

# Serum Leptin Levels in Wild and Captive Populations of Baboons (*Papio*): Implications for the Ancestral Role of Leptin

WILLIAM A. BANKS, JANE E. PHILLIPS-CONROY, CLIFFORD J. JOLLY, AND JOHN E. MORLEY

*Geriatric Research, Educational and Clinical Center (W.A.B., J.E.M.), Veterans Affairs Medical Center—St. Louis, St. Louis, Missouri 63106; Division of Geriatrics (W.A.B., J.E.M.), Department of Internal Medicine, Saint Louis University School of Medicine, St. Louis, Missouri 63104; Department of Anthropology (J.E.P.-C.), Washington University Department of Anatomy and Neurobiology (J.E.P.-C.), Washington University School of Medicine, St. Louis, Missouri 63110; and Department of Anthropology (C.J.J.), New York University, New York, New York 10003*

**Leptin has emerged as the major lipostat, regulating adiposity by affecting feeding behavior and thermogenesis. Leptin levels in normal-weight Western humans and in captive rodents are 5–15 ng/ml. But evidence suggests that these levels are abnormally high and that leptin may have evolved as a more general metabolic signal, with its most robust effects at lower levels. If this is true, then wild, healthy animal populations should have lower levels of leptin than captive populations and Western Man. We examined leptin levels in wild, East African populations of baboons (*Papio anubis*, *P. hamadryas*,**

**and *anubis/hamadryas* hybrids). Serum leptin levels averaged less than 1 ng/ml, and no differences occurred in leptin levels among the species. In wild baboons, serum leptin levels were highest in the youngest baboons, with a trend toward an inverse relation between dental age and serum leptin levels. In comparison, captive baboons had levels about three times higher than wild baboons, with a clear inverse relation between age and leptin levels. These results support the view that leptin evolved to be effective at low levels. (*J Clin Endocrinol Metab* 86: 4315–4320, 2001)**

LEPTIN IS A 16-kDa protein synthesized by fat and released into the blood (1). Leptin crosses the blood-brain barrier and acts within the central nervous system to regulate body adiposity by decreasing feeding (2–5). Obesity occurs when leptin synthesis, transport, or receptor binding is impaired (2, 4, 6, 7). As such, leptin has been viewed as a lipostat and shows promise as an antiobesity therapeutic.

Several theories have been advanced as to the main role of leptin. Originally, leptin was considered part of a lipostat, informing the brain of the amount of adipose tissue present. It has been suggested that the primary purpose of leptin is not to signal to the brain when an animal is becoming obese (8). Instead, leptin levels would signal to the brain when nutritional reserves were adequate to support expenditure of energy on activities such as initiation of puberty and reproduction. Consistent with this idea, leptin reverses many of the effects of starvation, including anovulation, the decreases in levels of thyroid and glucocorticoid hormones (9, 10), and impairment of immune function (6, 11). An extension of this idea would suggest that leptin evolved as a more general metabolic signal, relaying to the brain when energy stores are adequate to direct resources to activities other than seeking food. If this is true, then leptin should be most effective at lower concentrations and less so at higher levels. Supporting this is the observation that leptin, at low levels and through direct actions on the brain, affects onset of puberty, reproductive behavior, thermogenesis, neuroendocrine functions,

bone mass, and brain maturation (12–20). Additionally, the transporter for leptin at the blood-brain barrier is partially saturated, even at serum leptin levels below 1 ng/ml (21, 22).

The above observations, and ideas about what constitute normal serum leptin levels, have come from Western human populations and from domestic or laboratory animal populations. Leptin levels and functions have not been studied in wild populations and might be considerably different. Here, we compare serum leptin levels in wild, East African populations of baboons to those of captive baboons.

## Materials and Methods

### Collection of wild baboon data

Animals throughout these studies were treated humanely and in accordance with NIH guidelines. Baboons were captured from populations living in the Awash National Park (230 km east of Addis Ababa, Ethiopia) in the rainy seasons of June–July 1995 and July 1997, and a subsample of 71 animals was evaluated for serum leptin. Baboons were lured into traps, early in the morning, with corn used as a bait. When all the cages were full, baboons were sedated with im ketamine hydrochloride at a dose of 7.5–10 mg/kg BW. The time between capture and processing was between ½ and 3 h. The trapping was part of ongoing studies of the *anubis-hamadryas* baboon hybrid zone, which have monitored the Awash baboon population since the early 1970s. Droughts occur about once per decade, but these seasons had typical rainfall and ample forage, and the animals appeared to be healthy. The subsample represented a range of ages and was drawn from both taxa and from the hybrid population (23–25). The sample comprised 12 *anubis*, 13 hybrids, and 46 *hadmadryas*. All but 5 baboons were male.

The captured and tranquilized baboons were sexed and weighed. Blood was drawn from the femoral vein and stored under cool conditions (about 70 F), for 4–12 h, until centrifugation. The serum was immediately frozen in liquid nitrogen, returned to the lab on dry ice, then stored at –70 C until assay. Baboons were grouped into one of five age categories, based on dentition, as follows: D1, milk teeth only; D2,

Abbreviations (categories, based on dentition): D1, Milk teeth only; D2, at least one M1 but no M2 visible; D3, at least one M2 but no M3 visible; D4, at least one M3 erupting but dentition incomplete; D5, all molars fully erupted.

at least one M1 but no M2 visible; D3, at least one M2 but no M3 visible; D4, at least one M3 erupting but dentition incomplete; and D5, all molars fully erupted. The dental age distribution is shown in Table 1.

### Collection of captive baboon data

In 1999, venous blood from 17 male anubis baboons was obtained from Southwest Foundation for Biomedical Research (San Antonio, TX). These animals were kept in gang cages or corrals and maintained on a high-carbohydrate diet (Purina 5LEO Monkey Diet; 15% crude protein, 4% crude fat, 5% crude fiber; Purina Mills, Inc., St. Louis, MO) supplemented with fresh vegetables and fruit 3 times per week. Baboons were fasted 12 h and sedated with ketamine between 0800 and 1100 h. Whole blood was drawn within 10 min of sedation and immediately centrifuged, and the serum was frozen. Date of birth was also obtained, and the age in months was determined. Because accurate dental records were not available on these baboons, we converted chronologic age into dental age categories based on the correlation previously established for baboons from this facility (26).

### Quality control measures

Individually caged anubis baboons from the animal facility at Washington University School of Medicine, St. Louis, MO, were anesthetized; and whole blood was obtained. These samples were divided and used for two purposes: 1) to determine whether the immunoactivity diluted in parallel with the standard curve of the leptin assay; and 2) to examine the stability of leptin kept at room temperature for 1, 3, 6, 9, 12, or 24 h, mimicking the storage conditions of the samples obtained under field conditions.

The effect of storing serum at  $-70$  C for prolonged periods of time was determined. Ten samples (representing 10 different baboons) of serum that had been stored since 1994 (5 yr before assaying) at Southwest Foundation at  $-70$  C were randomly chosen for assay of leptin levels.

### Measurement of leptin

The primate leptin RIA kit from Linco Research, Inc. (St. Charles, MO) was used. The  $ED_{50}$  for this kit is 4.7 ng/ml, with the  $ED_{80}$  being 1.1 ng/ml. The assay does not detect human insulin, C-peptide, glucagon, IGF, somatostatin, or pancreatic polypeptide.

### Statistical analysis

Means are reported with their SE and numbers (n). Means were compared by ANOVA followed by Duncan's multiple-range test when more than 2 means were compared. Regression lines were calculated by the least-squares method and are reported with their slopes, intercepts, n, correlation coefficient (r), and *P* value when a statistically significant correlation existed between the x and y values. Regression lines were compared with the Prism 3.0 software program (GraphPad Software, Inc., San Diego, CA).

## Results

### Quality controls

The serial dilution curve (Fig. 1, top panel) for the immunoactivity in baboon serum detected by the leptin assay was parallel to the standard curves.

Leptin was extremely stable at room temperature. The relation between immunoactivity and time at room temper-

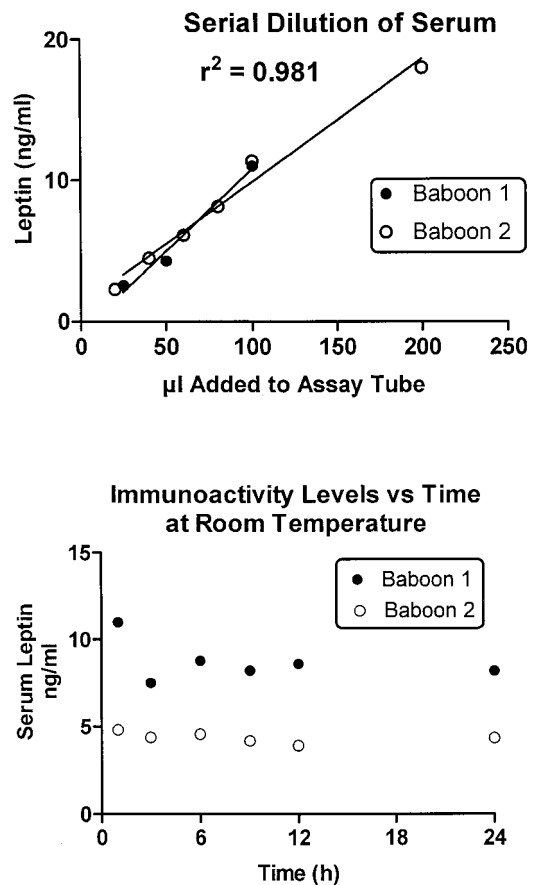


FIG. 1. Quality controls: measurement of leptin in baboon serum. Upper panel, Serial dilution curve for serum from two captive baboons. Each doubling ( $\mu$ l) doubled the amount of leptin detected, demonstrating parallelism with the standard curve. Lower panel, Stability of serum leptin at room temperature. The lack of change with time shows that leptin in serum does not degrade for up to 24 h.

ature was not significant, demonstrating that no statistically significant change in the immunoactive levels occurred with time for up to 24 h (Fig. 1, bottom panel). The mean level of leptin in serum stored for 5 yr at  $-70$  C ( $1.91 \pm 0.20$ ) was not different from that of serum freshly obtained and immediately processed and frozen ( $1.87 \pm 0.12$ ). The level is also similar to that previously reported in a captive baboon population (27).

### Leptin levels in wild populations of baboons

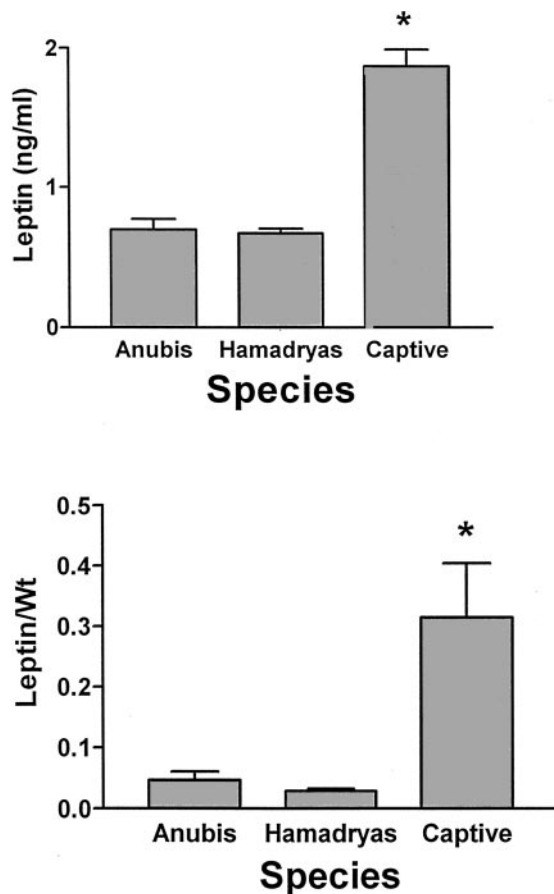
The levels of leptin in the serum for the various categories of wild baboons are shown in Table 2. One determination was excluded from analysis because its extreme value was suspected to be attributable to assay error. There were no differences in leptin levels among species or between sexes. A difference did exist among ages by ANOVA [ $F(4,64) = 5.01$ ,  $P < 0.005$ ], and the range test showed the youngest age group (D1) had a higher leptin level than the D5 ( $P < 0.005$ ), D4 ( $P < 0.005$ ), D3 ( $P < 0.05$ ), and D2 ( $P < 0.05$ ) groups. Regression analysis showed a trend ( $r = -0.235$ ,  $n = 70$ ,  $P = 0.05$ ) for a correlation between dental age and leptin levels: leptin =  $0.793 - 0.0423$  (age).

TABLE 1. Age distribution of wild anubis, hybrid, and hamadryas baboons and of captive anubis baboons

Dental Age	Anubis	Hybrid	Hamadryas	Captive anubis
D1	1	0	3	5
D2	3	3	7	7
D3	4	4	11	3
D4	1	0	8	0
D5	3	6	17	2

**TABLE 2.** Leptin levels in wild baboon populations

Species (n)	Leptin (ng/ml)	Dental age	Leptin (ng/ml)
Anubis (12)	0.72 ± 0.07	D1	0.93 ± 0.14 (4)
Hybrid (12)	0.59 ± 0.11	D2	0.65 ± 0.07 (13) <sup>a</sup>
Hamadryas (46)	0.67 ± 0.03	D3	0.66 ± 0.04 (18) <sup>a</sup>
		D4	0.55 ± 0.04 (9) <sup>b</sup>
		D5	0.61 ± 0.05 (26) <sup>b</sup>
Sex			
Male (65)	0.67 ± 0.03		
Female (5)	0.61 ± 0.10		

<sup>a</sup>  $P < 0.05$  when compared with age D1.<sup>b</sup>  $P < 0.005$  when compared with dental age D1.

**FIG. 2.** Levels of leptin in serum in wild Anubis, wild Hamadryas, and captive baboons. *Upper panel*, Leptin levels were significantly higher ( $P < 0.001$ ) in captive than in wild baboons; *lower panel*, the leptin/body weight ratio was significantly higher ( $P < 0.005$ ) in captive, than in wild, baboons.

#### Leptin levels in captive baboons: comparisons with wild baboons

For comparisons with captive baboons, only data from male anubis and male hamadryas were used with the data from females and from hybrids omitted. This was done to avoid inclusion of pregnant females, who have much higher leptin levels than males and cycling females (27), and to avoid confounding analysis with the difference in adiposity that occurs between male and female baboons (28).

The leptin levels in the three groups are shown in Fig. 2 (*upper panel*). ANOVA showed that these groups differed [ $F(2,71) = 63.2, P < 0.001$ ], and the range test showed that

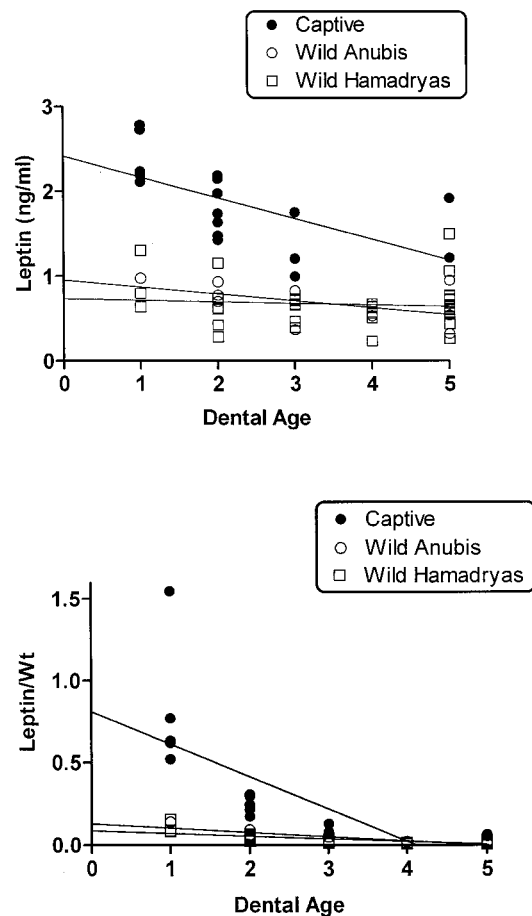
captive baboons had much higher serum leptin levels than the wild anubis ( $P < 0.001$ ) or hamadryas ( $P < 0.001$ ) baboons.

A correlation existed between dental age and leptin levels for the captive baboons (Fig. 3, *upper panel*): leptin =  $3.48 - 0.413$  (age),  $r = -0.636, n = 17, P < 0.01$ ). The correlation between dental age and leptin levels was not significant for the wild anubis or hamadryas males.

#### Morphometric characteristics of wild and captive baboon populations

The distribution of dental age among the three populations of wild baboons and the captive population are shown in Table 1. Fig. 4 shows the relation between chronological age and dental age, leptin levels, and body weight for the captive population of anubis baboons.

Differences in the leptin levels among the three populations raises the question of whether there were morphomet-



**FIG. 3.** Levels of leptin, as a function of dental age, in wild and captive baboons. *Upper panel*, Relation between leptin and dental age. A correlation existed for captive ( $P < 0.01$ ) baboons but not for the wild baboons. *Lower panel*, Relation between the leptin/body weight ratio and dental age. This ratio correlated with dental age for all three populations at the  $P < 0.005$  level. Prism software, used to compare the slopes for the leptin/wt ratio vs. dental age relation, showed that the captive baboons had a steeper slope ( $P < 0.001$ ), demonstrating that adiposity declined more steeply with age in captive baboons.

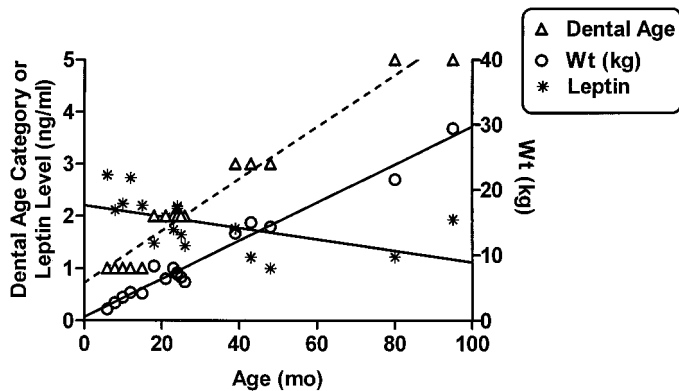


FIG. 4. Body weight and serum leptin levels, as a function of age, for captive baboons. Serum leptin decreased ( $P < 0.05$ ), and body weight increased ( $P < 0.001$ ), with age. The relation between dental age and chronologic age is also demonstrated.

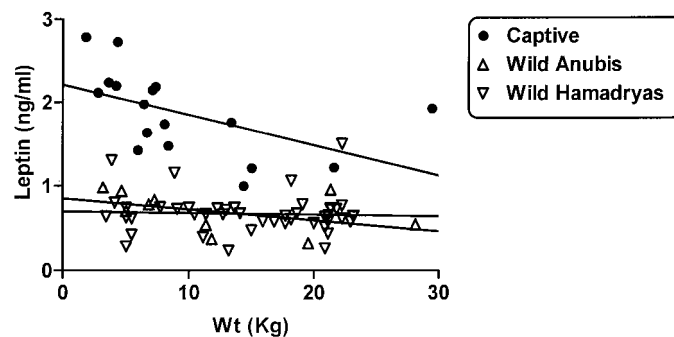


FIG. 5. Relation between levels of leptin in serum and body weight in captive and wild baboons. An inverse relation was statistically significant ( $P < 0.05$ ) for captive, but not for wild, baboons.

ric differences as well and whether those differences would correlate with leptin levels. Fig. 5 shows an inverse correlation of leptin with body weight for captive [leptin =  $2.21 - 0.0364(\text{weight})$ ,  $r = (-)0.522$ ,  $n = 17$ ,  $P < 0.05$ ] baboons but not for wild baboons. The slopes were statistically different among the three groups of baboons:  $F(2,67) = 4.02$ ,  $P < 0.05$ .

Whereas leptin inversely correlated with age, body weight positively correlated with dental age (Fig. 6;  $r > 0.9$  and  $P < 0.0005$  level for all three populations). Statistical differences existed among the slopes for the three groups ( $P < 0.01$ ).

To help place leptin levels in context with variations in body weight and age, we calculated the leptin/weight ratio (Fig. 2, lower panel). This ratio is an index of adiposity corrected for weight, and partially for age, because weight correlates closely with age (Fig. 6). Like leptin, the leptin/weight ratio was much higher in captive baboons [Fig. 2, lower panel;  $F(2,71) = 22.8$ ,  $P < 0.001$ ], and the range test showed differences between captive and the other two groups of baboons ( $P < 0.001$ ) but not between the wild anubis and wild hamadryas populations.

The leptin/weight ratio also correlated inversely with dental age ( $P < 0.005$ ; Fig. 3, lower panel) for the captive baboons with higher levels at younger ages. Leptin/weight ratios correlated with dental age in wild anubis ( $P < 0.005$ ) and hamadryas ( $P < 0.0001$ ) baboons as well, but statistical comparison showed that the slopes were much lower ( $P < 0.001$ ).

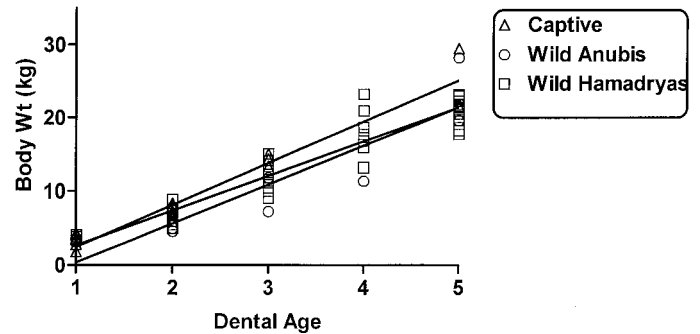


FIG. 6. Body weight vs. dental age in captive and wild baboons. Body weight increased with age in all three populations.

## Discussion

These results show that wild baboons exhibit very low leptin levels, comparable with those seen with starvation or disease in human and laboratory rodent populations (29). In wild baboons, leptin levels did not differ among species or between the sexes. Leptin levels were inversely related to age, and this relation was accentuated in the captive population. The correlation of leptin with the morphometric measure of body weight differed between wild and captive populations. A lower leptin/weight ratio for wild baboons showed that a lower percentage of their body weight represented adipose tissue. This difference in adiposity between captive and wild baboons tended to disappear with maturation. In comparison, differences in body weight between captive and wild baboons were less distinct than differences in leptin levels, especially at the younger ages, when leptin levels were most different. These findings suggest that the lower leptin levels were not caused by starvation but by a tendency for wild baboons at younger ages to carry a higher percent of their body weight as nonadipose tissue. These results and their implications for the role of leptin are discussed below.

These studies were possible because of the stability of leptin. Field conditions prevented the immediate refrigeration and centrifugation of blood samples. We showed (Fig. 1, bottom panel) with blood collected from the sedentary (Washington University) baboons that leptin in whole blood was stable at room temperature for at least 24 h. Interestingly, the leptin levels in these baboons, which were housed in individual cages, permitting less exercise, were higher than in either the wild or the Southwest Foundation baboons and approximated those seen in populations of laboratory rodents and in Western populations of humans (29). Field samples were stored at  $-70^{\circ}\text{C}$  for 2–4 yr before assaying. To determine whether leptin was stable for this period of time, we compared leptin levels in blood that was freshly obtained and in blood that had been stored for 5 yr. Because these two sets of blood came from the same population (the Southwest Foundation for Biomedical Research), were both randomly chosen from that population, and were of a statistically valid size ( $n = 10$  and 17), the mean of the two sets should be identical unless degradation of leptin had occurred. The finding that the means for these two sets were virtually identical, varying less than 3%, confirms the stability of leptin at  $-70^{\circ}\text{C}$ .

Comparison of leptin levels between wild and captive baboons was facilitated by a number of similarities between the study conditions of the two groups. Both groups were studied in the morning, negating diurnal effects on leptin levels. Both groups were anesthetized with im ketamine. The wild baboons had undergone a period of fasting similar to the 12-h fast of the captive baboons, given that wild baboons typically return to their sleeping sites before dusk and remain there beyond dawn the next morning. The Awash study site is within 10 degrees of the equator, with day-night cycles about equal year round. Consequently, the wild baboons have, alternately, a 12-h period of activity and feeding, and a 12-h period of confinement to the trees. The wild baboons were lured into the cage with corn; and so, many had broken their fast before being sedated. Fasting decreases (30) and high carbohydrate meals increase serum leptin levels (31). However, in humans, leptin does not begin to decline until more than 12 h of fasting, and high-carbohydrate meals do not increase serum leptin levels until 3–4 h after ingestion. Fasting and feeding probably had little effect on the measure of serum leptin levels under our sampling conditions. If fasting and feeding had affected serum leptin levels, they would have tended to decrease levels in the fasting captive baboons and to increase levels in the corn-fed wild baboons; thus, we would have underestimated the differences between wild and captive baboons. Baseline diets were also similar between wild and captive populations. The wild baboon diet (32) is about 30% leaves (6% fat), 10% flowers (8% fat), 45% fruits and seeds (6–7% fat), and 2% animal material (10% fat). Consequently, the wild baboons have a diet that is about 4% fat and 12% protein.

Leptin levels did not differ between wild anubis and wild hamadryas baboons (Table 2) in spite of their somewhat divergent ecological and developmental adaptations (23–25). Levels of leptin also did not vary as a function of sex (Table 2) in the wild baboons. The results for sex must be interpreted cautiously, because the number of females was small ( $n = 5$ ) and male/female differences may have been obscured by differences attributable to age or other factors. In humans, cycling females have higher levels of leptin in serum than males (33). In the wild baboons, a difference in leptin levels as a function of age was noted, but this was attributable entirely to the youngest animals having higher levels. No differences existed among the other age groups.

The majority of wild baboons, therefore, had levels of leptin in serum that were less than 1 ng/ml. These levels are seen only in humans with advanced states of starvation or with diseases such as cancer or anorexia nervosa. However, the evidence does not indicate that the populations of wild baboons were suffering from starvation when sampled. Mean sex- and age-specific body weights were normal for this population (unpublished data) and higher than those observed in animals measured during a known famine year, 1973 (23). In comparison with the homogeneity of leptin levels among the categories of wild baboons, leptin levels in captive baboons showed marked differences as a function of age and in comparison with the wild baboon levels. Captive baboons had leptin levels that were 3 times higher and leptin/weight ratios that were about 10 times higher than those for wild baboons (Fig. 2). Because levels of leptin in serum

strongly correlate with adiposity (21, 33, 34), this means that captive baboons had about 3 times as much fat as wild baboons and that fat represented a higher proportion of body weight. These results agree well with other estimates of adiposity. Altmann *et al.* (35) used the isotope dilution method to estimate that wild baboons contained about 1.9% fat, and Rutenberg *et al.* (36) calculated from autopsy that captive males from Southwest Foundation contained about 6.1% fat.

Leptin levels were not uniformly higher in captive baboons but were more pronounced at younger ages (Fig. 3). The decline seen here in leptin levels as a function of age is consistent with the work of Glassman and Coelho (28) and of Rutenberg *et al.* (36) showing that baboons become more lean with age. At the younger ages, when leptin was especially higher in captive compared with wild baboons (Fig. 3), there was little difference in body weight (Fig. 6). Therefore, body mass in wild baboons consists of less adipose tissue and more other tissues, such as bone or muscle. Interestingly, low leptin levels have been associated with increased bone density (18).

The simple explanation for differences in leptin levels is that these values reflect the different lifestyles of wild and captive baboons. Fat deposition occurs when caloric intake exceeds metabolic needs. In Western populations, obesity reflects overeating, or excess caloric intake, in the context of a sedentary lifestyle. In wild populations, however, the amount of fat deposited is more likely to reflect savings in energy expenditure. The more active lifestyle of a wild population would dictate that calories be first directed to building and maintaining muscle and bone rather than fat deposition.

Despite the differences in leptin at young ages between the wild and captive baboons, the adult populations differed little in their leptin levels. This is consistent with the findings of Lewis *et al.* (37, 38), who found that overfeeding or underfeeding during infancy did not affect the adipose mass of adult male olive baboons.

Leptin and its involvement in energy metabolism are presumably homologous in most (if not all) vertebrates, being found in chickens, lizards, and fishes (39, 40) as well as rodents, primates, and other mammals. It has been proposed (8) that the original role of leptin was to inform the brain not that adiposity was becoming excessive but that fat reserves were adequate to support expenditure of energy for other activities such as the initiation of puberty, reproduction, and enhanced immune function. Mating in primates, especially those with multiple sexual partners, is associated with challenges to the immune system (41). But the extra energy expended to support a challenged immune system can result in an increased mortality rate in a starving population (42). Finding an extremely low level of leptin in a healthy, wild nonhuman primate population supports the view that low levels of leptin may have been the norm during most of human evolution.

In conclusion, leptin levels are much lower in wild populations of baboons. Leptin did not vary with species or sex in wild populations. The wild baboons reported here were healthy and not starving, but their leptin levels were much lower than those of captive baboons, especially at younger ages. These observations are consistent with the view that the

original role of leptin as a signal of adequate, rather than excessive, fat stores was carried out at low concentration, and that, moreover, this original, low-concentration function is still retained in a natural, nonsedentary primate population.

### Acknowledgments

We thank the Ethiopian Wildlife Conservation Organization for permission to capture baboons in the Awash National Park, the Department of Biology at Addis Ababa University for facilitating the project, and students from Washington University and New York University who assisted in the field. We thank Joel Perlmutter (Washington University School of Medicine) for providing samples from captive anubis baboons (Washington University), and Terry Anderson for technical help.

Received January 10, 2001. Accepted May 25, 2001.

Address all correspondence and requests for reprints to: W. A. Banks, 915 North Grand Boulevard, St. Louis, Missouri 63106. E-mail: bankswa@slu.edu.

This work was supported by Grant NSF SBR-9615150 (to C.J.J. and J.E.P.-C.), funding from Veterans Affairs Merit Reviews (to W.A.B. and J.E.M.), and Grants R01-MH-54979 and R01-NS41863 (to W.A.B.).

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