with the proximal phalanges of the fingers and the carpals of the wrist. Metacarpals are conventional measurement sites for loss of cortical bone (Garn 1975). Plato and Norris (1980) also use radiographs of metacarpals from human sample populations to analyze loss of cortical bone. Radiographs of second metacarpals have been taken from rhesus monkeys to determine cortical bone loss (DeRousseau 1985).

Nonhuman primates have recently become more common in studies of bone mineral content (BMC), bone density, and bone mass. Nonhuman primates are studied in these areas mainly because both environmental and genetic aspects of such populations can be controlled or closely monitored. This study analyzes hand-wrist (specifically third metacarpal) radiographs from a colony of baboons (genus *Papio*) made available by the Southwest Foundation for Biomedical Research (SFBR) in San Antonio, Texas. For the purposes of this study, these radiographs have been digitized to determine cortical bone size using a computer video analysis system.

The purpose of this study is determining the genetic component of cortical bone size in baboon third metacarpals. Kelly et al. state that "genetic factors are major determinants of adult bone density" (1991: 808). It has also been shown that "genetic influences make a major contribution to variance in adult bone density" (Kelly et al. 1990). Heritability, a key component used in statistical analyses of bone measurement data, has been defined by Krall and Dawson-Hughes as "the proportion of total variance attributable to genetic effects" (1993: 2). In this analysis, it is possible to measure familial resemblances and produce accurate estimates of the additive genetic variance for cortical bone size measurements. One of the objectives in this study is to determine the heritability of cortical bone size in a sample population of baboons (*Papio hamadryas anubis*, *P.h. cynocephalus* and a hybrid of *P.h. anubis* and *P.h. cynocephalus*) of known genetic background (Williams-Blangero et al. 1990).

As with most nonhuman primate studies concerning bone, this study utilizes nonhuman primate data as an approach to model similar processes in humans. Specifically, this study examines cortical bone size in a number of *Papio* subspecies of known genetic background and relates the findings as a nonhuman primate model for determining the heritability of human cortical bone size. Williams-Blangero et al. (1990) have emphasized the importance of distinguishing subpopulations of baboons in

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biomedical research. In their study of polymorphic protein loci, genetic distances between baboon subspecies were statistically significant, supporting experiment designs structured with regard to subpopulation types. Failing to distinguish between subpopulations across experiments could lead to skewed statistical parameters and incompatible repeated experimented results. Consequently, Williams-Blangero suggest the designation of *hamadryas* for all *Papio* species, and the above-mentioned subspecies. The original taxonomic classification of baboon species dates back to Linnaeus' original designation of *P. hamadryas* for the long-tailed baboon (1758).

Eight quantitative traits are examined for six effects. The traits of quantitative bone size analyzed are kmax and kmin (radii of gyration), area, length, subperiosteal and medullary width, and three functional aspects of these traits, kmax / length, kmin / length, and kmax / kmin. Kmax / kmin is used for its mechanical convenience in determining the distribution of cortical bone and the consequent strength or fragility of the bone. Maximum likelihood estimates for six parameters describing these traits and functional aspects are estimated, including mean, sex, age, sex and age interaction, phenotypic variance, and heritability.

To thoroughly examine traits and functional aspects of cortical bone, particular issues inherent in this study must be resolved:

1.) What is the relationship between the functional properties of bone analyzed and their relevance to osteoporosis studies? 2.) What are the distributions and associations of the proportion of observed variance of cortical bone size with regard to heritability, sex, age and environment?

CHAPTER II

REVIEW OF LITERATURE

Evaluating the effects of quantitative traits obtained from baboon metacarpals and their relevance to osteoporosis-related studies is best understood with background information reviewing the pertinent literature. During the preparation of this study, several areas were reviewed: epidemiology of osteoporosis; histology of cortical bone; bone mass, measurement, and loss; nonhuman studies; *Papio* studies; hormonal and environmental effects on bone; and quantitative genetics. The relevance of each topic to this study is discussed in separate sections within this chapter.

EPIDEMIOLOGY OF OSTEOPOROSIS

As discussed above, osteoporosis-related injuries are common in the elderly, difficult to diagnose, potentially fatal, costly, and expected to become more common with the growing elderly population. Clearly the presence of osteoporosis needs to be diagnosed early (prior to fracture), and, more importantly, accurately. This situation necessitates a meth-

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odology for early diagnosis of osteoporosis and of those susceptible to pathological bone loss. The first step in this multi-faceted process requires an understanding of the properties of osteoporosis at the cellular level.

Among the components necessary for bone formation, four account for most of the bone matrix (Woolf and Dixon 1988): collagen (made by fibroblasts and osteoblasts), mucosaccharides, osteocalcin and bone minerals (primarily calcium and phosphorus). The bone multicellular unit (BMU) is composed of osteoids, osteoblasts and osteoclasts operating in unison.

If the rate of bone absorption is greater than that of bone formation and is unregulated by the BMU, the result is osteoporosis. Osteoporosis results in less bone mass, thus weaker bone. The dense, compact bone on external bone surfaces and in bone shafts is cortical bone, which makes up approximately 80 percent of the bone in the skeleton (Wahner 1987). Cortical bone becomes very porous with osteoporosis, and haversian canals which facilitate passages for nerve fibers, blood, and lymph (White 1991) become wider.

The properties of bone discussed above referred to the presence of cortical bone in bone shafts. The structure of long bones is divided into three primary parts relative to ossification centers: the epiphysis (articular surface at both ends of the bone); the diaphysis (center portion of bone or

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bone shaft); and the metaphysis (layer of cartilage between the epiphysis and the diaphysis). Cortical bone appears along the bone shaft, and extends roughly from the end of one epiphysis to the beginning of the other epiphysis. Bone is a dynamic organ, undergoing modeling during growth and remodeling (or continual change) after growth. To look at bone at any given stage of modeling or remodeling, radiography provides a comparably inexpensive, convenient, and accurately quantifiable means of analyzing cortical bone size.

Cortical bone undergoes endochondral ossification, or ossification antedated by cartilage, which is flexible and composed primarily of collagen. After long bones have reached their final stage of growth, they have undergone appositional growth (enlargement of shaft diameter) and lengthening of the shaft (the primary growth center). The overall density of bone at this stage is at best an inaccurate indicator of bone loss in adults. Undetected bone loss occurs primarily because only cortical bone can clearly be seen on radiographs, and loss of cancellous bone occurs long before it can be detected by radiographs. Riggs and Melton (1986) estimate that the peak level of cortical bone mass is reached by the time an individual is between 30 and 40 years of age, and the reduction of cortical bone begins shortly thereafter.

Clinically, osteopenia occurs when bone mass is below normal and fracture has not occurred, and does not indicate causality of osteoporosis

(Scheider 1984). Many authorities in the medical field use the term osteoporosis only when fracture has already occurred. Factors associated with osteoporosis are primarily interpreted as the amount of 'normal' bone mineralization reduced to a level conducive to fractures without the necessity of external catalysts such as trauma, including circumstances where fracture has occurred given undetected bone loss. With the exception of hip fractures, osteoporotic fractures in long bones respond favorably to orthopedic treatment, usually with complete recovery of both function and form. Although this information appears promising, osteoporosis continues to be increasingly common, painful, costly, fatal, and difficult to diagnose prior to fracture. It should be noted here that although there are two types of osteoporosis (Type I, or post-menopausal, and Type II, senile or age-related osteoporosis); the author, unless specifically stated, uses the term osteoporosis interchangeably for both types (following Raisz et al. 1989).

Osteoporotic fractures occur most frequently in the hip, humerus, vertebrae, and distal forearm (Cummings et al. 1985). The significant health impact of osteoporotic fractures is reflected in the 20 percent mortality rate of individuals experiencing hip fractures. Avioli (1991) views the increase of hip fracture incidence (about 40 percent per annum in the United States) as an indicator of osteoporosis-related disorders. Approximately 80 percent of all hip fractures occur in women, and after

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the age of fifty, white women experience approximately twice as many osteoporotic hip fractures as white men (Cummings et al. 1985). With the increase in hip fractures, an increase in medical costs can also be expected. The high incidence of osteoporosis-related injuries and health problems will only increase the costs associated with such injuries, not to mention the pain and suffering of affected individuals. Until the age of 75, white women in the United States and Europe are affected most commonly by distal forearm osteoporotic fractures (or Colles' fractures). Colles' fractures are only to be surpassed by hip fractures in ages greater than 75 (Cummings et al. 1985). The incidence of Colles' fractures in men is fairly constant at approximately eight percent from ages 45 to 85 (Cooper 1989).

Of the vertebral fractures, all are either complete compression fractures or partial deformities causing loss of height of vertebral bodies (wedge fractures). The majority (60 percent prevalence) of vertebral fractures occurring in women over 75 in the United States and Europe (Cooper 1989) are wedge fractures. These fractures can occur without trauma, and if trauma is involved, it is frequently induced by minimal catalysts, such as coughing (Parfitt and Duncan 1982). Cooper (1989: 755) states that the risk factors for osteoporotic fractures for individuals depends upon "the peak bone mass ...attained at maturity, and its subsequent rate of loss." Given the present and forecasted prevalence of

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osteoporosis-related injuries and health problems, accurate prediction, prevention, diagnosis prior to fracture, and health care implementation are all going to be imperative.

HISTOLOGY OF CORTICAL BONE

The cortical bone of physically mature individuals consists of lamellar bone, rather than immature or woven bone. Layers of homogeneous lamellae (collagen fibers) accumulated slowly produce both trabecular and cortical bone. Being more dense and less porous than trabecular bone, cortical bone cannot obtain essential nourishment from available marrow spaces or surface blood vessels. Instead cortical bone receives nourishment by means of haversian systems (White 1991).

Haversian systems are the central structural units of cortical bone. Within the haversian system exists an haversian canal, providing a passageway for lymph, nerve fibers, and blood, the latter supplying the nourishment for cortical bone. Both cortical bone formation and maintenance rely primarily on three cell types: osteoblasts (cells that form bone); osteocytes (cells that maintain bone tissue); and osteoclasts (cells that remove or resorb bone tissue).

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Bone is a dynamic tissue, and its formation continues throughout life. Garn et al. (1975) have found that bone growth continues up to and past 80 years of age. One aspect of this continual formation occurs at the cellular level and is referred to as remodeling. Bone remodeling can maintain bone shape through the resorption of bone tissue by osteoclasts and placement of new bone tissue by osteoblasts. The balance of these two processes also allows bone to exhibit plasticity, or the ability to change shape.

Any bone remodeling must occur on the foundation of original or preexisting bone (White 1991). This is because bone, during growth, is produced at a rapid pace and the matrix calcifies quickly, eliminating any possibility of augmentation of bone tissue from within the preexisting tissue (White 1991). Kelly et al. (1991) suggest that bone remodeling is the primary metabolic process occurring in adults (rather than bone modeling which is prevalent during bone development). Dequeker (1989) also suggests that osteoblasts could be the "target cells for oestrogens" (p. 86). Parfitt (1982) proposes that post-menopausal women suffering from osteoporotic fractures may not experience sufficient osteoblast "recruitment" or osteoblast "stamina" (p. 5). Thus, they exhibit an inability to compensate for resorption. An understanding of bone mass, measurement, and the remodeling process provides a better opportunity for understanding the underlying processes and causes of osteoporosis.

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BONE MASS

Review of Terminology

Before beginning a review of the development, measurement, and loss of bone, a clarification of the terminology used in this study is addressed. Bone mass refers to the quantity of matter forming a bone of indefinite shape or size. Bone density, in most osteological applications, refers to bone mass per area. In literal terms bone density would refer to bone weight per unit of volume, or grams per cm^3. However, in many anthropological studies, the measure of bone volume is not an available option. Bone mineral content (BMC) is literally the measurement of the content of bone minerals per grams of bone measured, or a cross-section of bone measuring mineral content in grams per centimeter. Bone mineral measurements of this type can be done using single-photon absorptiometry (SPA). In dual-photon absorptiometry, bone area is extrapolated , measuring true area as grams per cm^2. The term cortical bone size is used in the first two chapters of this study to simplify a complex description of the functional properties inherent in cortical bone, which will be addressed in the following chapter.

Development and Growth

The determination of heritability of bone size can best be understood with an examination of what constitutes bone mass, how it is measured, and how it is lost. Both trabecular and cortical bone contribute to the strength and mass of bone. Each individual bone has a fundamental proportion of trabecular and cortical bone components (Cummings et al. 1985). As mentioned earlier, about 80 percent of all bone in the body is cortical bone. Vertebrae are composed mostly of trabecular bone, while long bones are no less than 90 percent cortical bone (Crilly et al. 1981). Riggs et al. (1986) assert that conditions that cause rapid bone loss usually affect trabecular bone faster than cortical bone. This is due primarily to the fact that trabecular bone is more susceptible to influences of metabolic processes, including estrogen level changes. During childhood and adolescence, bone mass increases greatly, then plateaus between the ages of 30 and 40. Stevenson (1988) suggests that adult peak mass is reached by the conclusion of linear bone growth.

Environmental Effects

Environmental effects on peak bone mass such as exercise and diet are not well understood. It is clear, however, that malnutrition, physical stagnation, or intercurrent illness impede attainment of peak bone mass (Stevenson 1988). In severe cases, extreme amounts of exercise can

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actually decrease bone density through hypothalamic disturbance. During childhood and adolescence, it is unclear whether addition of calories or exercise beyond levels sufficient for general growth and well-being increase bone mass.

As previously stated, women lose bone mass faster than men after the age of fifty, which is the mean age of menopause (Worley 1981). Chow et al. (1987) indicate that moderate increases in exercise not only increase bone mass, but also preclude menopausal and age-related bone loss. Zhang et al. (1992) found that "perimenopausal women with more physical activity have significantly higher BMD when other determinants of BMD are taken into account" (p. 737). In addition, Stevenson et al. (1989) observed that neither dietary calcium intake nor family history had any effect on bone density.

Age, Sex, *and Summary of Effects*

It is evident that sex, age, and achieved peak bone mass are all factors affecting observed bone mass. One of the predominant factors affecting bone mass is age. In a study on differential changes in bone mineral density, Riggs et al. (1981) found that the most prominent effect in both sexes on BMD was age. After the age of fifty, gender distinctions become significant, evidenced primarily in the long bones of women. When within normal, healthy ranges, environmental factors such as

exercise and nutrition have little observable effects on peak bone mass. Hormonal factors that may affect bone mass, especially in pre-, peri-, and post-menopausal women are discussed below.

Hormonal Factors

Hormonal influences on bone mass in men and women are reviewed at this point, as some of these aspects are considered influential in bone mass and osteoporotic cases. Most studies of osteoporosis and bone mass focus on twins or female subjects. Obviously, most twin studies are focused on genetic aspects of bone mass. Studies isolating women are by the same token interested in hormonal effects on bone mass and osteoporosis associated with pre-, peri-, and post-menopausal hormonal fluctuations and changes. There are few studies concerned with hormonal aspects of bone mass and osteoporosis in men, mostly because of the relatively low incidence of osteoporotic-related injuries in men when compared to women. However, a few studies incorporating men in the examination of bone mass will be discussed.

It has been noted that hormonal effects contributing to osteoporosis may be heightened in women (as opposed to men) due to their more delicate and fragile skeletal structure (Dequeker 1989). Graham et al. (1979) emphasize that after the discontinuation of menses, several changes in hormones occur. Of these changes due to ovarian failure,

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noticeably low serum levels of progesterone and estradiol cause a decrease in their ratio to estrone. It is the deficiency of progestogen/estrogen that contributes to the aging affects of loss of bone mass in women. However, not all post-menopausal women will necessarily suffer osteoporotic fractures, because some experience less severe estrogen deficiency and have greater initial peak bone mass. The decrease in the secretion of progesterone "allows cortico-steroids to exert their action fully on bone" (Dequeker 1989: 87). This sug-gests the interaction of progesterone and cortisone, along with the deficiency of estrogen, contribute to the majority of hormonal effects on bone mass.

Nilas and Christiansen (1988) observed that the rate of bone loss was significant prior to menopause, and that this loss was significantly higher after the menopause. In post-menopausal women , it has also been found that fracture and non-fracture sites on the skeleton have a significant difference in bone mineral densities, with fracture sites having the lower densities (Nordin et al. 1988). Another study revealed that there is insignificant change in BMD in pre-menopausal women and a quick decrease in BMD in post-menopausal women (Sambrook et al. 1987).

Raisz (1988) states that the main hormonal results of menopause on women's bone mass is an increase in bone resorption coupled with a smaller increase in bone formation, resulting in a decline in bone mass.

The hormone primarily associated with this result is estrogen. Further studies indicate that this effect passes from mother to daughter. From a study of 95 premenopausal women and their daughters, Tylavski et al. (1988) found h^2 estimates in the distal radius of 0.80 and 0.56 for bone mineral content (BMC, measured as g cm^{-1}) and BMD, respectively. Lutz (1986) conducted a similar study, and concluded that mothers with low radius BMC are inclined to have daughters with low radius BMC, evidenced by high heritability estimates. Seeman et al. (1989) also found that pre-menopausal daughters of women with post-menopausal osteoporosis have significantly lower bone mass than women of the same age whose mothers do not have post-menopausal osteoporosis. Furthermore, Seeman and colleagues suggest that post-menopausal osteoporosis may be partly due to a predisposition to relatively low peak bone mass.

Worley (1981: 204) contributes the following to estrogen deficiency in women and its effects on bone mass:

> ...removal of functioning ovaries from women before age 45 leads to earlier loss of bone mass than if the ovaries remain intact. Furthermore, the degree of bone loss is dependent principally upon the time elapsed since oophorectomy or spontaneous menopause.

Stevenson (1988) supports Worley's conclusion with findings indicating bone loss is high immediately after natural menopause, and even higher in women who have undergone oophorectomy. Although Stevenson et al.

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(1989) found that genetic factors are highly significant in determining peak bone mass, it was also established that in any given site , the largest effect on bone density was menopause. However, this does not negate the effect of genetic influences on bone mass; rather, it emphasizes that the familial link between mothers and their daughters is expressed both in bone mass, and in hormonal effects of menopause on bone mass.

Androgen deficiency may have similar effects on bone mass in men as noted by Foresta (1985) and Riasz (1988). These studies suggest that androgen deficiencies increase the incidence of osteoporosis in men. However, such sex-hormone deficiencies are not the only determinants of osteoporosis. Other studies indicate that aging effects of hormonal changes in men may contribute to a decrease in bone formation but that they do not affect bone resorption (Francis et al. 1989; Kelly et al. 1991). Meier et al. (1984), in a study of bone loss in men, indicate that as healthy men age, they exhibit a substantial decline in vertebral BMC, but Meier and colleagues did not indicate any hormonal factors involved. Christian et al. (1989) found that their low h^2 estimates for bone mass loss in men can be attributed to an emphasis on environmental influences.

Genetic Factors

Stevenson et al. (1989: 926) conclude that "genetic influences are an important determinant of peak bone mass." Smith et al. (1973) further state that the variance of bone density is significantly less in homozygotic twins than in heterozygotic twins. It has also been suggested that parents and their adolescent children have significantly similar bone densities (Chesnut 1988). Kelly et al. (1991) assert that genetic factors are primary determinants of bone density in adults, and that bone density is directly related to bone resorption and formation. Many studies focusing on families and twins elicit a sound genetic effect on the bone densities of adults (Dequeker et al. 1987; Evans et al. 1988; Lutz 1986; Moller et al 1978; Pocock et al. 1987; Seeman et al. 1989; Smith et al. 1973). Pocock et al. (1987) found in their study of twin pairs (with separate analysis of premenopausal twin pairs) "a strong genetic component to the determination of bone mass" (p. 709). Smith et al. (1973) and Moller et al. (1978) found that particularly in the peripheral skeleton, the determination for the quantity of cortical bone is a direct result of genetic factors.

Dequeker et al. (1987) estimated the heritability (h^2) value of cortical bone mass at 0.75 in their adult sample, suggesting a significant heritable component to cortical bone mass. The h^2 value in the younger sample was 0.47, exhibiting a heritable component; the authors suggest

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differential environmental influences have a more pronounced effect in this age group. Relatives of osteoporotic patients have been found to have lower mean bone mass than in individuals without osteoporosis identified in relatives (Evans et al. 1988). A unique longitudinal study on the loss of mass and bone density in aging male twins found within-family factors to play a significant role in bone mass and bone mass loss (Christian et al. 1989). Gardsell et al. (1989) also found evidence in the axial and appendicular skeleton for a genetic component. Krall and Dawson-Hughes (1993) found bone density to be strongly correlated with familial aspects, even after site- and case-specific environmental factors were controlled. Heritability estimates of bone mass suggest that a genetic component has an apparent and observable effect on bone mass (Table II.1).

Table II.1. Bone mass heritability results form other studies.

Study Authors	Aspect of Bone Measured	h^2
Christian et al. (1989)	radial mass	0.50
	radial width	0.76
Krall and Dawson-Hughes	total body density	0.69
(1993)	radial density	0.51
	femoral neck	0.70
Pocock et al. (1987)	lumbar BMD	0.92
	femoral neck	0.73

Note: All h^2 estimates are significant at ($P < 0.05$).

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BONE MEASUREMENT

Current Techniques

Noninvasive bone methods have progressed steadily with technological advances. Many noninvasive methods are used to measure BMC and BMD, but are not necessarily appropriate for many aspects of bone measurement. Some of the prominent methods of noninvasive bone measurement include radiographic morphometry, radiographic photodensitometry, single-photon absorptiometry (SPA), dual-photon absorptiometry (DPA), and quantitative computed tomography (QCT), (Mazess 1989). Heaney et al. (1989) present detection of osteoporotic overall bone fragility instead of bone mass through ultrasound transmission velocity. Many of these methods are used to directly analyze osteoporosis or its prediction. Specific site studies provide information on, and recommendations for, direct measurements at high-risk locations (Barentsen et al. 1988). Some site-specific studies even suggest that measurement at one site can predict situational bone mineral aspects at other sites (Manicourt et al. 1981).

Bone Mineral Content and Density

Recently, the Food and Drug Administration has required the measurement of spinal bone mineral content in evaluating the treatment and/or prevention of osteoporosis (Riis and Christiansen 1988). Nordin et al. (1987) used densitometry to screen for osteoporosis, and found peak density to be the main predicting factor. Many studies using noninvasive measurement techniques are concerned with BMC, and measure such aspects as calcium, zinc, copper, and iron (Lei and Young 1979). Vogel et al. (1988) summarize some recent techniques and conclude that BMC relates to the risk of osteoporotic fractures. Some studies have used noninvasive techniques to clinically diagnose osteoporosis through BMC measurements. The units of measurement in BMD analyze mass per volume (density), rather than content, examining particular bone minerals or cortical index, the ratio of the total density to that of cortex thickness (Wahner 1983). One study on the detection of prefracture osteoporosis using bone mineral absorptiometry concluded that it is not so much the measurement technique that is important, but rather the site of measurement (Ross et al. 1988).

Bone density measurements relate to bone mass, but not to the quality of bone, making a diagnosis between metabolic bone diseases such as osteomalacia and osteoporosis clinically inadmissible (Alhava 1991). Although the noninvasive bone measurement techniques men-

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tioned above focus on current osteoporotic inquiries, they also apply to past problems.

Bone Mass

Bone mass measurements are taken primarily for their diagnostic and predictive possibilities. Although bone mass is not the only determining factor for predicting fractures, it provides an easily accessible means for measurement both in the clinic and in research. It is commonly accepted that as bone mass decreases, fracture risk increases (Chesnut 1988). Many of the current measurements mentioned above are limited in their application. QCT and DPA measure bone mass in the axial skeleton, and require large amounts of money, time, and space.

SPA only measures peripheral bone mass and cannot be used to accurately predict bone mass in the axial skeleton (Cosman et al. 1991). Furthermore, QCT can frequently overestimate bone loss and can only be used to measure trabecular bone. Radiographic Absorptiometry (RA) measurements are relatively easy to perform, inexpensive, and less time consuming. When radiographs are used in conjunction with computer-controlled digitization and scanning, RA measurements provide widely-accessible and accepted methods of bone mass measurement with low radiation exposure.

Since peak bone mass has been determined as significant in the occurrence of osteoporosis and osteoporotic fractures, research and clinical use for screening analysis are becoming increasingly important (Fogelman 1989). Measurement of bone mass at specific sites is one aspect of current osteoporotic fracture risk studies that is also increasingly common. One reason for specific site measurement is that the correlations between specific measurement sites and bone mass are higher than the correlations between particular site's rates of bone loss (Slemenda et al. 1988).

BONE LOSS

It has been established that as age increases, bone mass decreases, and with decreasing bone mass the risk of fracture increases (Ott et al. 1987). Vaananen (1991) asserts that during and after the fourth decade of life, bone mass begins to decrease from achieved peak bone mass. Moreover, most sex differences in age-related bone loss are attributable to decreased bone formation in men and increased bone resorption in women (Vaananen 1991). Specifically, age-related changes in bone loss relative to cortical bone consist of cortical thinning due to endosteal resorption.

In a study of long-term bone loss in men, Slemenda et al. (1992) found that along with genetic factors, cigarette smoking and alcohol con-

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sumption contributed to bone loss. They further concluded that the significance associated with exercise and bone loss should be cautiously regarded, since individual exercise history and exercise habits observed under research conditions may vary. It is commonly accepted that bone loss, whether attributable more to bone resorption or decreased bone formation, is the primary cause of osteoporosis. Furthermore, bone loss has been shown to be indirectly related to peak bone mass. Pollitzer and Anderson (1989) performed a comprehensive study of bone loss, including four major determinants: hormonal factors, dietary factors, physical activity, and ethnic-genetic factors. They conclude that environmental factors such as diet and exercise exhibit modulating effects on bone loss. More significant are their findings on ethnic factors; both menopause-related and age-related bone loss occur across several ethnic groups, including both black and white populations. Their most convincing findings suggest a significantly strong hereditary contribution to bone mass and loss.

Studies on Rats and Nonhuman Primates

Before beginning a review of nonhuman studies, it should be noted that especially in primates there is considerable life history variation. Harvey and Clutton-Brock (1985) reported a comprehensive study of life history variables in primates, including age at sexual maturity and length

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of estrous cycle. Any variations may have effects on findings of different genera and species studies, and although noted by the author when reported in specific studies, these variations should be kept in mind throughout the review.

Although only primates experience menopause, rats provide an accessible means to measure bone mass. In their study, Safadi et al. (1988) used both CT and SPA techniques to measure vertebral bone loss with age in female rats. Both measuring techniques appeared equally able to determine BMC. However, since female rats do not experience bone remodeling, this study is not pertinent to the post-menopausal model. The remaining reviews in this section consolidate several non-human primate studies dealing with both New and Old World primates.

An SPA study was performed on rhesus monkeys by Aguilo and Cabrera (1989) to model effects of osteopenia in humans. This study reasserted that age has a differential effect on trabecular and cortical bone. Aguilo and Cabrera also found that osteoporosis results in more hip fractures; consequently, a higher mortality rate. The findings of this study suggest that the high correlations of bone size and weight with BMC and bone density support the use of SPA on rhesus macaques as a model for similar procedures in humans. Another study on rhesus macaques by Grynpas et al. (1989) examined osteoporosis and BMC. Rhesus macaques have been found to experience age-related osteopenia,

and although females lose more bone mass than males, high parity appears to shield against bone loss (Bowden et al. 1979).

Although Bowden et al. (1979) found change in cortical thickness with age, Grynpas et al. (1989) found no change in percent cortical thickness in rhesus macaques with age. In essence, their study suggests a strong correlation between mineralization and cortical bone aging. Pope et al. (1989), in a rhesus monkey study of sex and age effects on bone density, observed changes in bone density directly related to age and sex. Furthermore, in females within the ages of 32 and 33, decrease in bone density was found to be related to a deficiency in estrogen, mirroring human post-menopausal bone density decrease.

Bowles et al. (1985) conducted a study on ovariectomized and intact *Macaca fascicularis*. This study presented a human post-menopausal model for osteoporosis. Utilizing the image analysis system "DARWIN" , accurate bone area and density measurements were taken. Conclusions suggested that this model is appropriate relative to human studies since vertebral densities were lower in the ovariectomized females than the intact, closely mirroring results found in humans. In addition, the mean percent of trabecular bone area was approximately 19 percent in the control group, and nearly 35 percent in the ovariectomized group. These findings, along with the fact that Old World monkeys experience menopause, indicate that *Macaca fuscicularis* provide a

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reliable model for human osteoporosis-related studies.

The genetic epidemiology approach to nonhuman primate population studies usually requires pedigree information. One type of approach in particular, quantitative genetic studies, "assume the traits in question are influenced by a large number of polygenes" (Williams-Blangero 1991: 85). After this assumption is made, the amount of variance due to genetic influences (heritability) can be estimated. This additive genetic component of complex traits is estimated along with genetic correlations between complex traits (when not performing a univariate study). Quantitative genetic studies in captive nonhuman primate colonies have increasingly improved and become more common among researchers. Although the number of captive nonhuman primate colonies is decreasing, their research potential remains high, especially when models are needed to research human genetic structure and function.

BENEFITS OF *PAPIO* STUDIES

Baboons (genus *Papio*) have been used as models for human diseases and disorders since 1960 (McGill et al. 1960; VandeBerg and Cheng 1986). Studies are done on wild or captive baboons, depending upon research topic, availability, and cost. Captive primate colonies pro-

vide researchers with nonhuman primates that serve as animal models for human diseases (MacCluer et al. 1987). The main benefit of using animal models comes from the ability to control many aspects of animal environment and breeding. Baboons provide scientists with the opportunity to work not only with animal models, but also with primate models for the study of human diseases. Another beneficial aspect of using baboons as animal models includes analyzing genetic components of diseases; with the ability to control environment and breeding, the complications associated with separating genetic and environmental effects are minimized. Although baboons were not used in genetic studies in the late 1960's, by 1983 approximately 11 percent of nonhuman primate genetic studies utilized baboons (Vandeberg and Cheng 1986). This increase in studies may indicate that as scientists' understanding of the role of genetics in humans increases, so will the use of baboon models increase. The net result of an increase of baboons used in genetic studies will be a better understanding of the role genetics plays in diseases affecting humans.

QUANTITATIVE GENETICS

Quantitative traits are traits that are "influenced by gene differences at many loci" (Falconer 1981: 1). Quantitative traits therefore cannot be measured or identified by single genes. Thus, Mendelian ratios

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seen in differences in genes at single loci in qualitative traits, cannot be applied to quantitative traits. The fundamental basis of quantitative genetics is structured around the same properties and transmission of genes as those in Mendelian genetics (Falconer 1981). However, the study of quantitative traits is different from the study of qualitative traits in that quantitative trait studies must be conducted on large numbers of individuals (populations), and that traits must be measured, not simply classified. Quantitative genetic models have also been developed for qualitative traits.

Konigsberg and Cheverud (1992) state the following: "One goal of quantitative genetics is the explication of phenotypic covariances between relatives in terms of environmental and genetic variances" (p. 133). In other words, quantitative genetics is concerned with the understanding of inherited differences in individuals which are prompted by differences in genes at several loci. To study the quantitative differences of the segregation of genes at several loci, the measurement of phenotypic traits (rather than the classification of qualitative traits) is partitioned into sources of variance (Falconer 1981). Genetic and environmental covariance is a "portion of the total phenotypic variance" (Falconer 1981: 135).

Quantitative genetics is concerned with understanding resemblance between relatives. Genotypic variance can be divided into three parts:

additive, dominance, and interaction. An important component of geno-
typic variance is the additive genetic variance. The estimated additive
genetic variance for an individual is the phenotypic value multiplied by the
heritability. The additive genetic variance exhibits three primary charac-
teristics that make it so important in quantitative genetic studies: 1) It is
the only part of genotypic variance that facilitates prompt estimation
based on population observation; 2) It is the primary cause of inherited
phenotypic resemblances; and 3) It is the primary determinant of measur-
able genetic aspects of populations (Falconer 1981).

Quantitative genetic studies have been applied to natural popula-
tions, population structure analysis, and captive nonhuman primate
colonies. Shaw (1987) studied estimation of quantitative genetic parame-
ters in natural populations, and found the estimates to be accurate for
large populations. Williams-Blangero et al. (1990) note the advantages of
using quantitative traits, asserting both the theoretical and practical
implications of quantitative traits. As an example of theoretical implica-
tions, Williams-Blangero et al. (1990) state the most important of
Darwin's evolutionary factors (fitness) is best examined as a quantitative
trait. They also suggest that measurement of metric traits is frequently
more accessible to anthropologists than gathering qualitative data on
genetic blood markers. Chakraborty (1990) describes the use of quantita-
tive traits in relation to population structure as appropriate and warranted.

More recently, Blangero and Konigsberg (1991) tested the practical implications of using quantitative traits in a captive baboon colony. They found that by using multivariate models, the "genotype-environment interaction" can be evaluated from trait measurements from individuals in different environments (Blangero and Konigsberg 1991:315). Another study of nonhuman primate quantitative genetics found that heritability estimates are not significantly different in cases of known pedigree compared to cases with the absence of paternity data (Konigsberg and Cheverud 1992).

SUMMARY OF LITERATURE REVIEW

In this chapter, many subjects pertinent to the goals of this study have been discussed. It has been shown that a major component of osteoporosis is the reduction of bone mass and the subsequent fragility of the affected bone. When any of a number of external pressures act on weakened bone, the result is frequently fracture. Osteoporotic-related fractures are forecasted to increase in the years ahead, with the trend towards a generally older population. Associated directly with the increasing incidence of fractures are other osteoporosis-related health problems, health care costs, and an increased mortality rate, primarily among

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the elderly. An understanding of the underlying causes of osteoporosis and their detectability are extremely important in the prediction and prevention of osteoporosis-related injuries.

Consequently, studies of the underlying causes of osteoporosis have begun to focus on the roles bone growth, formation, and subsequent loss play in the development of osteoporosis. As previously stated, bone is a dynamic tissue, and bone growth can continue up to and past the age of 80. With bone growth occurring in the elderly, the assessment and prediction of those individuals at risk for osteoporosis becomes a primary concern. Cortical bone constitutes approximately 80 percent of all the bone in the body and is found primarily in the appendicular skeleton (the arms and legs). Thus, obtaining cortical bone radiographs is relatively inexpensive and exposure to radiation is low. Several studies on osteoporosis and the role of bone mass and density have been done using a wide variety of measurement techniques. Two-dimensional measurement of cortical bone size has been shown to be easily accessible and financially prudent in light of other measurement sites and techniques. The environmental, hormonal, and age/sex influences on bone mass and measurement have been discussed, and their relevance to this study assessed. Their particular effects on the results of this study will be addressed in the discussion chapter.

Animal model studies have shown high correlations with similar studies in humans. Nonhuman primate studies, including those dealing with baboons, have proven to be appropriate and accurate models for human diseases. Vandeberg and Cheng (1984) address the extensive use of baboons as models dealing with a diversity of genetically mediated diseases, including lymphoma, hypertension, alcoholism, and diabetes (p. 317). Finally, the use of quantitative genetics has elaborated both theoretical and practical aspects of anthropological studies. Through the use of quantitative genetics, pedigrees or populations can be analyzed and the phenotypic variances can be separated into genetic and environmental variances. Heritability can then be estimated, isolating to what degree the expression of a quantitative trait is due to genetic factors, and the effects that specific variables have on these traits.

CHAPTER III

MATERIALS AND METHODS

THE SAMPLE

Originally founded in 1941, The Southwest Foundation for Biomedi-
cal Research (SFBR) in San Antonio, Texas, developed corrals to breed a
colony of baboons in 1979. Initially, the *Papio* colony was housed in a
dodecagonal (ten-sided) corral encompassing 6.0 acres. In 1984 a
second dodecagonal corral, also encompassing 6.0 acres, (Goodwin
1986) was built to house juvenile baboons. The initial colony was estab-
lished from 427 baboons. These baboons were either imported from
Kenya or obtained from an existing breeding colony from the Department
of Laboratory Animal Medicine at SFBR. The total number of baboons
imported from Kenya was 247, and those already bred in Texas numbered
180 (Goodwin and Coelho 1982).

All imported baboons were quarantined for at least six weeks. All
of the baboons in the initial colony and subsequent additions were tat-
tooed to provide permanent identification numbers. Two subspecies of
baboons were purchased for the initial breeding program, either *Papio*

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hamadryas anubis or *P.h. cynocephalus*. There are currently five subspecies available for biomedical research at SFBR, including the two above-mentioned and *P. h. papio, P.h. ursinus,* and *P.h. hamadryas,* totalling approximately 3000 animals (Williams-Blangero et al. 1990). *P.h. anubis, P.h. cynocephalus* and their hybrids are the subspecies analyzed in this study.

Close records of age were made and updated at SFBR. These records start at birth and are updated three times a year. Estimating ages was unnecessary because all of the individuals radiographed were colony born, and are consequently of known age. The baboons analyzed in this study were separated into single-male groups consisting of one adult male and several females and their offspring. These groups were maintained and monitored in separate gang cages.

The age of female baboons at first menarche induces hormonal changes possibly associated with peak bone mass. Consequently, age at first menarche in female baboons is presented as a possible contributing factor to observed cortical bone size in this study. Age at first menarche has been estimated in several studies; average ages reported from these studies are in Hayssen et al. (1993). Table III.1 presents the average ages given for *P. hamadryas*, and the mean age at first menarche from those estimates. For the purposes of this study, the mean age at menarche of the estimates will be used as a measure of age at first menarche.

Table III.1. Age estimates at first menarche for *P. hamadryas.*

Range of Age Estimates in Weeks	Average Age Estimate
81 - 297	189

Table III.2 presents the number of females and males of each subspecies

analyzed in this study.

Table III.2. Number of males and females by subspecies.

Subspecies	Males	Females
P.h. anubis	35	98
P.h. cynocephalus	5	0
hybrid	18	30
Totals	58	128

Table III.3 presents the age distributions of females by subspecies, and

Table III.4 presents the age distribution for males by subspecies. The

oldest female baboon in this study was 29 years old; the oldest male

analyzed in this study was 23. In the initial phase of this study, the

youngest age was six years for both females and males.

Table III.3. Age distribution of females by subspecies.

Age in Years	P.h. anubis	Hybrid	Total
4 - 9	31	17	48
10 - 15	25	11	36
16 - 21	26	3	29
21 - 29	15	--	15

Table III.4. Age distribution of males by subspecies.

Age in Years	P.h. anubis	P.h. cynocephalus	Hybrid	Total
4 - 9	13	--	7	20
10 - 15	14	2	11	27
16 - 21	8	--	--	8
21 - 29	--	--	3	3

Six years is the commonly accepted age of maximum fertility in baboons (Lapin et al. 1979). The number of baboon subspecies of known pedigree aged six and older did not provide an adequate sample size. Therefore, the youngest age was lowered to four for females and males. All subjects radiographed exhibited closure of all long bone epiphyses and were thus considered skeletally mature.

A total of 186 hand-wrist radiographs from the above baboon subspecies were analyzed in this study. Initially 208 radiographs were

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taken, but 22 were deleted from this study due to their poor radiographic quality or to metacarpals exhibiting bone remodeling resulting from fracture. All radiographs were taken between September 1989 and January 1991. Figure III.1 depicts a computer-generated copy of one of the hand-wrist radiographs used in this study.

PEDIGREE ANALYSIS

The identification numbers from the 186 radiographs were compared to the master file on all records of baboons at SFBR to match radiograph ID numbers with permanent ego ID numbers. To match the radiograph ID numbers with the permanent ego ID numbers, the Pedigree Data Management System (PEDSYS) was used (Dyke 1992). After obtaining the ego permanent ID numbers, a new file was created for the 186 subjects analyzed in this study. This file contained a list of subjects listed by ego ID, and cross-referenced by sire ID, dam ID, sex, age and subspecies. Twenty pedigrees were then constructed by sire ID numbers and included 73 dams. There were four cases where a dam was mated with two different sires.

Figure III.1   Hand-wrist radiograph X4156.

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The hand-wrist radiographs were taken to the Department of Geology, University of Tennessee, Knoxville and digitized using the Java Video Analysis Software, version 1.30 (Jandel Corporation 1988). The digitizations were done between September 1992 and November 1992 by the author. The video analysis system in the geology department consisted of an IBM 486 computer connected to both a digitization board and a 35mm camera that transmitted images from a back-lit translucent tablet to a high-resolution video screen. Digitization was done on the video screen, and x, y coordinates were recorded in hard disk files. The digitization process measured cortical bone area by plotting x, y coordinates of locations along the outer and inner edges of the third metacarpal. Cartesian coordinates were set to measure the bone in one millimeter increments and calibrated to one square centimeter (instead of default pixel units) on a one millimeter grid. To ensure consistency, all radiographs were oriented in the same position with the pollex oriented to the right. The third metacarpals were digitized by tracing the outer and inner edges of the cortical bone, totalling four lines per radiograph.

The metacarpals on each radiograph were traced by beginning at the bottom left edge at the end of the epiphysis and following the outer edge to the beginning of the other epiphysis. One digitization constituted

one "line" of x, y coordinates (Figure III.2). Each metacarpal had four digitized lines recording the x, y coordinates in a single file. Blank values were entered as markers to facilitate subsequent analysis.

The actual digitization process was primarily done automatically. The Java software offered options of automatic or manual edge tracing. In order to maintain consistent accuracy, the automatic option was used on all radiographs. To begin an automatic tracing, the cursor was placed at the initial point of measurement, defined by the beginning pixel in which cortical bone could actually be seen on the video screen. This point was determined by zooming in on the epiphysis at a scale 200 times the original size. The initial measuring point was designated, then the video was positioned to original size and tracing began. Tracing was manually stopped at the end of each "line" at a point designated in the same manner as the initial point. In some cases, automatic tracing automatically stopped when determination of edges was unclear (thus automatically untraceable) on the radiograph. At this point, the digitization was finished manually, one millimeter at a time, to approximate as closely as possible the automatic tracing.
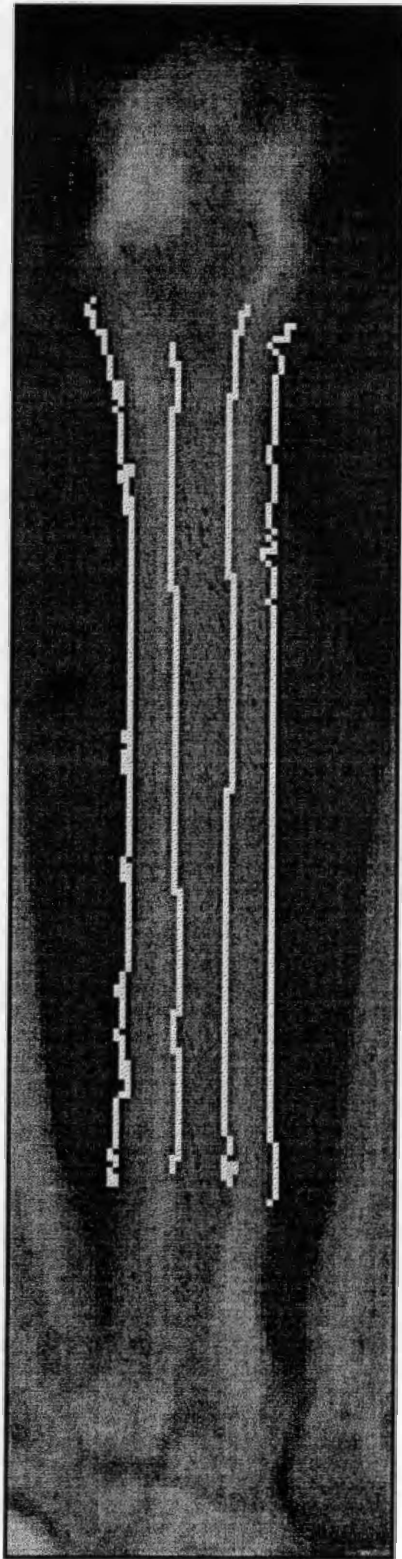
Figure III.2   Automatic computer digitization of four data lines.

The data gathered from the radiographs were 'smoothed' using a locally weighted regression presented by Cleveland and Devlin (1988). This "smoothing" process was performed because when line tracings were plotted, all x,y points were connected with either a parallel or perpendicular perimeter section. Consequently, the plots were jagged since curves could not be represented (Figure III.3). A form of "lowess" was used in this study because it is highly resistant to outliers (Cleveland 1979). By fitting simple linear regressions, "lowess" analyzed each data point of the edges of cortical bone. Each data point x_i (where i = 1 to n) was analyzed through a "window" of closest points on x around each point x_i . In this study, the "window" around point x_i was 25 percent. The vector x contained points plotted along the edges of cortical bone. For each plotted point of cortical bone x , a regression of y was calculated for the 25 percent closest points of x_i. Less influence is placed on x values the farther away from x_i they occurred by using weighted regression. For any point i, the kth closest point has the given weight:

$$W_{ik} = (1-d^3_{ik})^3$$

where d_{ik} is the scaled distance of x_i to x_k which was divided by the "window" width across units of x for point x_i (Cleveland 1979). The estimate of y from x_i can be calculated from the weighted regression.

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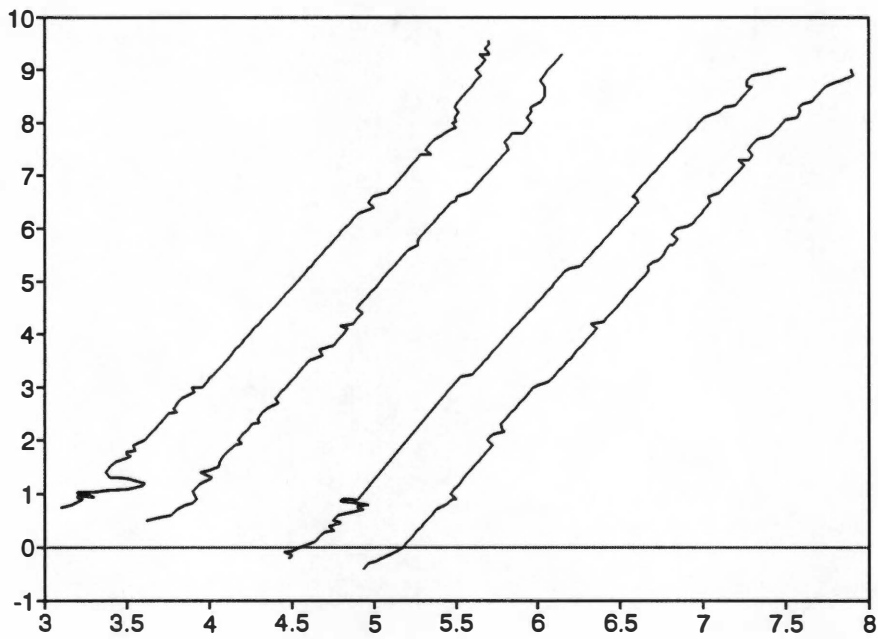
Figure III.3   Plot of "unsmoothed" data lines.

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The residuals can be calculated and used to repeatedly filter through the estimates. This process made the regressions more resilient to outliers. The residuals are calculated from their absolute values from the regression of y on x around point x_i. The residuals are represented as r_{ik} across the k closest points, and fractioned to six times their median value. Using Tukey's bisquare, a new weight can be calculated:

$$\delta_{ik} = (1 - \tilde{r}_{ik}^2)^2$$

where the symbol $\tilde{\ }$ indicates that r values have been fractioned to six times their median value (Cleveland 1979). The weights δ_{ik} and W_{ik} can be applied repeatedly, thus making weighted regressions that are more resilient to outliers (See "smoothed" plot, Figure III.4).

The relative position of the x,y coordinates traced from the radio-graphs was arbitrary, and consequently an x,y axis was superimposed onto this plot. First moments of area with respect to an arbitrarily positioned x and y axis are calculated as follows:

$$M_x = \int y\,dA \qquad and \qquad M_y = \int x\,dA$$

where y and x in the integrals are distances to the x and y axes (respectively), and the integration is across units of area (dA). When divided by the total area of the outline, the first moments can be connected to centroids (i.e., centers of gravity or mean locations):
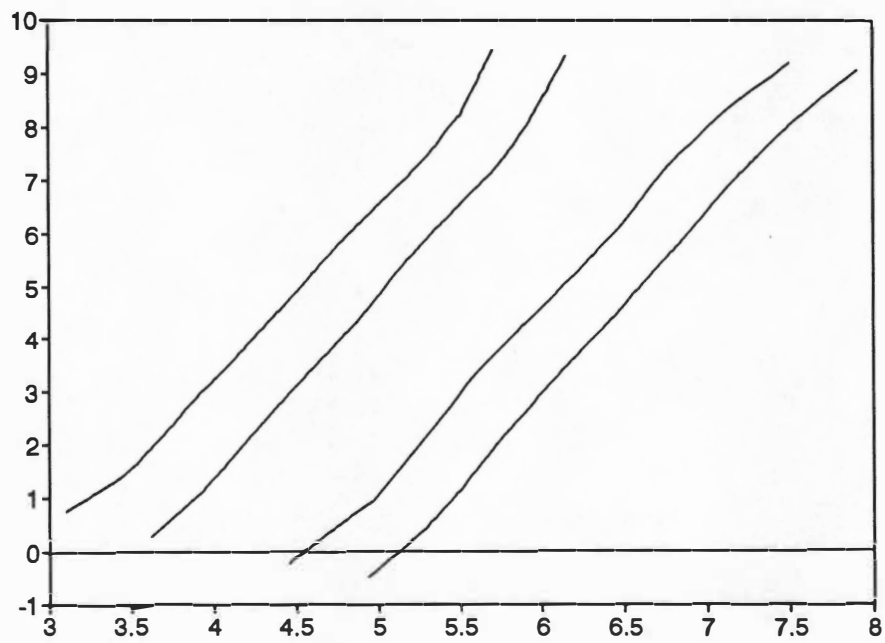
Figure III.4   "Smoothed" plot of data lines.

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$$\bar{x} = \frac{M_y}{area} \qquad and \qquad \bar{y} = \frac{M_x}{area} \ .$$

The second moments of area (or moments of inertia) follow immediately from the equation for the first moments. The second moments are calculated as follows:

$$I_x = \int y^2 dA \qquad and \qquad I_y = \int x^2 dA$$

and the product of inertia is then

$$I_{xy} = \int xy dA \ .$$

Two or more simple areas, such as rectangles, triangles, and trapezoids, are referred to in engineering circles as composite areas. Higdon and Stiles (1968) define the moments of inertia of composite areas "with respect to any axis is equal to the sum of the moments of inertia of its component areas with respect to the same axis" (p. 298). Composite areas usually include cross-sectional areas of structural elements, including I-beams (Higdon and Stiles 1968). Thus, when an area, such as cortical bone size, is removed from the larger area of the entire metacarpal shaft, the net moment of area is obtained.

From the net moment of area, the moments of inertia can be expressed as a function of length and area, or the radii of gyration (Higdon

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and Stiles 1968). The program "Slicer" (Nagurka and Hayes 1980) implemented for this study, uses a parallel axis theorem to determine moments of inertia with respect to a parallel axis. The parallel-axis theorem relates the moment of inertia of an area to two parallel axes. One of these parallel axes passes through the centroid of the area. Furthermore, the distance from the axis to the centroid is always less than the radius of gyration for any axis (Higdon and Stiles 1968). When radii of gyration are used to get moments of inertia, there is only one pair of major axes for any point in the area (circles excluded).

As described earlier, radii of gyration are quantitative traits, or structural dimensions of elements, specifically here dimensions of cortical bone. Radii of gyration (expressed in the first power) are used instead of second moments because if the radii are normally distributed, then the second moments which are in the fourth powers cannot be normally distributed. The radii of gyration can be calculated by reducing the second moments of area to diagonal form (an eigen structure problem), which produces I_{max} and I_{min} (see Figure III.5). The radii of gyration (kmax,kmin) can be calculated in the following manner:

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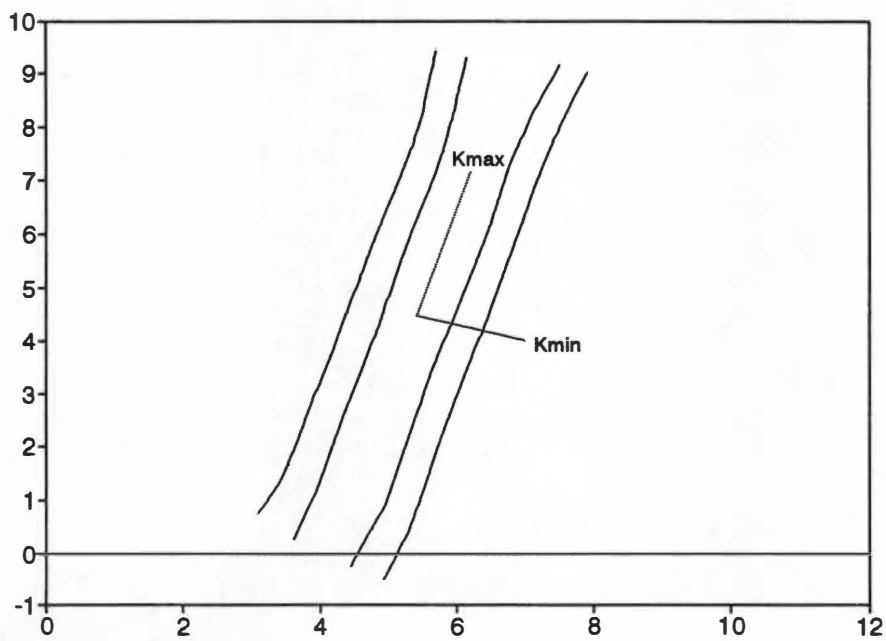
Figure III.5   Plot of KMAX and KMIN superimposed on data lines.

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$$kmax = \sqrt{\frac{I_{max}}{area}} \quad and \quad kmin = \sqrt{\frac{I_{min}}{area}}$$

where area is the total area of the outline excluding the medullary cavity.
Higdon and Stiles (1968) described the radius of gyration of an area as
"the distance from a given axis at which the entire area can be conceived
to be concentrated without changing the second moment of the area
about the given axis" (p. 297). Figure III.6 depicts a diagram of the radii
of gyration.

The traits kmax / length, kmin / length, and kmax / kmin are ana-
lyzed to determine the genetic effects and other parameter value effects
inherent in bone length and structural orientation. Specifically, kmax /
kmin addresses the strength of cortical bone after undergoing the above
processes. If kmax / kmin is high, the implications are that the bone has
a more pronounced linear orientation resulting in thin, more fragile cortical
strength. If kmax / kmin is low, the implications are that the bone is more
compressed, resulting in more compact, resilient cortical strength.
Although these implications are not direct predictors of osteoporosis, they
do address the genetic considerations of the functional properties of
cortical bone. These aspects of cortical bone may provide researchers
with a cross-sectional model for developing a longitudinal study for
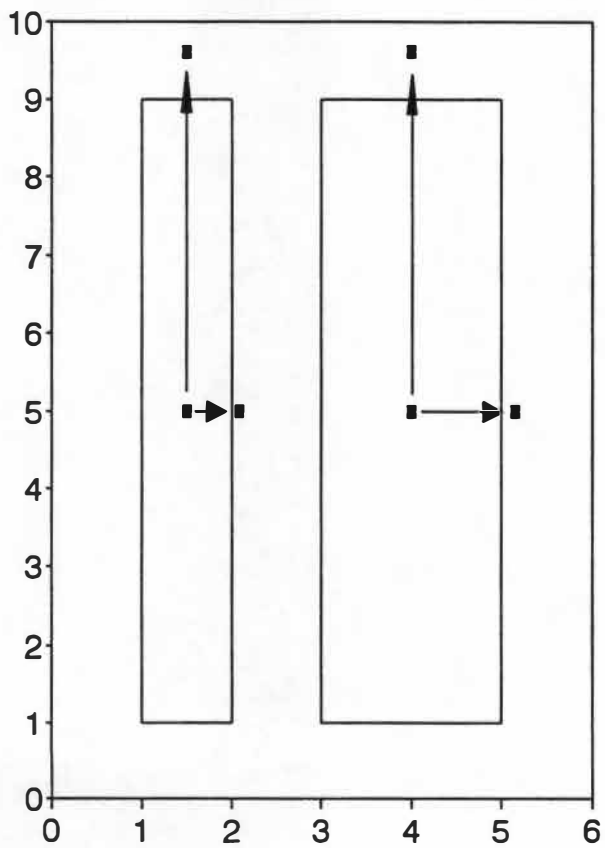
Figure III.6   Diagram of Radii of gyration.

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determining which subjects are predisposed to the onset of such bone diseases as osteoporosis. The statistical analyses performed on these traits are presented below.

Maximum Likelihood Estimates

To estimate the effects of measured genetic traits, maximum likelihood estimates were implemented. In pedigree studies, covariances between different groups of individuals are not independent (Hopper and Mathews 1982). To avoid this bias and to account for all trait values observed for all individuals, the maximum likelihood approach provided the best model for the data. The maximum likelihood estimate of a parameter is the best supported parameter value for the data. The likelihood (L) of, for example, hypothesis H given the data D can be written as $L(H \mid D)$. The log-likelihood (ℓn), then, is the natural logarithm of the likelihood (Edwards 1992). The maximum likelihood is the best $\ell n(H \mid D)$ for that parameter. When there are two or more parameters, parameter values are the most likely values over all parameters (Edwards 1992). Statistical analyses were performed using the program "Maxlikh2", which finds the maximum likelihood estimate for h^2, given the following calculations:

$$h^2 = \frac{\sigma_A^2}{\sigma_A^2 + \sigma_E^2}$$

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where σ^2_A is the additive genetic variance and σ^2_E is the environmental variance (Konigsberg and Cheverud 1992). The values calculated by "Maxlikh2" will be presented in the following chapter.

Maximum likelihood estimates (MLE) can be calculated using the complete pedigree data. The program "Maxlikh2" was used to analyze the above data fields. The values for kmax and kmin were calculated in "Slicer" (Nagurka and Hayes 1980). This program utilizes a simple algorithm that calculates cross-sectional area from perimeter coordinates. "Slicer" was used to calculate moments of area and orientations of major and minor axes, which were used to plot the radii of gyration for each metacarpal. Kmax and kmin were combined with the ego, sire, and dam ID numbers, sex designation, and age fields and placed in an input file. The values in this file were run through "Maxlikh2" to calculate MLE's.

The probability of obtaining the observed data is conditional upon the given parameters, where the parameters are the mean (μ), regression on the covariate (β), the environmental variance (σ^2_E), and the heritability (h^2), where the environmental variance is equal to the phenotypic variance minus the additive genetic variance. This probability can be represented as follows:

$$\text{Prob} (x \mid \theta)$$

where x represents the data and θ represents the parameters.

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This probability function can be restated as a likelihood:

$$L(\theta \,|\, x)$$

which leads to the estimation of the most likely parameter values given

the data using a probability density function (p.d.f.):

$$\text{Prob}(x_i \,|\, \theta) = (2\pi)^{-\frac{1}{2}}\, \sigma^{-1} \exp[-\tfrac{1}{2}(x_i - \mu/\sigma)^2]$$

where μ is the mean, σ is the standard deviation, and θ is μ, σ.

The next step in the MLE process calculates a joint density function:

$$L(\theta \,|\, x) = \text{Prob}(x \,|\, \theta) = (2\pi)^{-N/2}\, |\Sigma|^{\frac{1}{2}} \exp[-\tfrac{1}{2}(x-\mu)'\,\Sigma^{-1}(x-\mu)]$$

where θ is μ, Σ where Σ is the variance/covariance matrix (the statistical

symbol Σ is also known as Ω in genetics). The natural logarithm can be

calculated as follows:

$$\ln(L(\theta \,|\, x)) = -\tfrac{1}{2}\ln(2\pi) - N/2\,\ln|\Omega| - \tfrac{1}{2}(x-\mu)'\,\Omega^{-1}(x-\mu)$$

where $\ln(L)$ is the log-likelihood, N is the number of individuals in any

given pedigree, Ω is the variance/covariance matrix, and where

$$\mu = \mu_i + (\beta_{age} \circ age) + (\beta_{sex} \circ sex).$$

In order to identify genetic effects on quantitative traits and func-

tional aspects of cortical bone size, this study analyzed the above de-

scribed phenotypic measurements from related baboons. Heritability was

estimated from these measurements taken from full pedigree data.

Previously, it was stated that the phenotypic value is composed of the

total genetic and environmental effects. The expected genetic covariance

between individual baboons i and j is $cov_{ij} = 2\Phi_{ij}\,\sigma^2_A$, where the

covariance is i and j, σ^2_A is the additive genetic variance, and Φ is the probability of alleles being identical by descent (i.b.d., or kinship coefficient). The pedigree data were used to determine the Φ_{ij} values between individuals.

The next step requires searching for the σ^2_A and σ^2_E values that lead to the most likely model that explains the observed data. Finding these values is done by finding the likelihood of the values given the observed phenotypic data and the relationships established from the pedigrees. The phenotypic covariance can be calculated as follows:

$$\Omega = 2\sigma^2_A\Phi + I\sigma^2_E .$$

The additive genetic variance and the environmental variance must be adjusted to maximize the log-likelihood.

Metacarpal lengths and subperiosteal and medullary widths for the subjects were obtained from SFBR. The radiographs were measured for metacarpal length and subperiosteal and medullary width using calipers. Statistical analyzes estimated parameter values for mean, age, sex, sex and age interaction, heritability, and phenotypic variance, and calculated values for each quantitative trait kmax, kmin, area, length, (TW - MW)/TW, kmax / length, kmin / length, and kmax/kmin, where TW is the subperiosteal width and MW is the medullary width. The variables TW, MW and the calculation (TW - MW)/TW converted into percents because

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the estimates calculated by "Maxlikh2" would otherwise be too small for the program to recognize. These values will be presented in the following chapter.

CHAPTER IV

RESULTS

The statistical analyses performed by "Maxlikh2" are presented below. MLE's and standard error estimates for eight quantitative traits (kmax, kmin, area, length, (TW - MW)/TW, kmax/length, kmin/length, and kmax/kmin) were calculated within the parameters of the six effects mean, sex, age, sex o age (sex age interaction), phenotypic variance (vp), and heritability (h2). Values for the t-statistic were calculated by dividing MLE's by the standard error estimates. Agresti and Agresti (1979) define the t-statistic as symmetric around zero, and that this is "analogous ...of the z-statistic (the standard normal distribution)..." (p. 140). The t-statistic is used since its dispersion depends on the degrees of freedom. Furthermore, its variance decreases to one as the degrees of freedom increase, with no limit (Agresti and Agresti 1979). All P-values are asymptotic to a z-score. The resulting calculations for the first quantitative trait (kmax) are presented in Table IV.1. The analyses indicate that the trait "kmax" is moderately heritable with an h^2 value of 0.53, and a standard error of 0.22.

Table IV.1. Results of statistical analyses for trait KMAX.

Variable	MLE	Standard Error	t	P
mean	2.00341	0.10771	18.6000	<0.0001
sex	-0.10252	0.12488	-0.8209	0.4117
age	-0.00057	0.00829	-0.6876	0.4917
sex o age	-0.01183	0.00979	-1.2084	0.2269
vp	0.12030	0.21700	0.5544	0.5793
h2	0.53105	0.21703	2.4469	0.0072

Note: All p-values are 2-tailed except for h^2 estimates.

The statistical analyses of the second quantitative trait (kmin) are presented in Table IV.2. The trait kmin is not highly heritable, with an h^2 value of 0.23 and a standard error of 0.20.

Table IV.2. Results of statistical analyses for trait KMIN.

Variable	MLE	Standard Error	t	P
mean	1.02944	0.08149	12.6327	<0.0001
sex	0.05933	0.09425	0.6295	0.5290
age	0.01649	0.00630	2.6175	0.0088
sex o age	-0.01751	0.00736	-2.3791	0.0170
vp	0.06765	0.00782	8.6509	<0.0000
h2	0.22853	0.20408	1.1198	0.1314

Note: All P-values are 2-tailed except for h^2 estimates.

Statistical analyses for area, the third quantitative trait analyzed, are presented in Table IV.3. The analyses for this trait indicate that area is not highly heritable, since the h^2 estimate is 0.40 with a standard error of 0.21.

Table IV.3. Results of statistical analyses for trait AREA.

Variable	MLE	Standard Error	t	P
mean	6.30855	0.50482	12.4967	<0.0001
sex	-0.98549	0.59284	-1.6623	0.0964
age	0.02852	0.03975	0.7175	0.4731
sex o age	-0.06123	0.04642	-1.3190	0.1872
vp	2.64153	0.32482	8.1323	<0.0001
h2	0.40371	0.20652	1.9548	0.0253

Note: All P-values are 2-tailed except for h^2 estimates.

The statistical analyses calculated by "Maxlikh2" for the fourth quantitative trait (length) are presented in Table VI.4. These analyses indicate that length is a highly heritable trait.

Table VI.4. Results of statistical analyses of trait LENGTH.

Variable	MLE	Standard Error	t	P
mean	52.03370	0.82181	63.3160	<0.0001
sex	-5.80430	0.93266	-6.2234	<0.0001
age	0.24112	0.05710	4.2228	<0.0001
sex o age	-0.21946	0.07359	-2.9822	0.0029
vp	9.06650	1.11264	8.1486	<0.0001
h2	0.84422	0.08250	10.2330	<0.0001

Note: All P-values are 2-tailed except h^2 estimates.

Statistical analyses of the fifth trait, (TW - MW) / TW, are presented in Table IV.5. These results indicate that this quantitative trait is moderately heritable, with a standard error of 0.14 and a heritability of 0.63.

Table IV.5. Results of statistical analyses for trait (TW - MW) / TW.

Variable	MLE	Standard Error	t	P
mean	54.31484	2.27631	23.8610	<0.0001
sex	-4.86865	2.69335	-1.8077	0.0706
age	-0.00207	0.17084	-0.0121	0.9903
sex o age	-0.11751	0.21110	-0.5567	0.5777
vp	61.06803	7.66188	7.9704	<0.0001
h2	0.63222	0.13788	4.5830	<0.0001

Note: All P-values are 2-tailed except for h^2 estimates.

The statistical analyses performed by "Maxlikh2" for quantitative traits kmax/length and kmin/length are presented below in Table IV.6 and Table IV.7. Analyses of both traits indicates that neither trait is heritable. Heritability was set at zero for these two analyses.

Table IV.6. Results of statistical analyses for trait KMAX / LENGTH.

Effect	MLE	Standard Error	t	P
mean	38.14938	2.0185	18.90030	<0.0001
sex	2.69010	2.3585	1.14060	0.2540
age	-0.12402	0.1620	-0.76570	0.4438
sex o age	-0.11751	0.1825	-0.64410	0.5159
vp	37.57272	4.2957	8.74670	<0.0001

Note: All P-values are 2-tailed.

Table IV.7. Results of statistical analyses for trait KMIN / LENGTH.

Effect	MLE	Standard Error	t	P
mean	20.0834	1.6454	12.2062	<0.0001
sex	3.2777	1.9459	1.6844	0.0921
age	0.1729	0.1330	1.2999	0.1936
sex o age	-0.1939	0.1510	-1.2840	0.1991
vp	27.1290	2.9752	9.1182	<0.0001

Note: All P-values are 2-tailed.

The statistical analyses for trait "kmax/kmin" are presented in Table IV.8. The heritability estimate 0.28 is significant, as indicated by a t-value of 1.76.

Table IV.8. Results of statistical analyses for trait KMAX / KMIN.

Effect	MLE	Standard Error	t	P
mean	1.8584	0.0841	22.1025	<0.0001
sex	-0.0931	0.1007	-0.9251	0.3549
age	-0.0157	0.0067	-2.3583	0.0183
sex o age	0.0086	0.0080	1.0843	0.2782
vp	0.2814	0.1602	8.7742	<0.0001
h2	0.2814	0.1602	1.7566	0.0395

Note: All P-values are 2-tailed except for h^2 estimates.

Table IV.9 presents the maximum likelihood ratio tests for the first five traits, and their corresponding significance values. A comparison between two models was evaluated using heritability set at zero in one model, and estimated between zero and one in the other model.

Table IV.9. Maximum likelihood ratios for KMAX, KMIN, AREA, LENGTH, and (TW - MW)/TW.

Trait	x^2	P
kmax	9.0426	.0013
kmin	1.5338	.1078
area	6.3502	.0059
length	48.1674	<.0001
(tw-mw)/tw	93.3648	<.0001

Figure IV.1 presents the results of kmin plotted on age for both females and males. In males, there is a positive correlation between kmin and age. Females exhibited a slight negative correlation between the two traits. A discussion of the results is presented in the following chapter.

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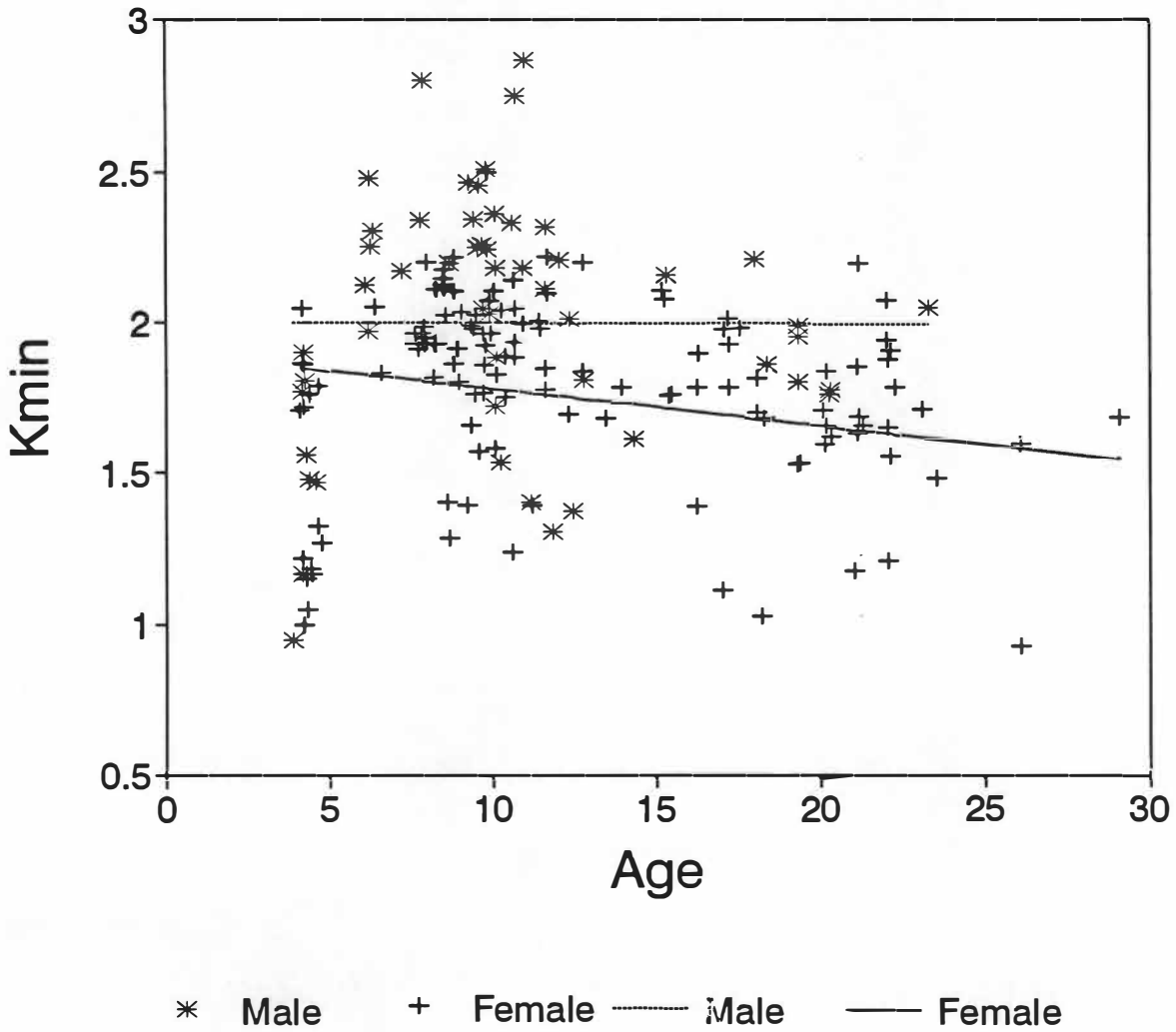
IV.1   Regression of age and sex on KMIN.

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CHAPTER V

DISCUSSION

The results indicate that the most heritable quantitative trait ana-
lyzed is length, with an effect estimate of 0.84. Heritability of length is
significant as evidenced by the t-value of 10.23. The data obtained from
Table IV.4 indicate that sexual dimorphism also exhibits a significant
effect on length with a t-value of -2.98. Estimates of heritability are
significant in both traits "area" and "(TW - MW) / TW", with t-values of
1.95 and 4.58, respectively. These significance estimates indicate that
area, length, and aspects of bone width exhibit significant genetic compo-
nents.

The significance of heritability estimates for these traits may be in
part due to the overall genetic influences on body size. The sexual dimor-
phism exhibited by this trait suggests that as age increases, so does
expression of sexual dimorphism. This trend has recently been examined
in humans (Harris et al. 1992). Harris and colleagues found that as both
males and females aged, the percent sexual dimorphism averages in-
creased based on length measurements of metacarpals and phalanges.
Furthermore, DeRousseau (1985) found that the amount of cortical bone

decreases proportionately with length after peak bone mass is reached: the longer the bone, the more cortical bone present. Thus, if there is more cortical bone present, the amount of loss would be higher. In this study, aspects of third metacarpal length, width, and area are significantly heritable. Analysis of these traits may prove beneficial in longitudinal studies identifying genetic components associated with a predisposition for osteoporosis. In terms of sexual dimorphism, the proportional decrease of cortical bone would in part account for the larger amount of change associated with length effects exhibited in Table IV.4. Garn et al. (1975) found that long bones exhibit an increase in area with age even after bone resorption and apposition have been taken into account.

The data presented in Table IV.8 indicate that age effects on the trait kmax / kmin are significant, with a t-value of 1.76. In 1970, Garn proposed that in diaphyseal bones of all sizes, age is highly correlated with subperiosteal cortical expansion. However, as age increases, so do the size and number of haversian canals (Garn 1970; Harris et al. 1992). Although this may promote fragility of cortical bone, observed total bone loss results in large part from degenerative changes of the medullary cavity (Harris et al. 1992). This trait is also significantly heritable, with a t-value of 1.76. This suggests that the biomechanical properties of bone analyzed here are heritable and thus have significant biological/functional implications for the growth and maintenance of cortical bone.

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The heritability effects on trait "kmax" are statistically significant, evidenced by a t-value of 2.44. This indicates that the structural orientation of the first radius of gyration exhibits significant genetic components. Figure IV.6 illustrates a slight ontogenetic relationship in females for the trait "kmin". Although age at menopause has not been reliably determined in nonhuman primates, Pope et al. (1989) suggest that menopause may occur in macaques between the ages of 25 and 30. If this is the case, any significant ontogenetic relationship between females and age with any traits analyzed here may not be apparent from the analyses of this study, since the oldest female analyzed was 29 years old. The observed difference of trait "kmin" between sexes is most likely not associated with female menopause since the data indicate a wide array of values for kmin across ages for both sexes up to age 29.

The range of heritability estimates among the quantitative traits reflects that some traits may be more responsive to genetic or environmental influences than others. Even though many environmental variables can be manipulated in nonhuman primate colonies, the effects of same-environment cannot be monitored. Krall and Dawson-Hughes (1993) imply that familial associations become less enhanced in bone expression because environment becomes more influential in processes affecting bone. The common environment shared by the baboons analyzed in this

study may contribute to the range of values estimated for heritability. Sharing a common environment would increase the observed heritability estimates. Age at menarche did not appear to have any affect on the traits analyzed here. However, age at menarche is estimated to be around four years, and that is the youngest age of baboons analyzed in this study.

The data in Table IV.9 indicate that heritability estimates are significantly greater than zero for all traits kmax, area, length, and (TW-MW)/TW, using the likelihood ratio test. The results of this study indicate that there is a genetic component affecting quantitative traits in cortical bone. Genetic traits analyzed in this study do not completely explain the intra-population variation of metacarpal morphometry. In light of the results, biomechanical parameters, such as body size and weight for metacarpal morphometry analysis, may prove more informative, because peak bone mass is related to body size, and size-related traits are typically highly heritable.

CHAPTER VI

SUMMARY

This study has examined quantitative genetic parameters in 186 baboons (*P. hamadryas*) of known genetic background. The Southwest Foundation for Biomedical Research life history database was used to obtain pedigree, age, and sex information for a colony sample of 58 males and 128 females. The radiographs used in this study were measured for cortical bone size in the third metacarpal using a computer video analysis system made available by the Department of Geology, University of Tennessee, Knoxville. The data obtained were "smoothed" using a locally weighted regression.

The quantitative traits examined included kmax, kmin, area, length, (TW - MW) / TW, kmax / length, kmin / length, and kmax / kmin. The quantitative traits "kmax" and "kmin" were identified using the program "Slicer". Length and width measurements from the radiographs analyzed were done manually using a caliper and obtained from SFBR. Statistical analyses of the quantitative traits calculated MLE's and standard error estimates for parameter value effects mean, sex, age, sex and age

interaction, phenotypic variance, and heritability using "Maxlikh2".

Quantitative traits (excluding kmax / length and kmin / length) exhibited

significant heritability estimates for parameter value effects heritability,

sex and age interaction and for age in trait "kmax / kmin".

Length is the most heritable trait. The significance of area, length,

and aspects of bone width estimates may be partially due to the overall

genetic influences on body size. The value for the sex and age interaction

effect is significant for the trait "kmin" . Although this effect may be

partly due to body size, sexual dimorphism may account for aspects of

their morphometric variation.

Functional properties of structural orientations are only one aspect

of bone properties that may play a role in bone diseases such as osteopo-

rosis. Quantitative genetic models for human diseases are an important

part of understanding the role genetics has in possible predispositions to

diseases. The use of baboons in this study presents their appropriateness

as models for intra-family studies of properties of bone. Consequently,

longitudinal quantitative genetic studies of baboons as models for human

bone diseases may be warranted. The quantitative traits analyzed in this

study are only one aspect of bone morphology. This study determined

that radii of gyration are a useful component in the analysis of heritability

estimates for observed cortical bone size in skeletally mature baboons.

Furthermore, the methodology implemented here provides researchers

with a model for estimating heritability of quantitative traits as a compo-
nent of cortical bone morphology. These effects could help determine the
role biomechanical traits play in the development of bone diseases,
specifically osteoporosis.

An aspect of environmental variance not analyzed in this study
could provide more information on the effects of age on bone. Another
parameter value estimate that may prove significant in the analysis of
bone size is parity effects. The number of parous females and their stage
of reproduction may have hormonal influences on bone size. Parity may
determine if the ontogenetic relationship in females and kmin is more
significant than the relationship observed in this study.

Radiographic analysis of other cortical bone properties, as well as
noninvasive analysis of trabecular bone, may provide even more infor-
mation on quantitative traits in bone, including structural/functional
properties. Other biomechanical parameters, such as body weight effects
and extreme muscle activity effects, might prove beneficial in better
understanding functional properties inherent in bone. It is suggested that
multivariate longitudinal studies of this nature be conducted to further
determine if baboons are appropriate models for analyzing bone properties
in humans.

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Appendices

Appendix A

Pedigrees

Ego ID#	Sire	Dam	Sex	Subspecies	Age
"1X1224"	," ",	" ",	"F",	"A",	19.36
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"7098  ",  "1X2231",  "1X2072",  "F",          "A",              4.23
"7071  ",  "1X2231",  "1X2159",  "F",          "X",              4.26
"7119  ",  "1X2231",  "1X2788",       "F",          "X",
4.2
"7333  ",  "1X2231",  "1X3299",  "M",          "A",              3.91
"7123  ",  "1X2870",  "1X1709",  "F",          "A",              4.19
"7090  ",  "1X2870",  "1X2271",  "F",          "A",              4.24
"7020  ",  "1X2870",  "1X2277",  "M",          "A",              4.31
"7077  ",  "1X2870",  "1X3707",  "M",          "X",              4.26
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Appendix B

Trait Data

KMAX,   KMIN,   AREA, LGTH, TW-MW, KMAX/KMIN, KMIN/KMAX

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2.865797,1.51409,10.80947,64.05,.603129,.044743,.023639
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Vita

Katherine Christine Park was born on 6 December, 1967 in Gallipolis, Ohio. She lived in Ravenswood, West Virginia until she graduated from Ravenswood High School in June 1986. During high school she was president of the National Honor Society and graduated co-salutatorian.

Katherine started college in August 1986 and attended Washington and Lee University in Lexington, Virginia. She majored in Anthropology with a concentration in Geology. She graduated *cum laude* in June 1990 with a Bachelor of Arts degree.

In August 1990, Katherine began graduate school at the University of Tennessee, Knoxville. Her studies focused on biological anthropology, with an emphasis on nonhuman primate research. She was awarded a Graduate Assistantship in the Anthropology Department in the fall of 1992. Her assistantship responsibility was the curation of the U.T. Marmoset and Tamarin Collection. She held this position until her departure from the University of Tennessee. She received her Master of Arts degree in June, 1994 with a major in Anthropology.