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MEAT-ADAPTIVE GENES AND THE EVOLUTION OF SLOWER AGING IN HUMANS

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ABSTRACT

*The chimpanzee life span is shorter than that of humans, which is consistent with a faster schedule of aging. We consider aspects of diet that may have selected for genes that allowed the evolution of longer human life spans with slower aging. Diet has changed remarkably during human evolution. All direct human ancestors are believed to have been largely herbivorous. Chimpanzees eat more meat than other great apes, but in captivity are sensitive to hypercholesterolemia and vascular disease. We argue that this dietary shift to increased regular consumption of fatty animal tissues in the course of hominid evolution was mediated by selection for "meat-adaptive" genes. This selection conferred resistance to disease risks associated with meat eating also increased life expectancy. One candidate gene is apolipoprotein E (*apoE*), with the E3 allele evolved in the genus* Homo *that reduces the risks for Alzheimer's and vascular disease, as well as influencing inflammation, infection, and neuronal growth. Other evolved genes mediate lipid metabolism and host defense. The timing of the evolution of* apoE *and other candidates for meat-adaptive genes is discussed in relation to key events in human evolution.*

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DURING THE LAST several million years, our human ancestors evolved two major changes in life history that would appear to be mutually antagonistic: a shift from vegetarian to meat-rich diets and an increase in adult life expectancy. "Meat eating" as used here represents all animal tissues, includes fat, bone marrow and brains, as well as skeletal muscle. The major increase in meat eating in human ancestors would be expected to elevate blood cholesterol, which is a risk factor in both Alzheimer's disease and vascular disease. Other hazards of meat-rich diets include diet-induced hypercholesterolemia and infections. Thus, the increases in meat eating would be predicted to shorten life expectancy by promoting chronic diseases. We propose that *meat-adaptive genes* were evolved to delay dysfunctions and diseases of brain and heart caused by this increasingly meat-rich diet. We then consider candidates for meat-adaptive genes that would favor long life spans by minimizing acute and chronic diseases. Much is known about the unique human allele of apolipoprotein E, the *apoE* ε3 allele ("*apoE3*"), which decreases the risk of Alzheimer's and vascular disease in aging adults. We discuss the timing of evolution of *apoE* and other genes in relation to anatomical and physiological changes in our human ancestors that enabled increased hunting and meat eating. This discussion extends the arguments in Finch and Sapolsky (1999) that the evolution of prolonged reproductive schedules, intergenerational knowledge transfer, and slowed aging in humans relative to chimpanzees selected for *apoE3*. First, we evaluate the evidence for faster aging in chimpanzees. Supplemental information is given in the Appendix.

Life Expectancy and Aging in Chimpanzees

The aging patterns of chimpanzees and other great apes are very incompletely characterized (Cyranoski 2002; Hof et al. 2002; NHGRI 2002). Of the species closest to humans (*Pan* sp.), the chimpanzee (*Pan troglodytes*) has been studied longer and in more detail than the bonobo (*P. paniscus*). Evidence is consistent that survival beyond 50 years is rare in both species. Table 1 summarizes the substantial demographic data and the sparse information on physical and behavioral changes in aging chimpanzees with reference to human norms. Wild and captive animals are distinguished, because the latter are often fed dairy and meat products that may promote chronic disease, as discussed in detail below.

Relative to humans, chimpanzees have a 30-year shorter life span and an earlier acceleration of mortality rate (Goodall 1983, 1986; Kaplan et al. 2000; Hill et al. 2001) (Table 1, Note 1). The maximum life span of chimpanzees is about 60 years. At age 15, the chimpanzee life expectancy is about 15 more years in the wild. In contrast, human foragers have a life expectancy at age 15 of 40 more years. Hill et al. (2001) concluded that the mean adult life span of chimpanzees was about 60% shorter than hunter-gatherers and that manifestations of senescence begin about 20 years earlier. However, mortality rate differences between species or populations may not correspond directly to functional changes during aging. For example, the age of menopause has changed very little during the last 200 years in Europe and North America (Gosden 1985; vom Saal et al. 1994), despite the major increases in adult life expectancy.

Longitudinal studies of wild chimpanzees began at Gombe National Park (Tanzania) in 1960 by Goodall (1983, 1986) and show frailty and weight loss in individuals aged 35 or more (Table 1, Note 2). External indications of senescence include sagging skin, slowed movements, and worn teeth. Longitudinal life histories are being recorded in many other African sites, but a more complete geriatric profile of wild animals is needed for comparison with the ongoing studies of captives (e.g., the Great Ape Aging Project: FCCB 2002).

Postmortem studies of wild chimpanzees are largely restricted to skeletal remains. Bone thinning (osteopenia) may be earlier and more extensive than in modern humans (Table 1, Note 9). Lovell (1990a, 1990b, 1991; Lovell et al. 2000) showed in detail that traumatic bone injury from fractures and piercing wounds are very common in adults (Table 1, Note 10). Intriguingly, osteoarthritis was rarer than in most human populations (Table

1, Note 8), which Jurmain (2000) suggests may be due to better load distribution from quadrupedal locomotion. Dental malfunctions that would impair food ingestion are common, due to tooth wear from mastication of abrasive plant foods; tooth breakage and abscesses; and tooth loss from fighting (Table 1, Notes 2 and 11, and Appendix). To survive, wild chimpanzees must contend with the cost of accumulated injuries to bones and teeth, as well as to soft tissues.

Reproduction persists to advanced ages, despite indications of lengthened cycles and perimenopausal changes (Table 1, Note 12 and Appendix). At Gombe, one mother and her daughter, both high ranking, remained fertile until after 40 years; the subsequent cessation of sexual swellings strongly implies perimenopause. The late age fertility of these individuals may be unusual, because in humans natural fertility declines sharply after age 40 due to loss of oocyte quality as the ovarian stock of oocytes enters the final stages of depletion (Gosden 1985; vom Saal et al. 1994; Burger et al. 2002). In captivity, lengthened menstrual cycles may continue up to 50 years, just before death. The ovaries of aging chimpanzees and bonobos show very extensive oocyte depletion (Graham 1979; Graham et al. 1979; Gould et al. 1981). Oocyte depletion, as in human menopause, was apparently complete in one individual, who had no active luteal tissues or growing follicles (Gould et al. 1981). The very late menopause in chimpanzee, when it occurs, allows for a relatively short postmenopausal phase before death. Reproductive aging in other primates is surveyed in Table 1 (Note 12) and the Appendix.

As proposed by Hawkes et al. (1998), humans have evolved a prolonged postmenopausal phase, not found in the other great apes. The few other laboratory studies of primate species indicate a diversity in reproductive aging (Table 1, Note 12 and Appendix). Macaques have a definitive postmenopausal phase that is somewhat briefer than humans, when scaled to the maximum life span, whereas the grey mouse lemur resembles chimpanzees in retaining fertility until nearly the maximum life span.

Male chimpanzees are fertile beyond 40 but have an early onset of benign prostatic hyperplasia (BPH), according to a laboratory study that was unique by its sizable sample and rigorous clinical criteria (Steiner et al. 1999) (Table 1, Note 13). BPH occurred in 70% of males aged 30 or older. Serum prostate specific antigen (PSA) increased progressively during aging and in correlation with the degree of BPH. These findings suggest a 20-year earlier onset of senescence in male chimpanzees than in men.

Brain-aging changes are mild in laboratory chimpanzees relative to the devastations of Alzheimer's disease in humans. Preliminary findings do not show neuron loss or shrinkage (Erwin et al. 2001). The postmortem diagnosis of Alzheimer's disease is based on localized neurodegeneration in the frontal cortex and hippocampus, with neurofibrillary tangles and senile (neuritic) plaques containing amyloid β-peptide (Aβ) mingled with degenerating neurites. Humans with Alzheimer's disease, and to a lesser extent during normal aging, also have extracellular Aβ deposits around cerebral blood vessels (amyloid angiopathy) (see Table 1, Note 5 and the Appendix for criteria of Alzheimer's disease and controversies about Aβ). Two of the three aging chimpanzee brains showed amyloid angiopathy and some senile plaques containing Aβ in the same places afflicted in Alzheimer's disease (Table 1, Notes 4 and 5). There was no evidence of neurofibrillary degeneration, however (Table 1, Note 6). In contrast, the grey mouse lemur, rhesus monkey, and some other primates develop more typical Alzheimer changes during aging (reviewed in Finch and Sapolsky 1999). Although more chimpanzee brains must be evaluated at later ages, it is possible that chimpanzees and other great apes have less intense Alzheimer-type changes because their *apoE* gene sequence predicts an apoE protein with functions more like apoE3 than apoE4 (see below). There are limited indications that cognition becomes impaired during aging (Table 1, Note 7).

Vascular pathology in adult chimpanzees may be more prevalent than often thought, according to early observations that could not be as comprehensive as enabled by current technology. In the only report on wild adults shot in their habitat, half (2/4) had atherosclerotic plaques in the thoracic aorta (Vaste-

TABLE 1

Comparative aging in chimpanzees (Pan troglodytes) *and humans*

Trait	**Chimpanzee**		**Human**
	Wild	Captive	
Demographics			
• life expectancy, age 15 yrs[1]	30 yrs	30–45 yrs	55–85 yrs
• survival to 40 yrs[1]	10%	20–40%	40–95%
• survival to 60 yrs[1]	<1%	<1%	30–90%
Appearance of the Aged[2]	Frailty and emaciation are common	Not reported (NR)	Varies widely
Heart: Cardiovascular Lesions[3]	NR	May be common	Common by 65
Brain			
• cerebrovascular amyloid[4]	NR	May be common	Common by 75
• senile plaques[5]	NR	May be common	Common by 85
• neuritic degeneration[6]	NR	Not found	Common by 85
• Alzheimer's disease neurodegeneration with specific neuron loss[7]	NR	Not found	Common by 85
Bone			
osteoarthritis[8]	Rare		Common
osteoporosis[9]	May be common		Very common
fractures[10]	Traumatic fractures common		Spontaneous fractures common
tooth wear and loss[11]	Common		Varies widely
Reproduction Female: Menopause and Postmenopausal Interval[12]	Fertile throughout most of the life span	Fertile throughout most of the life span	Menopause is universal by 55 yrs; 25 year life expectancy after menopause
Reproduction Male: BPH (Benign Prostatic Hypertrophy)[13]	NR	Common by 30	Common by 65
Sensory Impairment: Eyes[14]	NR	NR	Lens opacity and cataracts are common by 75

Notes to Table 1

1. Chimpanzees from five African populations (Kaplan et al. 2000; Hill et al. 2001) and one laboratory (Dyke et al. 1995) versus humans: foragers, lower limit (Kaplan et al. 2000; Hill et al. 2001) and affluent populations, upper limit (Kinsella and Tauber 1992).
2. Field observations at Gombe indicate geriatric conditions (Goodall 1983, 1986; Courtenay and Santow 1989; Hill et al. 2001). Old age is about age 32 to death. Chimpanzees become "increasingly frail and emaciated" in their last years (Goodall 1986:113; Craig Stanford, personal communication). "There is a gradual slowing down of activity . . . tendency to withdraw from intensive social interaction. Teeth become worn or broken, there is thinning of the hair. Very few lived long enough to be classified as old . . . little doubt that old age itself was primarily responsible for their deaths." See Appendix and Tarou et al. 2002.
3. Extensive "spontaneous" vascular lesions are reported in captive adult chimpanzees. At Yerkes, all adults had focal fatty lesions on the aorta and cerebral arteries; the severity was increased by adding dietary fat (Andrus et al. 1968). Zoo animals show progressive coronary arterial thickening and lipid accumulation (Vastesaeger and Delcourt 1962, 1966; Ratcliffe 1965; Lindsay and Chaikoff 1966; Bourne and Sandler 1973) and fatal myocardial infarcts (Manning 1942; Ratcliffe 1965). Comparisons with human vascular disease were emphasized decades ago: "The more conspicuous lesions of chimpanzees were human-like atheromatous plaques with foam cells and cholesterol crystals" (Vastesaeger and Delcourt 1962) and "both the human and chimpanzee on a general diet not necessarily rich in cholesterol can develop atheromas spontaneously . . . the chimpanzee is a practically perfect model for the study of human atherosclerosis" (Bourne and Sandler 1973). See Appendix for other examples. These reports appear to challenge a widely quoted statement (Schmidt 1978): "Widespread vascular disease (other than atherosclerosis) has not been commonly reported in chimpanzees." However, Table 1 of that source shows gross cardiovascular lesions in 13.5% of autopsies (268 captive animals). The age range (not given) is cogent because young or juveniles should have fewer or smaller lesions than adults, e.g., as shown in samples from the Philadelphia Zoological Gardens (Ratcliffe and Cronin 1958). Although no aortic or myocardial pathology was reported in a sizable sample of young females, 1 to 14 years (Kennard and Willner 1941), more detailed histopathology showed intimal sclerosis in neonates (Vastesaeger 1965). Small fatty streaks with inflammatory cells are now considered ubiquitous in human neonates and children (Napoli et al. 1999).
4. The two oldest chimpanzee brains from females aged 56 yrs (Bula) and 59 yrs (Gamma) (Yerkes Primate Center) had cerebrovascular deposits of the amyloid β-peptide (Aβ) (Gearing et al. 1994, 1996, 1997; Erwin et al. 2001). In humans, cerebrovascular amyloid increases with age in association with focal ischemia and infarcts (Olichny et al. 2000; Thal et al. 2002).
5. These aging brains (Note 4 above) had Aβ-containing diffuse amyloid plaques in the cerebral cortex and hippocampus (Gearing et al. 1994, 1996, 1997); i.e., in the regions of human AD brains where there are extensive Aβ deposits and neuron loss (Terry et al. 1999; Klein et al. 2001; Hardy and Selkoe 2002). See Appendix for criteria of AD.
6. In contrast to brains in human AD or in aging monkeys, these two oldest chimpanzee brains (Note 4) did not have indications of degenerating neurites in the diffuse amyloid deposits (Gearing et al. 1994, 1996, 1997; Erwin et al. 2001). Neurofibrillary degeneration was absent and Alz-50 immunoreactivity for hyperphosphorylated tau, though present, was rare. This is important, because neuritic or neurofibrillary degeneration, with aggregated and hyperphosphorylated tau in microtubules, is a major characteristic of AD.
7. There are no detailed studies of cognitive changes in aging chimpanzees. Observations of two captives aged 50 at Yerkes did not show notable changes in behavior (Tarou et al. 2002). However, one elderly female may be showing "cognitive and behavioral disturbances" (Erwin et al. 2001). The effectiveness of the 40-year-old Evered as a hunter (Appendix) indicates normal cognition. Macaques show extensive cognitive impairments in correlation with neuropathologic changes (Price et al. 1991; Finch and Sapolsky 1999; Hof et al. 2002).
8. Osteoarthritis was rare in skeletons at Gombe (Jurmain 1977, 1989, 1997). Human foragers differ widely in the incidence and severity of osteoarthritis (Jurmain 2000).
9. Osteoporosis may be common in aging chimpanzees, as indicated by decreased bone density with loss at endosteal surface and cortex (Sumner et al. 1989; Zihlman et al. 1990). Data are limited: two females with ages estimated at 40+ years had a 40% lower bone mineral index than three aged 25 to 33 years (Sumner et al. 1989). This difference, if validated in more specimens, would far exceed the bone loss of most premenopausal women.
10. Traumatic injury from falls and fights is common; healed breaks or wounds in 25% to 54% (Duckworth 1911; Schultz 1939; Goodall 1983; Lovell 1990a; Jurmain 1997). See Appendix.
11. In natural death at Gombe, the teeth of those ≥33 years had extensive tooth loss and erosion to the cement-enamel junction; abscesses were common (Kilgore 1989; Lovell 1990a, 1990b; Zihlman et al. 1990; Morbeck et al. 2002; Table 1, Note 2). See Appendix.
12. Captive chimpanzees >40 yrs showed lengthened menstrual cycles and decreased perineal swelling (Graham 1979; Gould et al. 1981). Cycles continued until the year before death, even in individuals aged 49 to 50 yrs. The ovaries of aging chimpanzees and bonobos show extensive oocyte depletion (Graham 1979; Graham et al. 1979; Gould et al. 1981), which resembled the human postmenopausal ovary in one individual (Lokalema) (Gould et al. 1981). Ovarian tumors are also reported (Graham and McClure 1977). It is unlikely that chimpanzee ovary aging differs fundamentally from that of humans. See Appendix for reproductive aging in other primates.
13. Aging males show definitive benign prostatic hypertrophy (BPH) by state-of-the-art clinical criteria (Steiner et al. 1999). See Appendix.
14. The effectiveness of the elderly Evered as a hunter (Appendix) indicates normal vision.

saeger and Delcourt 1961). In captives, vascular pathology is not rare (Table 1, Note 3) and clinical levels of hypercholesterolemia are common (Table 3A, below). The diets provided in captivity typically have more animal fat than in the natural diet (Conklin-Brittain et al. 2002) as discussed below, often including dairy and milk products (Table 3, Note 9). Other factors promoting vascular lesions are lack of exercise and the stress of confinement.

The data on aging for chimpanzees generally fit the canonical pattern of aging in humans and other primates (Finch 1990; Finch and Sapolsky 1999). The indicated absence of osteoarthritis and menopause would be an important difference from humans, whereas the presence of BPH and osteoporosis is consistent with the human pattern. Many mammals have similar schedules of the progression of BPH, osteoporosis, and amyloid accumulation, when normalized to the life span. This general proportionality of changes in aging to the life span resembles the "life history invariants" and "scaling factors" in life history models (Charnov 1993). However, the demographics of mortality may not inform the details of aging. For example, accelerations of mortality during aging may arise from different factors in wild and captive chimpanzees, which have different traumatic injuries and activity patterns. There is an urgent need to characterize aging in the wild because of catastrophic declines in natural populations of the great apes (Walsh et al. 2003). Otherwise we may not draw sound conclusions about aging using captive populations, for the cellular and physiological basis of the scaling factors of life history that changed during human evolution.

Diet and Hominid Evolution

vegetarians and meat eaters

The anthropoid primates have been primarily vegetarians for the past 35 million years (Andrews and Martin 1991; Milton 1993; Stanford 1999). Foraging by the great apes for scattered locations of ripe fruit and other choice foods occupies most of the waking hours (75% for chimpanzees) and begins even before weaning at 4 to 5 years. Chimpanzees in particular are considered as specialists in ripe fruit. However, among the higher primates, chimpanzees and humans are the most omnivorous (Milton 1999a, 1999b; Stanford 1999; Conklin-Brittain et al. 2002; Eaton et al. 2002).

Only chimpanzees are frequent eaters of mammalian meat among the four great apes, which helps to interpret the meat-eating behaviors of prearchaeological hominids. Chimpanzees routinely and systematically hunt colobus monkeys and other smaller mammals (Goodall 1986; Boesch and Boesch 1989; Stanford et al. 1994; Stanford 1998; Bunn 2002), but the amounts consumed are generally minor. At the upper range, some individual chimpanzees have a daily intake of about 70 g of animal tissues, averaged over the year. Hunting and meat eating is mainly by adult males and appears to serve social interactions, such as favors by subordinate males or to attract females (Stanford et al. 1994; Stanford 1998). More meat may be eaten in the dry season when hunting is easier (Stanford 1998). The amount of hunting and meat eating varies widely between individuals and is negligible in some communities (Goodall 1986; Stanford 1998).

Overall intake of fat by chimpanzees is considered to be much less than that of humans. Note that the available figures for natural anthropoid diets are not easily compared with the human, which by convention give components as a percent of the total energy. Dietary lipid intake at one site (Kibale National Park) was estimated at about 2.5% by dry weight annual average (Conklin-Brittain et al. 2002). Although these data are very limited, it is hard to imagine that chimpanzees could ever consistently obtain the level of dietary fat in humans. Westernized diets of 15% to 25% fat by dry weight are even exceeded by the 38% to 49% fat of foragers' diet (Kaplan et al. 2000; Cordain et al. 2001, 2002a, 2002b; Conklin-Brittain et al. 2002; Eaton et al. 2002).

Most of the fruit, leaves, and stems eaten by anthropoids have negligible cholesterol and are low in saturated fats (Cordain et al. 2001; Eaton et al. 2002; Table 1, Note 3). Fats may be obtained from oily nuts, however (Goodall 1986; Conklin-Brittain et al. 2002; Mercader et al. 2002); e.g., Panda nut (*Panda*

oleosa) is rich in fatty acids (saturated, 32%; polyunsaturated, 26%) (Foma and Abdala 1985). Chimpanzees avidly search for and eat termites and other insects, which provide rich fat sources. At single sessions of termite foraging, chimpanzees harvest an average of 65 g wet weight (McGrew 2001), which is close to the 70 g daily intake of meat by some individuals, as noted above. Females are the most active insect eaters the year round, eating threefold more termites than males (McGrew 1992; Craig Stanford, unpublished). Although many anthropoids search for and eat bird eggs (rich in fatty acids and cholesterol), the quantities are negligible in the total caloric intake of chimpanzees. A detailed inventory of the types of plants and insects eaten by various wild chimpanzee populations is being developed (Stanford 1998; McGrew 2001; Rodman 2002). However, little is known about the annual intake of specific macro- and micronutrients.

During the 5 to 8 million years since divergence from a common *Pan* ancestor (Ruvolo et al. 1991; Brunet et al. 2002; Tavaré et al. 2002; Wall 2003), humans have evolved major anatomical and physiological differences that can be understood in relation to hunting and diet. Bonobos, which diverged from common stock with chimpanzees about 1 to 2 million years (Mya) ago (Stone et al. 2002), do not hunt or eat meat as avidly as chimpanzees (Hohmann and Fruth 1993). The gorilla and the orangutan eat little meat in the wild (Table 2). These major species differences in meat consumption could be due to cultural or physiological factors.

Since Dart (1953), reconstructions of early hominid behavior have been based on diet. In many social animals, behaviors and social interactions are profoundly influenced by energy balance; i.e., the need to balance energy output with nutrient energy intake for growth and reproduction. Vertebrate tissues ("meat"), if a major part of the diet, give a concentrated packet of nutrients and calories that reduces the time spent in searching for lower yield plant foods. This new dietary resource may have conferred key advantages to later hominids, when tool use enabled the acquisition and eating of large, transportable amounts of meat (Isaac and Crader 1981; Milton 1999a; Stanford 1999; Kaplan et al. 2000).

Meat eating is often considered as a critical dietary adaptation in human evolution. However, the timing of its emergence in the diet of human ancestors and their mode of meat procurement are unclear (Stanford and Bunn 2001; Teaford et al. 2002). The current view of hunting and scavenging is based on three areas of study: meat eating by nonhuman primates; meat eating by modern foragers; and fossil evidence of meat eating (Table 2). By 2.5 Mya, early humans were becoming omnivores, as indicated by tool manufacture and hominid-made cutmarks on mammalian bone fossils (Bunn and Kroll 1986; Shipman 1986; Asfaw et al. 1999) (Table 2). By 100,000 years ago, anatomically modern humans had sophisticated tools for hunting and removing flesh.

Early hominid diets are inferred from patterns of tooth wear (Teaford and Ungar 2000; Teaford et al. 2002), associated tool artifacts (Bunn and Kroll 1986; Shipman 1986), and from isotopic signatures in fossilized bone (Sponheimer et al. 1999; Schoeninger et al. 2001). Skeletal remains show that *H. ergaster* extracted bone marrow, whereas Neandertal and paleolithic (anatomically modern) humans also extracted brains. The organs consumed are important because of differing content of pathogenic factors as discussed below. However, the fossil record does not inform about the relative amounts of different organs eaten; nor the total meat consumed (Conklin-Brittain et al. 2002); nor the relative yield from hunting (Stiner et al. 2000; Speth and Tchernov 2001) versus scavenging (Isaac and Crader 1981; Bunn 2002). Meat consumption is hard to estimate because small mammals, such as those hunted by chimpanzees, leave fewer archeological traces than larger animals (Stanford 1998).

Developmental Schedules

The postnatal developmental schedules of chimpanzees and hunter-gatherers (foragers) give an important perspective on the evolution of meat eating. Acquisition of hunting and foraging skills generally requires extensive training, which may be prolonged beyond adolescence, depending on the task (Kaplan et al.

TABLE 2
Meat sources of African great apes and human ancestors

	Gorilla[1]	*Pan*[1]	*Australopithecus*[2]	*Homo ergaster*[3]	*H. neanderthal*[4]	*H. sapiens*, Paleolithic[5]
mammal skeletal muscle	No	Yes	Yes	Yes	Yes	Yes
mammal brain	No	Yes	?	?	Yes	Yes
mammal brain marrow	No	Yes	?	Yes	Yes	Yes
mammal viscera	No	Yes	?	?	?	Yes
reptile/bird	No	Rare	?	?	Yes	Yes
eggs	No	Rare	?	?	?	Yes
fish	No	No	?	?	?	Likely
insect	Yes	Yes	Likely	Likely	Likely	Likely
cannibalization	No	Yes	?	?	Yes	Yes

Notes to Table 2

1. Organs consumed by chimpanzees (Stanford 1999; Stanford and Bunn 2001). Both sexes occasionally kill and eat the infants of other females in their group. Cannibalism is very rare in bonobos, gorillas, or orangutans (Goodall 1986).
2. Australopithecines 2.5 Mya extracted marrow from long bones, as indicated by induced fractures (e.g., de Heinzelin et al. 1999). Some australopithecines ("robust taxa") had large chewing muscles and large, thickly enameled cheek teeth indicative of herbivory (e.g., Andrews and Martin 1991). Stone tools were very limited and crude.
3. Early *Homo* had smaller molars than *Australopithecus* (Andrews and Martin 1991), suggesting less reliance on tough fibrous plants, consistent with evidence for tool use in obtaining meat by scavenging or hunting.
4. Neanderthals obtained most protein from animal sources (isotopic analysis, $\delta^{15}N$), approximating that eaten by nonhuman carnivores (Richards and Hedges 2000; Richards et al. 2000; Speth and Tchernov 2001). The hypothesized cannibalism by Neanderthals is consistent with evidence for defleshing in skulls by stone tools; e.g., at one Neanderthal cave site (Moula-Guercy, 0.1 Mya), all human crania and limb bones had cut marks and fractures; other cut marks indicate defleshing, including removal of the tongue (Defleur et al. 1999). However, such findings do not evaluate the frequency of kills and meat eating (O'Connell et al. 2002).
5. Some modern hunter-gatherers, e.g., the Aché, save prey animal brains for their young children (Hillard Kaplan, personal communication).

2000; Bliege Bird and Bird 2002). Kaplan et al. (2000) argue that the transition from an ape subsistence forager to a human hunter-gatherer was enabled by biological changes associated with increased meat eating. First, human hunting requires long years of skills training. Humans lack the anatomical weapons (specialized teeth and claws) of other hunting mammals, which necessarily extends their time to full independence. The high-risk period of juvenile and adolescent development is offset by the increased return-rates that hunters gain as adults. Multigenerational transfers of knowledge and materials are unique to humans; the evolution of grandmothering (Hawkes et al. 1998; O'Connell et al. 1999) may be a special case. The coevolution of prolonged postnatal development of large brains and increased life span has been analyzed in terms of the theory of embodied capital (Kaplan and Robson 2002).

Net food production is dramatically greater among foragers than among chimpanzees, as measured by the ratio of calories consumed to calories expended (Kaplan et al. 2000). Human foragers typically do not achieve maximum skills and yield of hunting live prey until their third decade, or 5 to 10 years after puberty. Chimpanzees become fully capable foragers far earlier, during their first decade (Kaplan et al. 2000). However, in one location (Taï Forest) hunting yields may peak later, around 20 years (Boesch and Boesch-Achermann 2000).

Physical and mental development of humans shows corresponding delays relative to chimpanzees, which could only have been achieved by the evolution of tradeoffs in reproductive success, including slower aging (Finch and Sapolsky 1999; Kaplan et al. 2000). Humans have a spurt in long-bone growth during adolescence that is absent in chimpanzees (Bogin 1999a, 1999b). Brain maturation continues after puberty and takes 5 to 10 years longer than in the great apes, whose brains are mature by puberty. Dendritic maturation in humans continues into adolescence (Huttenlocher and Dabholkar

1997; Sowell et al. 1999, 2001), the prefrontal cortex maturing later than other regions. Myelination, which enables high-speed neural traffic, continues into the third and fourth decades, depending on the brain region (Allman and Hasenstaub 1999; Giedd et al. 1999; Sowell et al. 1999, 2001, 2002; Bartzokis et al. 2003). This schedule of maturation matches the slow maturation of complex executive functions and emotional control, which are seated in the prefrontal cortex (Sowell et al. 1999) and which are crucial to hunting and other cooperative human activities.

Women achieve their full capacity for child bearing later after menarche than in chimpanzees. Notably, the birth canal (pelvic inlet) does not reach full size until at least five years after menarche (Moerman 1982; Abitbol 1996; Berge 1998; Bogin 1999a, 1999b), even later than long-bone maturation occurs. Delayed pelvic maturation is one factor in the danger of pubertal pregnancies to mother and child, even in modern circumstances. Chimpanzees do not show a comparable delay in pelvic development (Berge 1998), consistent with their five-year earlier onset of female reproduction (Goodall 1983; Bogin 1999b) and acquisition of adult foraging skills (Kaplan et al. 2000).

Mortality of infants and all later ages is much lower among foragers than among chimpanzees (Goodall 1986; Kaplan et al. 2000). Few chimpanzees survive beyond 35 years in their natural habitats, an age when some human hunters have just reached their peak. Milton (1999b) has proposed that meat eating was required for sufficient dietary quality to enable this prolonged learning curve to be evolutionarily favorable. The extended life spans of humans may have been evolved at least in part to allow for the prolonged training to acquire meat (Kaplan et al. 2000; Kaplan and Robson 2002).

Meat in Normal Development

Despite the weight of evidence for the social value of capturing and sharing meat, we do not know if meat was nutritionally essential for optimum growth and development in early humans. Vegetarian diets give a hint of the evolved importance of meat eating. On one hand, humans do not require meat for high performance, e.g., vegan athletes can be competitive on carefully chosen diets supplemented with micronutrients (Nieman 1988; Houtkooper 1992; Kleiner 1995; ACSM 2000), with larger portions to compensate for the slower digestion of plant fibers. On the other hand, vegan diets are risky for children. Those raised on vegan-type macrobiotic diets have a high risk of deficiencies in vitamins D and B_{12} (cobalamin) in association with slower growth, rickets, and mild cognitive impairments; the latter persisted despite subsequent diet improvements (Dagnelie et al. 1990; van Dusseldorp et al. 1996, 1999; Haddad et al. 1999; Louwman et al. 2000). Vitamin B_{12} is not provided by plant foods.

Polyunsaturated fatty acids (PUFAs) are another key dietary factor. Cordain, Eaton, and colleagues proposed that meat became an essential source of PUFAs for postnatal brain development during human evolution (Eaton 1992; Cordain et al. 2001, 2002a, 2002b). Paleolithic efforts to open the skulls of prey and their own species (Table 2) might also have supplied PUFAs, in which the brain is rich. At some time in our prehistory, fish became another source of PUFA precursors and other fats, possibly in the Rift Valley (Crawford 1992; Broadhurst et al. 1998). Some hunter-gatherers feed brains to their young children (Table 2, Note 5), implying the importance of fat (possibly PUFAs) for growth. Meat eating greatly increases access to PUFAs with two double bonds that are scarce in plant material (Eaton 1992; Youdim et al. 2000; Cordain et al. 2002a). Mammals lack enzymes to synthesize the "essential" PUFAs (Innis 2000; Nakamura et al. 2001). In particular, arachidonic acid (AA) and docosahexaenoic acid (DHA) are made from different dietary precursor fatty acids (AA from linoleic acid, DHA from linolenic acid) by desaturases and elongases (Nakamura et al. 2001). DHA deficits can impair brain development (Ravnskov 1998; Sanders 1999; Innis 2000; Nakamura et al. 2001). However, PUFA requirements are unclear; e.g., infant formulas in the USA contain precursors, but not AA or DHA, which are added elsewhere (Bowen et al. 1999). Even on normative diets, the level of PUFA intake influences brain development, e.g., the ratio of AA:DHA in

mothers' milk correlated strongly with neonatal brain growth (Xiang et al. 2000), whereas PUFA intake at 5 years correlated with speech and motor skills (Rask-Nissila et al. 2002). Yet these individual differences fall within the normal range.

The developmental deficits among vegans raise the question of whether variations in chimpanzee diets compromise postnatal brain development or adult health. Although there is no strong indication that meat eating by chimpanzees is critical for successful pregnancy and weaning or normal postnatal development (Conklin-Brittain et al. 2002; Craig Stanford, unpublished), detailed studies are needed. We conclude that meat eating was important to human evolution by reducing the risk of marginal neurological impairments from sporadic deficits of micronutrients, as well as providing a highly efficient energy source. A lower risk of retarded motor and learning functions during prolonged development would favor the hunting and gathering skills required for reproductive success.

Meat Eating in Cardiovascular and Cognitive Health

Has tolerance been acquired during human evolution to adverse effects of meat eating? This question is important because diets based on mammalian tissues have risk factors for cardiovascular and Alzheimer's disease, particularly cholesterol and fats. Other risk factors may include infectious organisms and excessive metal ions. Evidence discussed next indicates that chimpanzees are highly susceptible to hypercholesterolemia and obesity when fed diets rich in animal tissues or dairy products and maintained under sedentary conditions.

hypercholesterolemia in captive chimpanzees

Lacking information on blood lipids in wild populations, we can learn much from studies of captives on different diets, especially the baseline diets that are widely used in nonhuman models of atherosclerosis (Wissler and Vesselinovitch 1968; Armstrong et al. 1974; Clarkson 1998). Hypercholesterolemia, as we show below, is common in captivity under standard husbandry, which markedly deviates from the wild vegetarian-based diet and the reduced level of physical activity.

Most laboratory animals on baseline "nonatherogenic diets" had elevated total cholesterol (>200 cholesterol mg/dL serum in 13/17 groups of animals from 12 colonies). Table 3A presents studies in rank order, high to low, of serum total cholesterol for chimpanzees (Column III); other primates are shown in Column IV; darker shadings in Columns III and IV indicate high and borderline cholesterolemia, respectively, by the clinical criteria of the National Heart, Lung, and Blood Institute (NHBLI). Diet composition is given in Table 3A and Notes, if reported. Wild-born captives in some early studies had a high incidence of illness, which could alter blood lipids (Bereznay 1959).

The highest and lowest blood cholesterol were reported from African laboratories where animals were fed vegetarian diets, which implies strong effects from captivity (lack of exercise, stress, or illness). The highest plasma cholesterol was reported for wild chimpanzees in captivity which were fed a "quite vegetarian diet" containing palm oil (Vaestesager and Delcourt 1961). Although palm oil is considered antiatherogenic, it may contain oxidation products (particularly if reheated for cooking), which induce hyperlipidemia and are also cytotoxic to heart, liver, and kidney (Edem 2002). Thus, the high cholesterol values in this early study could have been diet-induced. Few of the other baseline diets resemble natural diets, which are mostly ripe fruit. The fat content of 5% to 10% in many commercial chows is two to fourfold higher than the 2.5% fat indicated for wild diets, as discussed above and in the Appendix. Although some studies assumed that the baseline diets had low cholesterol, none directly analyzed cholesterol. Hypercholesterolemia (>240 mg/dL) persisted for many years in two colonies (Table 3, Notes 2 and 3). The wide individual differences in blood lipids on standard diets implies genetic influences, for which there is direct evidence in laboratory populations (see below).

Steinetz et al. (1996) gives the most detailed characterization of blood lipids and

TABLE 3A

Total plasma cholesterol of primates on control diets

I: Human Clinical Criteria	II: Study and Daily Diet	III: Chimpanzee Cholesterol (mg/dL, no. animals, sex)	IV: Other Species in Cited Study (no. animals, sex; range)	
High ≥240 mg/dl	Quite vegetarian . . . bananas, rice, palm oil [1a]	286 ± 76 (N = 56)		
	Purina Monkey Chow 25™ + fruit + 7% butter[2]	282 ± 27 (N = 4)	Baboon 101 ± 5 (N = 12) Green 173 ± 24 (5) Rhesus 148 ± 7 (5)	
	Mostly vegetarian . . . a little milk, and sometimes eggs [1b]	272 ± 18 (7)		
	Fruit, vegetable, 1 egg, 0.5L skim milk[1c]	259 ± 21 (10)		
Borderline High 200—239 mg/dl	PMI Jumbo Monkey Diet 5037; 11% fat[3]	248 ± 64 (5 F-lean)		
		232 ± 55 (13 F-fat) 207 ± 63 (12 M-lean)		
	Purina Monkey Chow + some cereal grains, fruit, vegetables[4]	233 ± 20 (18 F; 152—314) 202 ± 26 (8 M; 135—269)	Baboon 97 ± 25 (10 F, 27—167) 101 ± 13 (15 M, 52—150)	
	purified diet + fruit[5]	225 (3)		
	Fruit, green vegetables, milk[1c]	223 ± 25 (9; 155—373)	Gorilla 253 ± 26 (6)	Orangutan 307 (2)
	primate chow (7.5% fat) + fruit[6]	218 ± 15 (6)		
	Purina Chow[7]	203 ± 48 (43)	Gorilla 272 ± 85 (5)	Rhesus 155 ± 31 (142)
Normal <200 mg/dl	basic ape + full milk[1d]	185 ± 12 (4 M)		
	standard monkey chow[2]	167 ± 27 (13)		
	classic vegetarian diet fruit, vegetables + 0.75L Cerelac[8]	168 ± 8 (15 F) 157 ± 7 (13 M)		

Data in Columns III and IV list the number of animals, sex, and data range (mean ± SE<). Studies (Column II) are ranked in descending order of plasma cholesterol for chimpanzees (Column III); shadings correspond to human clinical criteria for elevated cholesterol (Column I); other species, where reported in the same study (Column IV).

TABLE 3B

Blood lipid responses to increased dietary cholesterol

Species, Diet, Citation	Response	Comment
Chimpanzee and baboon Control diet (N = 4): "basic diet" + fruit + 1 egg + 0.5L skim milk Atherogenic diet (N = 6): 2.5% cholesterol (est. 7.5 g/d) + butter + 1.0L skim milk for 1.5–3.0 years [1c]	The atherogenic diet increased total plasma cholesterol in chimpanzees from 259 ± 21 to 606 ± 76 mg/dL (+134%); in baboons, from 117 to 203 mg/dL (+73%). LDL (β-lipoproteins) were increased twofold more in chimpanzees than baboons. One chimpanzee with extreme cholesterolemia (600–900 mg/dL) died suddenly of myocardial infarction after 20 months.	These baseline values of total and LDL cholesterol were at the upper range in Table 3A above. The much greater hyperlipidemic response could be due to the much longer cholesterol feeding (1.5–3 years) than in Srinivasan et al. 1976 (three weeks) (Note 2).
Chimpanzee, dog, human, rhesus Control diet, "purified diet" with low cholesterol: casein 20%; sucrose 61%; lard 15%; salt and vitamins Atherogenic diet (N = 3 chimpanzees), sequential increases and decreases of cholesterol 0.05% to 1% (up to 5g/d)[5]	The added cholesterol increased plasma total cholesterol from 225 mg/dL up to 500 mg/dL within 30 days on 150 mg cholesterol/d. Return to control diet decreased cholesterol to baseline values in 3 weeks (Mann 1972: Figure 4). The dietary cholesterol to double serum cholesterol: chimpanzee, 3.7 mg/kg/day (ca. 150 mg/day); rhesus, 5.5 mg/kg/d for; dog, 13 mg/kg/d; human, 18 mg/kg/d (Mann 1972: Table II).	Mann's (1972) conclusions must be viewed cautiously because this pilot study had only three animals and the report was very brief. However, the chimpanzee-human differences may be even larger because plasma responses to dietary change in clinical studies are smaller than in Mann's figures (Note 5).
Chimpanzee (N = 7, mostly adults) Supplements of 2–8 g cholesterol/d for two months, equal to huge numbers of eggs (Note 1d); two month pre and posttreatment samplings; the basal diet was "mostly vegetarian . . . a little milk, and sometimes eggs"[1b]	The increased dietary cholesterol had no consistent impact on blood cholesterol.	These "negative" results resemble those of Srinivasan et al. (1976a,b) below (Note 2) may be due to the much shorter duration of cholesterol feeding (two months) that in Peeters and Blaton (1972) and Blaton et al. (1974a,b) (see Note 1c).
Chimpanzees and five monkey species Control diet (N = 6), Purina Monkey Chow 25 + fruit+ 7% butter (cholesterol<0.005%) Atherogenic diet, with cholesterol add for 3 weeks in a series of 0.05 % to 1.5% cholesterol (3.8 g/day, see note 1); return to control diet for 3 weeks between steps[2]	Chimpanzees had higher initial serum cholesterol than five monkey species (see Note 2). Dietary supplements of cholesterol caused modest increases of total serum cholesterol and HDL. Green, patas, and rhesus had greater proportionate increases than chimpanzee above considerably lower initial serum cholesterol.	The modest % increases of serum cholesterol and LDL over most of the range could be due to ceiling effects from the very high initial values of controls, total plasma cholesterol (282 mg/dL) and LDL (290 mg/dL). Note that chimpanzees were fed different batches than the other species and that the duration of treatment was much less than in Peeters and Blaton (1972) and Blaton et al. (1974a,b) (see Note 1b,c).

Notes to Tables 3A and 3B

1a. The Medical Laboratory of Stanleyville (Kinshasa, formerly Belgian Congo). Vastesaeger and Delcourt (1961, 1962) summarize data from 60 chimpanzees aged 1–9 years (infants to preadults) who were wild born and captive for 0.5 to 3 years; age groups had averages in the range 263–307 mg/dL; serum cholesterol was not related to age, sex, or length of captivity.

1b. Antwerp Zoo (Bereznay 1959; Vastesaeger and Delcourt 1961, 1966), including wild caught specimens.

1c. Simon Stevin Instituut, Brugge (Vastesaeger et al. 1972; Peeters and Blaton 1972; Blaton et al. 1974a, 1974b).

1d. Algemmeen Ziekenhuis Sint Jin, Brugge (Rosseneu et al. 1979). In Table 3B, Blaton et al. (1974a, 1974b), animals were 2–3 years old; an adult on an atherogenic diet ingested 7.5 gm cholesterol/day equal to cholesterol in 50 eggs (150 mg/egg) or 7.5 kg muscle. Prior samples had up to 470 mg/dL (Vastesaeger and Delcourt 1966).

2. Delta Regional Primate Center, Covington (LA) (Srinivasan et al. 1976a, 1976b, 1979). On the control diet in Srinivasan et al. 1976a, 1976b, total cholesterol of chimpanzee (290 ± 25 mg/dl) > squirrel monkey (225 ± 18) > green monkey (196 ± 25) > spider monkey (160 ± 15) > rhesus monkey (139 ± 14) > patas monkey (95 ± 7). Serum LDL (β-lipoprotein) had similar ranking (see Appendix).

3. Laboratory for Experimental Medicine and Surgery in Primates (LEMSIP), NYU Medical Center, Tuxedo Park (NY) (Steinetz et al. 1996). LDL cholesterol was also elevated to human clinical criteria for hypercholesterolemia (>160 mg/dl) in 50% of the fat (F) and 35% of the lean (L). A subset (20% total) had elevated LDL-C:HDL-C (5.9–10.7), which in humans would be considered a cardiovascular risk. A hypercholesterolemic subgroup was also found 20 years before (Steinetz et al. 1996). See Appendix.

4. Southwest Foundation for Biomedical Research, San Antonio (Hainsey et al. 1993). Sampled from "clinically normal," randomly bred population housed in outdoor cages. The HDL cholesterol (sexes combined) was chimpanzee (83 ± 10, mg/dL) > baboon (56 ± 9), which parallels the species ranking for total serum cholesterol.

5. Vanderbilt University School of Medicine, Nashville (Mann 1963, 1972). The pioneering studies of George V Mann may be represented by one brief report (Mann 1972) and abstract (Mann 1963). The value for chimpanzees of 150 mg cholesterol intake/d to double serum cholesterol approximates that of the C05 diet which contains 0.05% cholesterol, assuming an intake of 300 g food/d (see Table 3A for composition). Calculated for body weight, chimpanzees are about fivefold more sensitive than humans: chimpanzee, 3.7 mg cholesterol/kcal/d; cebus monkey, 5; rhesus monkey, 5.5; domestic dog, 13; human, 18 mg cholesterol/kcal/d. However, the amount to double cholesterol in humans may be underestimated. Using the formula from a major meta-analysis of dietary studies(Howell et al. 1997), an extra 1 mg dietary cholesterol increases total serum cholesterol by 0.022 mg/dL. Thus, one egg yolk/day (150 mg cholesterol) changes total cholesterol by 3.3 mg (2% increase), which is within assay error. The dietary cholesterol of 1200 mg/d (Mann 1972) to double human cholesterol would, by Howell's formula, increase serum cholesterol by 26 mg/dL, i.e., only a 15% change within the normative range. If Mann's (1972) values are valid for chimpanzees, the chimpanzee may be even more sensitive to dietary cholesterol than humans.

6. Institute Pasteur, Paris (Chapman et al. 1984). Subadults fed commercial primate chow (UAR; 7.5% fat, 53% carbohydrate, 20% protein) plus fruit and micronutrients; 0.004% cholesterol(w/w).

7. Gulf Research Institute, New Iberia (LA) (Nelson et al. 1984).

8. Regional Centre for Training and Research in Human Reproduction, Gabon (Doucet et al. 1994). Chimpanzees had slightly lower plasma total cholesterol and HDL cholesterol than in humans. These are the lowest values in Table 3A, which may be due to diet or better husbandry and living conditions. The supplement of Cerelec (Nestlé Inc.) is a maize-milk weaning food with 9% cultivar vegetable fat and 15% protein (Okorie and Nwanekezi 2002).

9. Commercial diets often contain vertebrate tissues (animal fat, fish meal, offal), dairy products (eggs, milk, butter), and cultivars (grains, soy), within a stated range. "Nonatherogenic" diets may vary from natural diets in the higher cholesterol (negligible in seed oils and other plant foods of feral chimpanzees) and in fatty acids (linoleic acid of maize and corn oils).

obesity on a "nonatherogenic" diet and observed hypercholesterolemia in the clinical range in adults of both sexes, 203–248 mg/dL (Table 3A). Obesity was common, particularly in females (>90%). Table 3A distinguishes lean and obese animals since obesity in humans is often associated with hypercholesterolemia and other dyslipidemias. Hypercholesterolemia was found in both fat and lean individuals. The LDL-cholesterol was elevated to clinical criteria for cardiovascular risk (>160 mg LDL-cholesterol/dL) in 40% of all animals. Steinetz et al. (1996) considered the "sedentary life style" on ad libitum feeding as a factor in the prevalent hypercholesterolemia, but there is also reason to consider the high dietary fat content (11%) (Table 3A and Appendix).

Other primates may be compared on the same control diet in some studies (Table 3A, Column IV). Gorillas had hypercholesterolemia (Berzenay 1959; Nelson et al. 1984), whereas seven Old World monkey species had lower serum cholesterol than chimpanzees (Srinivasan et al. 1974, 1976) (Table 3, Note 1). Provisionally, relative to other Old World primates, chimpanzees and gorillas may be more sensitive to induced cholesterolemia. No data are available for wild animals.

These observations are relevant to vascular

disease, which is observed in feral and captive chimpanzees as noted above (Table 1, Note 3). Atherogenic diets can induce accelerated vascular disease and premature death of chimpanzees (Andrus et al. 1968; Vastesaeger et al. 1972, 1975; Blaton et al. 1974), e.g., an adult with extreme cholesterolemia died suddenly of myocardial infarction after 20 months on a cholesterol-rich diet (Table 3B). Similarly, a gorilla fed eggs and commercial monkey chow for many years died suddenly of coronary occlusion (Gray et al. 1981). Some zoos now recognize that gorillas require strictly vegetarian diets to minimize premature death from cardiovascular disease (Thomas Meehan, personal communication; Appendix).

We note that the serum cholesterol of wild baboons (Kemnitz et al. 2002) and captives is below the lowest in chimpanzees and gorillas (Table 3A). Nonetheless, baboon cholesterol is socially and ecologically responsive. Social stressed lower ranking baboons had decreased HDL cholesterol; total cholesterol was lower, though not to statistical significance (Sapolsky and Mott 1987). In a serendipitous natural experiment, wild baboons that foraged in refuse dumps had higher cholesterol and were heavier than in nearby troops (Kemnitz et al. 2002), which may be an outcome of the richer diet and different daily activity.

The vulnerability of chimpanzees to hypercholesterolemia was also shown in two of four studies of cholesterol supplements (Table 3B). In the most prolonged exposure of high dietary cholesterol intake for 1.5 to 3 years, serum cholesterol was markedly elevated and more so than in baboons (Peeters and Blaton 1972; Blaton et al. 1974; Note 1c). Similarly, Mann (1972) briefly reported that chimpanzees were fivefold more sensitive than humans to dietary cholesterol (Table 3, Note 5). However, two well-designed studies with shorter treatments showed contrary results that chimpanzees are not notably sensitive to dietary cholesterol (Table 3B): Vastaesager and Delcourt (1966; Note 1b) found very slight serum response to large increases of dietary cholesterol, whereas Srinivasan et al. (1976a, 1976b; Table 3, Note 2) showed increases above a hypercholesterolemic baseline during cholesterol ramp feeding which, though statistically significant, were less for chimpanzees than five monkey species.

We conclude that captive chimpanzees show strong tendencies for hypercholesterolemia on "nonatherogenic diets" and under some circumstances are highly sensitive to diet-induced hypercholesterolemia and vascular mortality. We note two general issues of husbandry that are germane to long-term studies of vascular disease and aging: some mammalian and avian models are largely vegetarian and in the wild do not regularly consume the animal fats of lab diets (Table 3, Note 9). Moreover, chimpanzees in most of these colonies would be considered sedentary and certainly are less active than in the wild, where the relentless search for food occupies most of the waking hours as noted above.

DISEASE RISK FACTORS IN MEAT

Fat and Cholesterol

We hypothesize that the major increase of meat eating (vertebrate muscle and other organs) during the last few million years would also have increased the risk of slow chronic diseases that reduce health during aging. To achieve more prolonged development and delayed reproduction, humans would have acquired genes that enabled this new diet, as well as the unique human life history with delayed maturation, slower aging, and increased life expectancy (Finch and Sapolsky 1999; Kaplan et al. 2000).

We focus here on mammalian meat because there is little evidence that other vertebrate flesh (amphibia, reptiles, birds) was eaten in significant amounts until 200,000 years ago (Stiner et al. 2000), with fish not widely consumed until 20,000 years ago (Cordain et al. 2002a). The evidence shows meat-associated risk factors for chronic disease, fat and infectious agents, are found at much higher levels (in mammalian tissues eaten by early humans) than in the vegetarian diets of chimpanzees (Table 2). Animal tissues differ widely in the content of cholesterol and in the proportions of saturated and unsaturated fatty acids (Cordain et al. 2002b). The lack of information on the intake of brain, marrow, visceral fat, and skeletal muscle of human ancestors precludes detailed discussion.

Blood cholesterol elevation was one of the first risk factors identified for vascular disease (Mahley and Rall 2000) and is being considered as an Alzheimer risk factor. In particular, Alzheimer risk increases in association with high consumption of animal fat (Notkola et al. 1998; Kalmijn 2000; Deschamps et al. 2001; Kivipelto et al. 2002; Luchsinger et al. 2002; Morris et al. 2003). For example, mid-life levels of blood cholesterol at > 251 mg/dL increased the subsequent risk of Alzheimer's disease by 2.8-fold, independently of the presence of the *apoE4* allele (Kivipelto et al. 2002). Overall, cardiovascular disease and Alzheimer's disease share dietary risks of saturated and *trans*-unsaturated fat (Morris et al. 2003).

The influence of diet on Alzheimer's disease is observed in developed countries that have richer diets but much less physical activity than hunter-gatherers. This distinction is important because most hunter-gatherers also consume large amounts of cholesterol in diets rich in animal tissues, yet typically maintain a nonatherogenic profile of blood lipids (Mann et al. 1965; Mann and Shaffer 1966; Eaton 1992; Cordain et al. 2002a). Traditional foragers may not have much vascular disease (Mann et al. 1965, 1972; Eaton 1992; Cordain et al. 2002a); the incidence of dementia is not known. Game meat has lower levels of saturated fatty acids than domestic animal muscle (Eaton 1992; Cordain et al. 2002a, 2002b). The extensive daily physical activity (Mann et al. 1965; Eaton 1992; Cordain et al. 1998) would also be expected to lower blood cholesterol (Bernstein et al. 2002).

Dietary fat and cholesterol accelerate vascular disease and Alzheimer's disease in many disease models. In particular, cholesterol consistently increases the accumulation or production of the Aß-peptide, which is strongly implicated in Alzheimer's disease. In a key ongoing study, vervet monkeys (African green monkeys) fed for five years on a diet rich in saturated fats had accelerated deposits of Aß (Schmechel et al. 2002). Similarly, diets rich in cholesterol and fat induce Aß deposition and other Alzheimer-like changes in rabbits and transgenic mice with a human Alzheimer gene (Refolo et al. 2001; Levin-Allerhand et al. 2002; Shie et al. 2002). In cell culture, added cholesterol increases Aβ apparently by direct effects on secretases, which cleave APP on an amyloidogenic pathway (Bodovitz and Klein 1996; Mills and Reiner 1999; Kojro et al. 2001; Wahrle et al. 2002; Puglielli et al. 2003). Thus, the shift to cholesterol-rich diets in human ancestors could have selected for genes that modulate both circulating and subcellular cholesterol.

Lastly, we note that the evolution of meat eating poses paradoxes, because the major increases of animal tissue consumption during human evolution would be predicted to shorten, not lengthen, life span. Caloric restriction in laboratory rodents shows an opposite effect. Restricting ad libitum food intake by 20% to 40% slows many aging degenerative processes and increases life span in proportion to the reduced calories (Finch 1990; Masoro and Austad 1996; Sohal and Weindruch 1996; Roth et al. 2002). These benefits of caloric restriction to health and longevity in rodents are broadly independent of the proportions of protein, fat, and carbohydrate, given sufficient micronutrients. Laboratory monkeys show similar benefits in the reduction of obesity and improved blood lipids and blood glucose (Edwards et al. 2001; Lane et al. 2001; Roth et al. 2002). However, these strong effects of diet in captive animals must be considered in the context of their lower physical activity than in the wild, where foraging occupies most of the waking hours. The high activity of human foragers may protect against their high intake of fat, as noted above. Wherever mechanisms are at work in caloric restriction, it is striking that human life expectancy is nearly double that of the great apes, and presumably our shared ancestors, despite a severalfold increase in fat intake.

Infectious Organisms

Vertebrates typically harbor a wide range of infectious invertebrates and microbes, e.g., prions, viruses, bacteria, amoebae, protozoans, and worms. Eating raw or lightly cooked tissues can transmit many infectious agents. Lacking a detailed profile of the diseases acquired by chimpanzees or hunter-gatherers from raw meat, we note some biohazards of eating raw meat, which may have selected for host-resistance factors that also enhanced longevity.

TABLE 4

Gene candidates for disease resistance associated with meat eating

Animal Organ Component	Main Source	Disease Risk	Gene Candidate
Fats and Lipids	subcutaneous fat, bone marrow,	Alzheimer's disease,	*apoE*[1a,b,c,d]
cholesterol	brain	vascular disease	*apoE*[1b,d,e], *Lp(a)*[2]
unsaturated fatty acids			
Infectious Agents		dysenteries, hepatitis	*apoE*[1d]
viruses			CMAH[3]
			HLA[4a]
prions	bone marrow, brain, viscera	spongiform encephalopathies	*apoE*[1f], *Prp*[5]
			HLA[4b]
bacteria	viscera	cholera and dysenteries	*CFTR*[6], *apoE*[1d]
			HLA[4b]
amoeba		dysenteries	*Hb*[7], *apoE*[1f]
protozoa		malaria	
nematodes			*HLA*[4c]
Metals	red meat, blood	vascular disease, Alzheimer's	Fe: ferritin, lactoferrin,
copper, iron, zinc		disease?,	transferrin[8]
		infectious diseases?	*PHYH*[8]

Notes to Table 4

1a. African Americans and Latin Americans show less association of *apoE4* with Alzheimer's disease than Caucasians (Farrer et al. 1997; Tang et al. 1998; Hendrie et al. 2001; Stewart et al. 2001). *ApoE4* also increases the risk of heart disease, although the effect is weaker than for Alzheimer's disease (Eichner et al. 2002); the allele effect diminishes at later ages, as in Alzheimer's disease (Meyer et al. 1998). *ApoE4* potentiates hypercholesterolemias to dietary cholesterol (see Appendix).

1b. *ApoE* mediates bone matrix formation through transport of vitamin K (Zmuda et al. 1999; Newman et al. 2002). In some studies, *apoE4* increases risk of osteoporotic fractures and lower bone mineral density (Zmuda et al. 1999; Olson 2000).

1c. The *apoE3* genotype favors neurite outgrowth in response to neuron death during Alzheimer's disease (Arendt et al. 1997). Cell culture models show the neurite-promoting effects of *apoE3* >*E4* (Teter et al. 1999; Mahley and Rall 2000; Nathan et al. 2002). *ApoE3* decreases neurodegeneration due to Aβ-peptide in transgenic models (Fagan and Holtzman 2000; Mahley and Rall 2000) and reduced Aβ accumulation (Holtzman et al. 2000; Carter et al. 2001). Traumatic brain injury and hemorrhagic stroke have worse outcomes in *apoE4* carriers, with more memory impairments (Crawford et al. 2002; Liberman et al. 2002).

1d. *ApoE4* enhances inflammatory responses and may influence susceptibility to infections by HIV and *Chlamydia* (see Appendix). In AD, *apoE4* carriers show greater brain inflammatory processes, e.g., activated microglia around senile plaques (Egensperger et al. 1998; Akiyama et al. 2000; Finch et al. 2002; Ophir et al. 2003), whereas *apoE4* carriers have higher blood levels of proinflammatory cytokines during injury (Drake et al. 2001). Mouse models with human *apoE3* and *-4* alleles show these effects (Brown et al. 2002).

1e. *ApoE* isoforms influence cholesterol responses to diet. *ApoE4* carriers responded more to dietary shifts in LDL and possibly total cholesterol (Tikkanen et al. 1995; Sarkkinen et al. 1998; Hagberg et al. 2000; Ordovas and Mooser 2002).

1f. Prion diseases do not show consistent associations with *apoE* alleles (see Appendix).

2. *Lp(a)* elevations in the blood are a mild risk factor in heart disease, the highest category of increasing risk by twofold (Seed et al. 2001; Sharrett et al. 2001). Human *Lp(a)* levels vary >1000-fold between individuals under genetic control (Boerwinkle et al. 1992).

3. CMAH (CMP-N-acetylneuraminic acid (CMP-Neu5Ac) hydroxylase) is an enzyme that modifies CMP-Neu5Ac (N-acetylneuraminic acid) to the hydroxylated CMP-NeuGc (N-glycolylneuraminic acid). CMAH and NeuGc are found in anthropoids but not humans (Crocker and Varki 2001; Varki 2001; Chou et al. 2002). Siglec-4a in myelin-associated glycoprotein shows species differences pertinent to white matter diseases such as multiple sclerosis and amyotrophic lateral sclerosis.

4a. The *HLA* gene system (human lymphocyte antigens) is the human main histocompatibility complex (MHC) and contains hundreds of genes that mediate immune responses, including acute phase inflammatory responses. *HLA* is the most polymorphic complex gene locus known in human populations with a remarkable number of different alleles at certain genes. Human and chimpanzee share nearly all the *HLA* class I genes (Adams and Parham 2001; Adams et al. 2001). Some combination of *HLA* alleles (haplotypes) are ancient and shared with chimpanzees (Venditti et al. 1996; Cooper et al. 1998; O'hUigin et al. 2000). The persistence of these ancient haplotypes is attributed to balancing selection, but the pathogens or environmental factors are not known. West African chimpanzees also have extensive MHC I heterogeneity (de Groot et al. 2000).

4b. In humans, the *HLA-B27* allele is associated with reactive arthritis following many types of infections (Urvater et al. 2000). Reactive arthritis after enteric infections with bacteria is associated with MHC haplotypes in gorillas and macaques (see Appendix).

4c. *Onchocerca volvulus,* the nematode parasite that causes river blindness, is endemic in West Africa. *HLA-DQ* variants influence outcomes of infection (Meyer et al. 1994, 1996). One haplotype associated with more severe disease in West Africa shows less malaria (Hill et al. 1991), implying balancing selection (Meyer et al. 1996).

5. The prion gene *PrP*^{c} influences transmission of infectious prions *PrP*^{sc} between species and the age of disease onset (Telling et al. 1996; Prusiner et al. 1999). Primates are relatively vulnerable to prion infections (Cervenáková et al. 1994; Schätzl et al. 1995). The human *PrP*^{c} gene evolved two polymorphisms about 200,000 years ago, which increase resistance to infection in heterozygotes (Mead et al. 2003). *HLA-DQ7* is 75% less frequent in those with vCJD than normals (Jackson et al. 2001).

6. *CFTR* (cystic fibrosis transmembrane conductance regulator) heterozygotes may be resistant to diarrhea from cholera and other dehydrating diseases transmitted by intestinal bacteria, and to typhoid fever, as indicated in transgenic mouse models (Gabriel et al. 1994; Pier et al. 1998; Kirk 2000; Figure 1). However, population genetics models allow persistence of high frequency disease alleles without selective advantage (Reich and Lander 2001). *CFTR* may also regulate immunity to *Pseudomonas aeruginosa* infections (Pier 2000).

7. Resistance to malaria from *Plasmodium falciparum* is mediated by variants of hemoglobin that cause sickle cell anemia; milder forms in heterozygotes are maintained by balancing selection. Variants in *G6PDH* and *HLA* genes (Note 4c), which confer relative resistance to malaria, may have spread in association with agriculture (Hill et al. 1997; Rich et al. 1998).

8. Muscle contains iron, copper, zinc, and other divalent metal ions, which are implicated in Alzheimer's disease and vascular disease and infections (see Appendix). Because most plant sources have low metal concentrations, transitions to meat eating would have sharply increased iron intake. Diet also influences metal bioavailability, e.g., iron absorption is inhibited by plant-derived phyates and tannins that bind free iron, whereas absorption is enhanced by vitamin C (Benito and Miller 1998). The greater expression of *PHYH* (phyantol CoA reductase) in humans could be associated with dietary changes (Karaman et al. 2003).

Chimpanzees are vulnerable to infections acquired from meat eating. For example, Ebola virus infections are transmitted in proportion to the eating of colobus monkeys (Formenty et al. 1999), a favored chimpanzee prey (Stanford 1998). The present HIV epidemic may have originated in a simian virus acquired from chimpanzees eaten as bush meat (Chitnis et al. 2000; Sharp et al. 2001). Chimpanzees carry many enteric parasites (Ashford et al. 2000) and suffer bouts of diarrhea (Goodall 1986), but the etiology and modes of transmission are not clear.

Prions are another important meat-carried pathogen, first recognized in New Guinea aborigines (Foré women) who developed spongiform encephalpathies after eating raw brains of recently deceased relatives (Prusiner and Hsiao 1994; Liberski and Gajdusek 1997; Prusiner et al. 1999; Mead et al. 2003). Brain and marrow were also extracted by paleolithic hunters (Table 2). Prion diseases are of major concerns in mad cow disease and in the iatrogenic transmission of Creutzfeldt-Jacob disease from corneal transplants (Prusiner et al. 1999; Bosque et al. 2002). Primitive cooking of hunted or scavenged mammalian organs could not have reliably eliminated infectious prions, which can survive autoclaving at >120°C (Taylor 1999).

Vibrio bacteria are among many species harbored in the gastrointestinal tract that are potentially pathogenic, and like *Vibrio cholerae,* can cause enterotoxin-mediated dysenteries (Blake 1983; Holmberg 1988). Vibrios, though most widely known as waterborne pathogens, can also be transmitted by eating raw turtle eggs (Campos et al. 1996) and uncooked meat (Swaddiwudhipong et al. 1990, 1992). Vibrios and many other pathogens are endemic in inland populations of domestic animals (Sanyal et al. 1974; Visser et al. 1999).

Some enteric pathogens cause systemic inflammatory responses that, in turn, promote vascular disease with long-term consequences. For example, inflammatory responses to the protozoan *Trypanosoma cruzi* that causes Chagas' disease caused vascular disease in mice of a genotype that otherwise is resistant to vascular disease (Sunnemark et al. 2000). Trypanosomes are widely carried by monkeys and other small mammals. Nematode parasites are also common in vertebrates. Hoberg's (2002) genomic analysis of tapeworms indicates that *Taenia* evolved infectious cycles with human-specific hosts, 0.8 to 1.7 Mya, which is consistent with fossil evidence that early humans were facultative carnivores (Shipman 2002).

MEAT-ADAPTIVE GENE CANDIDATES

We propose that the increased consumption of mammalian tissues during evolution of *H. sapiens* selected for "meat-adaptive genes" to increase resistance to harmful effects of fat, toxins, and pathogens. In general, these agents are at low concentrations in the plant materials predominantly eaten by great apes. Gene candidates are discussed below (Table 4 gives details and other references). Importantly, the Aß peptide implicated in Alzheimer's disease is highly conserved throughout vertebrates (Finch and Sapolsky 1999; Musa et al. 2001). Other gene differences between human and chimpanzee and the estimated time of the genetic changes are shown in Figure 1. This discussion is necessarily weighted by the burgeoning literature on the *apoE* gene, which we expect to be soon joined by many other candidates from the chimpanzee and human genome projects. These arguments extend the Finch-Sapolsky (1999) hypothesis that the *apoE3* allele was selected for by its positive effects in reducing cardiovascular and Alzheimer brain disease to include other additional genes that enabled prolonged maturation and intergenerational transfers.

GENES MEDIATING FAT METABOLISM

Apolipoprotein E (*apoE*): Allelic Differences

ApoE is a major carrier of cholesterol in the blood and mediates the uptake of cholesterol and lipids by cells throughout the body (Davignon et al. 1988; Mahley and Rall 2000). (This brief description is intended to represent the broadest features of apoE and is oversimplified.) *ApoE* alleles are implicated in a broad range of adult pathological conditions, particularly Alzheimer's disease, head injury, and cardiovascular disease (Breslow 2000; Eichner et al. 2002). Humans have three main *apoE* alleles (*apoE*-ε2, -ε3, and -ε4), referred to here as *apoE2–E4*. In all human populations, *apoE3* is the most prevalent, at 65% to 85% (Sandholzer et al. 1995; Corbo and Scacchi 1999). In most populations, *apoE4* is present at 10% to 20%, but African and Asian aborigines have notably higher levels of *apoE4* (25% to 40%). *ApoE2,* the least common, is not considered in detail.

ApoE variants continue to receive great attention and account for more genetic variance (25%) in cholesterol metabolism than any other gene (Sing and Davignon 1985; Eichner et al. 2002). *ApoE4/E4* versus - *E3/E3* carriers have 3% to 15% higher total cholesterol and LDL cholesterol, depending on the population, diet, and exercise. *ApoE* alleles show marked effects on blood lipids during dietary shifts. For example, in humans on a low-fat baseline diet, adding 300 mg cholesterol/day (2 egg yolks) caused serum total cholesterol to increase fourfold more in *E4/E4* carriers than in *E3/E3* and even greater relative increases of LDL cholesterol (Sarkkinen et al. 1998; Table 4, Note 1e and Appendix). Besides these major alleles, *apoE* in human populations has 18 additional sequence variations with quantitative effects on lipid metabolism (Stengård et al. 2002).

The major physiological differences between apoE4 and -E3 are attributed to the amino acids at two key positions in the peptide chain, numbered 112 and 158, each of which can be either arginine (R) or cysteine (C) (Table 5). The presence of R121 in apoE4 causes its preferential binding to triglyceride-rich lipoproteins (chylomicrons and very low density lipoproteins, VLDL), whereas apoE3 binds preferentially to high-density lipoproteins (HDL). These differences in lipoprotein binding by apoE3 and -E4 influence lipoprotein clearance and the LDL/HDL ratios that are risk factors in cardiovascular disease.

ApoE4 is the most common Alzheimer risk factor throughout the world, with > tenfold higher risk of *E4/E4* in Caucasians that brings a nearly 50% incidence of Alzheimer's disease by the ninth decade (Meyer et al. 1998). There are important population and ethnic differences, however (Farrer et al. 1997; Evans et al. 2000; Eichner et al. 2002). For example, Yorubans in Nigeria showed 70% less dementia than African Americans (Hendrie et al. 2001), which may be related to a low-fat diet (Table 4, Note 1a), consistent with the dietary risk factors discussed above. *ApoE4* has smaller effects on the risk of cardiovascular disease than of Alzheimer, in the range of 10% to 50%, with effects during middle age (Ilveskoski et al. 1999; Eichner et al. 2002). Again, the impact of *E4* on cardiovas-

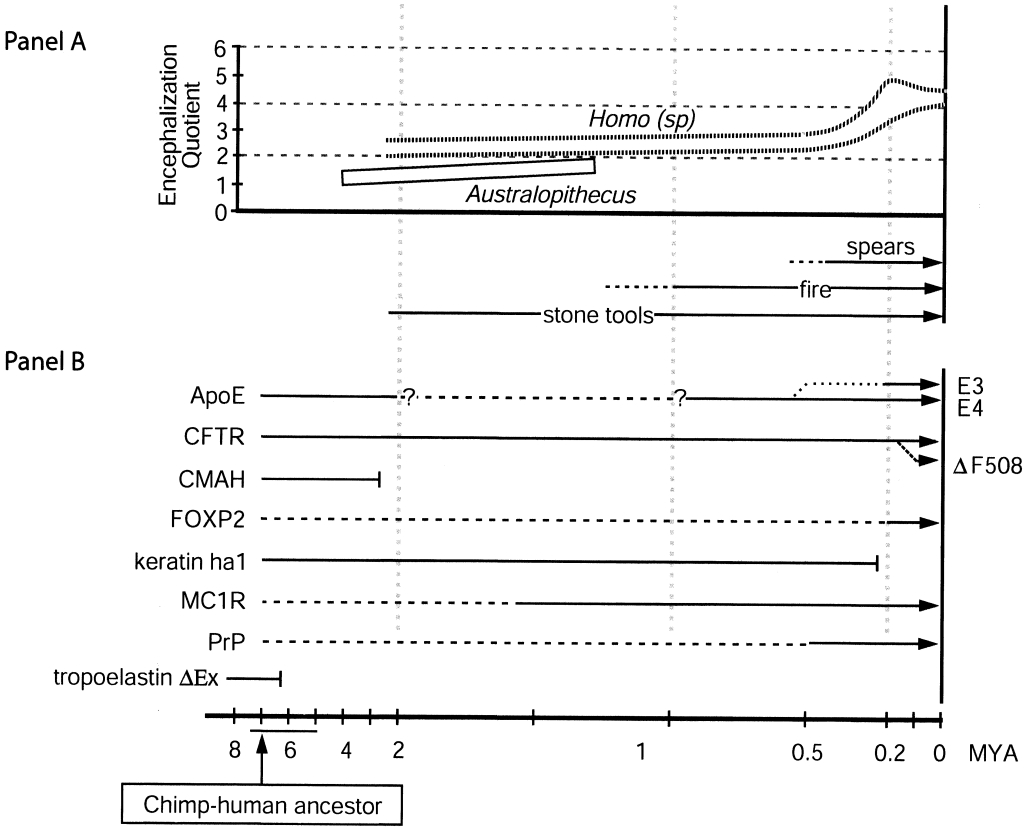

Figure 1. Brain and Gene Changes During Human Evolution

Panel A: The encephalization coefficient (EQ) during human evolution (see bottom scale). The EQ adjusts brain size relative to body size according to the brain: body regression for Old World monkeys and apes (Fleagle 1998). The relative brain size during the evolution of australopithecenes and early *Homo* increased modestly until 0.5 Mya (Collard and Wood 2000; Elton et al. 2001; Kaplan and Robson 2002).

Panel B: Gene changes during human evolution (see Tables 4 and 6 for further details).

ApoE4 (apoliproteinE4) is the ancestral human gene, but differs from chimpanzee apoE at a critical substitution at residue 61 (Table 5). The unique human apoE3 allele spread during later human evolution about 0.226 Mya (Fullerton et al. 2000).

CFTR (cystic fibrosis transmembrane conductance regulator) has a common allele in human populations which is similar to the single CFTR haplotype of great apes which may be an ancestral allele. About 2% of human populations carry a CFTR mutation and about 1/2500 newborn have the disease. The ΔF508 mutation is the most common variant, 50–80% of all mutants. ΔF508 originated about 0.05 Mya and is the oldest known mutant (Bertranpetit and Calafell 1996; Mateu et al. 2001). The high prevalence of ΔF508 and other CFTR mutations may give heterozygotes resistance to cholera and other infectious causes of diarrhea (Table 4, Note 6).

CMAH (CMP–N-acetylneuraminic acid hydroxylase) modifies CMP-Neu5Ac to the hydroxylated CMP-NeuGc. The CMAH gene was inactivated by a mutation 2.8 Mya (Chou et al. 2002), possibly before emergence of the genus *Homo*. The loss of CMAH could increase resistance to pathogens (Table 4, Note 3).

FOXP2 is implicated in human language capacity and evolved two amino acid changes from the chimpanzee gene about 0.2 Mya (Enard et al. 2002a) (Table 6).

hHaA (keratin hHa1) is a pseudogene in humans. In chimpanzees and other great apes, the intact gene encodes a hair protein (Langbein et al. 1999; Winter et al. 2001), which was inactivated by a mutation 0.25 Mya, approximating the emergence of *apoE3* (Table 6).

MC1R (melanocortin receptor-1) is the only gene known to cause variations in human skin pigmentation. The human gene is closer to chimpanzee than gorilla (Rana et al. 1999; Makova et al. 2001). Human *MC1R* diversified about 1.5 Mya, after the appearance of *H. ergaster* (Table 6).

PrP: Prion polymorphisms, which increase resistence to infectious prions in heterozygotes, may have originated 0.5 Mya (Mead et al. 2003).

Tropoelastin differs from chimpanzee in the loss (Δ) of exons 34 and 35 about 6–8 Mya (Szabo et al. 1999), which approximates the divergence of human and chimpanzee lines (significance to skin, Table 6).

TABLE 5

Apolipoprotein E: polymorphisms in humans and species differences

ApoE residue[1] (+signal peptide)	61[2] (79)	**112**[3] (130)	135[2] (153)	**158**[3] (176)
Human:				
apoE2	R	C	V	C
apoE3	R	C	V	R
apoE4	R	R	V	R
Chimp	T	R	A	R
Gorilla	T	R	A	R
Orangutan	T	R	A	R

Notes to Table 5

1. The table identifies amino acid residue numbered positions of polymorphisms in the mature plasma protein, as used in this text and in Finch and Sapolsky (1999). The other numbering system includes the "+ signal peptide" of the full protein sequence (the 18 residue signal peptide is cleaved before secretion by the liver into the blood). Data from National Center for Biotechnology (NCBI), http://www.ncbi.nlm.nih.gov/entrez.
2. Residue 61 is a determinant of species differences in *apoE* functions by its strong effect on apoE structure through the "domain interactions." According to much evidence on other nonprimate species, the apoE of chimpanzee and other great apes (T61) is predicted to function more like human apoE3, despite their R112 and R158, as in human apoE4 (see text). Residue 135 also differs between humans and great apes with substitutions that would not be expected to modify the domain interactions. For example, though mouse and human apoE are only 72% similar, the R61 substitution in mouse apoE induced apoE4 domain interactions that modified blood lipid binding (Raffaï et al. 2001; Karl Weisgraber, personal communication).
3. Bolded numbers are the positions of the human *apoE* polymorphisms.

cular disease and mortality depends on the population and lifestyle (diet, physical activity).

ApoE4 is also associated with subtle impairments of brain functions in cognitively normal adults. For example, normal elderly *apoE4* carriers showed a greater cognitive activation (fMRI) during memory tasks than the *E3,* indicative of compensation to cryptic impairments (Bookheimer et al. 2000). Clinically normal *apoE4* carriers aged 50+ years show more mild cognitive impairments and lower cerebral glucose metabolism by PET (Reiman et al. 1996, 2001, 2002; Small et al. 2000; de Leon et al. 2001; Mortensen and Hogh 2001; Smith et al. 2002). Moreover, in younger adults (31 ± 5 years), the *E4* carriers had lower cerebral glucose metabolism, despite testing for normal cognition (Reiman et al. 2002). Because myocardial dysfunctions are associated with cognitive impairments even in the absence of stroke (Sparks et al. 1990), the effects of *E4* on cognition during middle-age may involve independent effects of *E4* on coronary insufficiency (Kivipelto et al. 2002; Table 4, Note 1a).

ApoE isoforms influence blood lipid responses to physical activity, with the largest effects in sedentary lifestyles. For example, in a large sample across Switzerland, sedentary *E4* carriers had the most atherogenic profile of HDL and triglycerides (Ordovas 2001; Bernstein et al. 2002). Exercise interventions also show the most benefit to sedentary *E4* carriers (Taimela et al. 1996; Schmitz et al. 2001). These findings are consistent with the low incidence of hypercholesterolemia and cardiovascular disease in human foragers, despite their high consumption of fat, as noted earlier. The mechanisms of physical activity and *apoE* allele interactions are not understood (Bernstein et al. 2002).

Other functions of *apoE* are pertinent to human evolution (Table 4, Notes 1b and 1c). In bone, *apoE* mediates vitamin K uptake, which is important for bone matrix formation. In turn, *apoE4* is associated with lower bone mineral density and increased risk of osteoporotic fractures (Table 4, Note 1b). Thus, *apoE3* would be adaptive by protecting ancestral humans against the high frequency of broken bones observed in adult chimpanzees and osteoporosis during aging (Table 1, Notes 9 and 10). *ApoE* also is directly involved in sex steroid synthesis and transport of thyroxine, although allele effects are not indicated.

In neural tissues, *apoE* transports lipids that

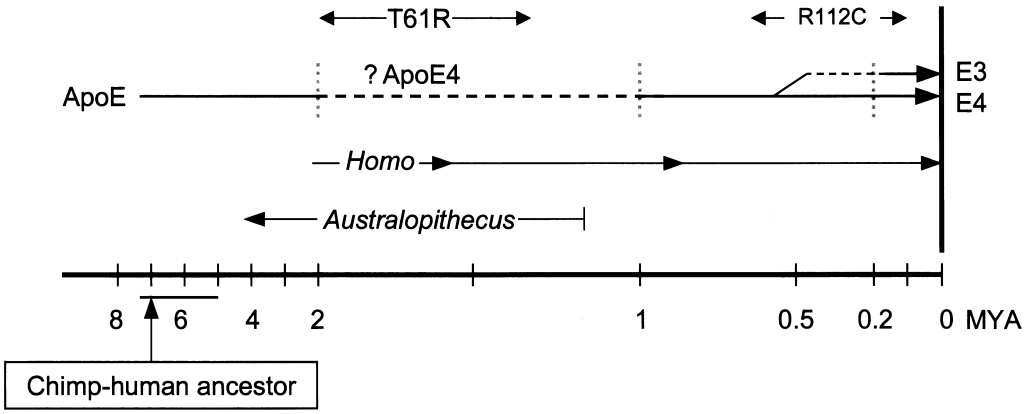

Figure 2. The Evolution of apoE from the Common Ancestor

Human apoE arose at an unknown time from mutation at position 61 (threonine to arginine, TGIR), yielding *apoE4* as the ancestral gene. The uniquely human *apoE3* isoform originated from mutation at position 112 (arginine to cysteine R112C) and is estimated to have spread 0.226 Mya (Fullerton et al. 2000).

support axonal growth. Transgenic mouse models with transgenic human *apoE* isoforms show that neurite outgrowth is greater with *apoE3* than *E4* (Table 4, Note 1c). Head injury is a risk factor in Alzheimer's disease and is worsened by *apoE4* (Table 4, Note 1c), as seen in "punch-drunk" boxers who prematurely develop Alzheimer's disease. The effects of *E4* would be maladaptive to males who are more likely than females to encounter physical trauma. In general, *E4* enhances inflammatory responses of macrophage-like cells in host-defense responses (Table 4, Note 1d).

apoE Gene Evolution

ApoE3 appears to have spread during later stages of human evolution after originating from an ancestral *apoE4*-like gene (Figure 2). According to DNA sequences representing four ethnic groups, *apoE3* is estimated to have spread 0.226 Mya. The depth of the tree is estimated at 0.311 Mya (range 0.176–0.579) (Fullerton et al. 2000). Although these sequences do not inform when *E3* originated as a mutation, they imply that *E3* arose before anatomically modern *H. sapiens* first migrated from Africa about 100,000 years ago. This range also allows *E3* to be present in Neandertals (from 300,000 years ago) and in earlier *Homo* of Africa or Europe from which *H. sapiens* is thought to have diverged. The present dating defines *apoE4* as the ancestral gene in the genus *Homo*. However, the dates on the spread of *apoE3* do not inform about the australopithecene *apoE* sequence, which is an important gap because early hominids had already acquired increased tool use and hunting 2 Mya.

Only one *apoE* genotype has been reported in chimpanzees and other primates that resembles human *apoE4* with arginine (R) at positions 112 and 158 (Table 5) (Mahley 1988; Hanlon and Rubinsztein 1995). All other primates examined also have arginine at 112 and 158 (see Finch and Sapolsky 1999). Because of these similarities of human *apoE4* to primate *apoE,* and because of sequence analysis of the genealogical depth of human *apoE* alleles (Fullerton et al. 2000, discussed above), the human *apoE4* is considered the ancestral allele in primates (Mahley 1988; Hanlon and Rubinsztein 1995; Mahley and Rall 2000).

Another important difference, however, between human and great ape apoE is at position 61, which is arginine in all the human *apoE* isoforms, but predicted to be threonine in the chimpanzee, gorilla, and orangutan, as in most other mammals (Table 5). Experimental studies using site-directed mutagenesis showed that substituting 61T→61R in apoE from several nonprimate species has major effects on lipid affinity and catabolism, which converts their apoE3-like molecule into one

that functions more like human apoE4 (Dong et al. 1994; Raffaï et al. 2001). On this basis, the chimpanzee apoE (T61) is predicted to be functionally more like human apoE3 than apoE4. Further genetic and physiological studies of chimpanzee apoE are needed, because the sequence data are based on very few individuals and so could miss genetic diversity. Moreover, chimpanzee-human differences at other apoE residues (Table 5) might be physiologically important.

As noted above, we do not know when the ancestral *apoE4* allele arose or when the prior mutation of 61T→61R occurred (single base change, A**G**G→A**C**G) in early *Homo* or *Australopithecus*. Subsequent single base changes (**C**GC→**T**GC, Table 5) lead successively to *apoE3* (R112C) followed by the evolution of *apoE2* from *apoE3* (R158C). Other substitutions may inform about the timing of these changes as more human and chimpanzee *apoE* genes are sequenced. It is likely that other gene changes influence lipoprotein evolution and differ from chimpanzees, as indicated by the evidence for greater sensitivity of chimpanzees to hypercholesterolemia, as discussed above. We next discuss other lipoprotein differences between chimpanzees and humans and evidence for genetic heterogeneity in chimpanzee lipoproteins.

Other Lipoproteins: Lipoprotein(a) and Apolipoprotein H

Chimpanzees have 2 to 4 higher plasma *Lp(a)* levels than humans (samples from a colony on a vegetarian diet, see Table 3, Note 8; Doucet et al. 1994; Huby et al. 2001). *Lp(a)* levels are cogent because in humans elevated *Lp(a)* increases the risk of cardiovascular disease up to twofold. This LDL-like protein circulates as a complex with *apo[a],* which has a similarity to plasminogen that may be a link to atherosclerosis and thrombosis (Doucet et al. 1994, 1998). The chimpanzee *Lp(a)* gene promoter differs at three bases that increase transcription by threefold (Huby et al. 2001), which is the first example of change in a noncoding sequence (promoter) with functional implications to human evolution. The majority (80%) of chimpanzees in this colony had plasma *Lp(a)* higher than the threshold for elevated cardiovascular risk in humans (Doucet et al. 1994). Of great interest, individuals had extensive heterogeneity in *apo[a]* isoform size, which implies genetic polymorphisms, as found in humans.

ApoH also showed genetic heterogeneity in a large captive sample of African-born chimpanzees and their offspring (husbandry probably as in another colony of Table 3, Note 4) (Sanghera et al. 2001). ApoH is implicated in cardiovascular disease because it binds antibodies to phospholipids that are associated with thromboses. The majority (64%) of the chimpanzees had anti-*apoH* antibodies, which is much higher than in most human populations. Chimpanzees have two alleles, of which the *apoH*3* is considered ancestral.

Another colony also showed evidence for genetic variation in levels of cholesterol, although the genes involved were not identified. In the colony of Table 3, Note 4 (nonferal diet), the total serum cholesterol showed high heritability (48% additive genetic variance, 212 chimpanzees with 19 pedigrees: Williams-Blangero et al. 1994).

Besides *apoH* and *Lp(a),* many other genes mediate variations in lipid metabolism, transport, and subcellular distribution and give candidates for chimpanzee responses to diet, as well as for meat-adaptive genes in human evolution. The low density lipoprotein receptor-related protein (LRP) mediates the endocytosis of apoE and also of α2-macroglobulin that binds the Aβ peptide, as well as binding other inflammatory peptides. Because genetic variations in α2-macroglobulin (Blacker et al. 1998) and LRP (Sánchez et al. 2001) are associated with Alzheimer's disease risk, it is cogent to determine the great ape LRP sequences. At the subcellular level, cholesterol modulates production of Aβ peptides (see above), through cholesterol esters and the enzyme ACAT (acyl-coenzymeA: cholesterol acyl transferase), a gene of interest in this context (Puglielli et al. 2001). Other lipid metabolizing genes pertinent to brain development are the desaturases and elongases that synthesize brain PUFAs. Acquisition of genes that allow increased fat consumption without hypercholesterolemias would also favor intake of PUFAs needed for brain development. Other candidates may be sought in the rare familial genes that confer resistance

to elevated blood cholesterol (Eurlings et al. 2001; Stein et al. 2002).

The genetic variations in lipoproteins of captive chimpanzees suggest a genetic involvement in the major individual and population variations in eating of meat, insects, eggs, and oily nuts in the wild. The greater meat eating by males than females could also be associated with sex differences in gene frequencies.

Need for Dietary Fat

Meat eating may involve another fat-related adaptation besides resistance to hypercholesterolemia, because the catabolization of nitrogen from proteins requires sufficient nonprotein carbon from fat or carbohydrate. Fat availability in the animals found in cave sites varies seasonally, particularly in herbivores which suffer big losses of body fat in cold or dry seasons when there is little vegetation (Speth 1991; Cordain et al. 2002a). Diets dominated by lean meat with insufficient carbohydrate and fat can cause toxic elevations of blood ammonia and amino acids (the "rabbit starvation" of 19th-century trappers) (Speth and Spielmann 1983; Cordain et al. 2001). Elevated ammonia and amino acids can result from a saturation of the hepatic urea cycle, which requires carbon substrates derived from carbohydrate and fat (Rudman et al. 1973). No data are available on the chimpanzee urea cycle or of protein catabolism as a function of diet. The fat and carbohydrate needed for lean meat intake could have been met in part by brain and bone marrow, as well as by seeds and nuts with high fat content. These foods are sought seasonally by modern hunter-gatherers (Speth 1989), as is likely for paleolithic hunters and ancestral hominids (Table 2), (Eaton et al. 1998).

HOST RESISTANCE GENES

Next, we consider genes that would protect meat eaters from pathogens in animal tissues as host defense or resistance factors. Again, *apoE* is a candidate.

apoE4 as a Host Defense Gene

Surprisingly, *apoE4* has a protective effect to certain infections that may contribute to the persistence of this allele in human populations, despite its adverse effects at later ages. In chronic infections by hepatitis C virus (HCV), *apoE4* carriers had milder liver disease (Wozniak et al. 2002). The protection against HCV by *apoE4* is consistent with the role of lipoproteins in transmission of HCV and other viruses (Wozniak et al. 2002), and fulfills hypotheses that *apoE4* is a resistance factor for lipophilic parasites (Martin 1999) and that *apoE4* confers advantages in early life (Charlesworth 1996). *ApoE* may also influence infections by other viruses and by prions, but the evidence is less clear (Table 3, Note 1d and Appendix).

Among general host defense mechanisms are the inflammatory responses mediated by macrophages that can destroy microorganisms by phagocytosis. In peripheral macrophages and in brain microglia (a macrophage-like cell derived from bone marrow), the *apoE4* genotype promotes greater inflammatory responses relative to *E3* (Table 4, Note 1d). *ApoE4* carriers also had greater increases of TNFα after surgery, indicating enhanced inflammatory responses (Drabe et al. 2001). In another setting that could also involve immune interactions, *apoE4* may protect against spontaneous miscarriage (Zetterberg et al. 2002).

These observations of a protective role of *apoE4* can be viewed from several perspectives. Because the human-chimpanzee ancestor appears to have had an apoE with apoE3-like properties (see above and Table 5), the acquisition of a human apoE4 isoform by the T61R mutation might have been adaptive by increasing host defense responses in human ancestors. Finch and Sapolsky (1999) hypothesized that the subsequent evolution of *apoE3* in human populations would be advantageous to the evolution of longer human life spans by enhancing the health in the 40 to 70 age range when *E4* carriers have higher risk for cognitive and myocardial impairments. In this case, *E3* would be under positive selection for its benefit to aging parental and grandparental providers of food and care. Moreover, indications of *apoE4* benefits to younger ages as short-term host defenses would add another mechanism, antagonistic pleiotropy, as hypothesized by Williams (1957), for genes

with advantages to the young but deleterious effects to the old, when the force of natural selection is decreasing (Rose 1991; Charlesworth 1996).

CMAH and Sialic Acids

Sialic acids are specialized sugars on cell surfaces that differ biochemically between human and chimpanzee in ways that can influence resistance to certain pathogens. In an important series of studies, Varki and colleagues have shown that humans lack CMAH, an enzyme that converts the sialic acid precursor Neu5Ac to Neu5Gc (Table 3, Note 3). In chimpanzees and other anthropoids, Neu5Gc is the major sialic acid. Modern humans and Neandertals have Neu5Ac but lack Neu5Gc, in a new biochemical analysis of fossilized bones and teeth (Chou et al. 2002). Traces of Neu5Gc in human tissues may have dietary origins. The lack of Neu5Gc in humans is due to a mutational inactivation of the *CMAH* gene, which occurred 2.7 Mya by the insertion of a mobile repetitive element *AluY* (Chou et al. 2002). Thus, the CMAH mutation probably precedes the origin of the genus *Homo* and almost certainly precedes the increased brain size in the past 0.5 Mya (Figure 1).

The lack of Neu5Gc in humans may modify resistance to viral and bacterial pathogens that attach to host cell surfaces through Siglecs (sialic acid-binding immunoglobulin superfamily lectins), including those that discriminate Neu5Ac and Neu5Gc. For example, Neu5Gc influences the host range of rotavirus infections, which are a major cause of diarrhea and morbidity in young humans and domestic animals (Delorme et al. 2001). The absence of Neu5Gc in *Homo* for two million years could have influenced early expansions of geographic range of both paleo- and modern humans, as well as the recent spread of domesticated animals that carry infectious organisms with Siglecs. Siglec-1 differs in humans and chimpanzees by a single mutation that can modify the tissue distribution of macrophages (Brinkman-Van der Linden et al. 2000; Varki 2001a, 2001b), which could be why humans have fewer circulating macrophages and more myeloid cell precursors in spleen and marrow than chimpanzees.

HLA Gene System

The *HLA* (human lymphocyte antigens) gene system mediates many aspects of immunity and is remarkable in its great variation in human populations. Many *HLA* haplotypes (combinations of alleles at different loci) are highly conserved and are also found in chimpanzees (Table 4, Note 4a). *HLA* haplotypes influence reactive arthritis from bacterial infections (Table 4, Note 4b) and resistance to nematodes (Table 4, Note 4c). Of particular interest, chimpanzees are more resistant than humans to infections by hepatitis C, HIV, and malaria (Adams et al. 2001; Mizukoshi et al. 2002), which implies specific genetic resistance. For example, a class *HLA* I gene of chimpanzees is missing in human, bonobo, and gorilla (Adams et al. 2001). Other class I genes are less diverse in chimpanzee than human (de Groot et al. 2002). These major shifts are interpreted as outcomes of selection for resistance to different pathogens.

Prion Gene

Prion gene sequences can influence resistance and onset age of neurodegeneration to infectious prions in raw brain and bone marrow (Prusiner et al. 1999; Mead et al. 2003; Table 4, Note 5). The human and chimpanzee genes differ at six sites. Human populations differ widely in the distribution of prion alleles, which show extensive linkage disequilibrium and which may have originated 0.5 Mya (Mead et al. 2003). This heterogeneity is important in exposure to raw meat, because heterozygotes are resistant to Creutzfeldt-Jacob disease and probably to kuru. The linkage disequilibrium of prion alleles suggests balancing selection arose in association with prehistoric cannibalism. *HLA* alleles may also influence resistance to "variant Creutzfeldt-Jacob disease" (vCJD) (Collinge 1999; Jackson et al. 2001).

Cystic Fibrosis Gene

The cystic fibrosis gene, *CFTR* (cystic fibrosis transmembrane conductance regulator), also shows recent evolution (Table 4, Note 6). *CFTR* mutations are the most common autosomal recessives of Caucasians, with a total

carrier frequency of about 4%. The great apes have a single *CFTR* haplotype, which may be an ancestral allele and which is also the most common in modern humans (Mateu et al. 2001, 2002). Heterozygotes of *CFTR* mutants are hypothesized to be more resistant to cholera (*Vibrio cholerae*) and typhoid fever (*Salmonella typhi*). Resistance to waterborne cholera would have been important with the limited sanitation of high density human encampments before the establishment of permanent settlements and agriculture. Cholera can also be acquired from uncooked meat (see above).

Domestic Animals and Agriculture

The acquisition of meat-adaptive genes by early humans could also have added further disease resistance genes during the domestication of animals and development of agriculture in the past 12,000 years. As noted above, the lack of Neu5Ac could have increased resistance to rotaviruses and other pathogens of domesticated animals in high density human-animal communities. Other host resistance factors are more clearly associated with agriculture. For example, resistance to malaria from *Plasmodium falciparum* is mediated by several genes (hemoglobin, *G6PDH, HLA*) apparently selected during the relatively recent spread of malaria throughout human populations (Table 4, Note 7).

Other Adaptations that Support Hunting and Meat Eating

Having discussed gene candidates that protect against specific pathological consequences of meat eating, we briefly consider other evolutionary changes in brain and behavior, gut, hair and skin, and developmental schedules that may be considered as a larger suite of hunting related adaptations that enabled large scale meat eating (Appendix and Table 6). The major early transitions were a shift to bipedalism (5 to 6 Mya) and increased stone tool use (2 to 2.5 Mya) in the early genus *Homo* (Figure 1). With the emergence of *Homo erectus* at 1.8 Mya, brain size increased relative to body size in association with hunting of big game and use of fire (e.g., Shipman and Walker 1989). Language may have evolved later when brain size increased sharply and when hunting and tool making became progressively more sophisticated.

The gene *FOXP2,* first recognized in relation to familial language disorders, evolved changes about 0.2 Mya. These changes may have enabled human language (Enard et al. 2002a, 2002b). The *apoE3* allele (Fullerton et al. 2000) and the *FOXP2* gene (Enard et al. 2002a) appear to have spread in the same time range, clearly within the genus *Homo. ApoE3* was discussed above as protecting against dietary-induced hypercholesterolemia. Moreover, *apoE3,* by its greater support of neurite outgrowth than *apoE4,* could have enabled the relative increase of the prefrontal cortex, which is a seat of executive and language functions.

Other changes adaptive for hunting and meat eating occurred in the human digestive system, in particular the lengthening of the small intestine where meat is digested. The integument also changed with enhanced heat exchange, which would be adaptive for much greater walking and running of human foragers than in wild chimpanzees. The changes include reduction in coarse hair and increased sweating and increased pigmentation, for which some gene candidates are shown in Figure 1 (melanocortin receptor, MC1R; tropoelastin; keratin hHa1). Lastly, the slower developmental schedule of bones, teeth, and brain myelin are associated with delayed independence and increased intergenerational transfers of knowledge. Gene candidates for these include thyroid homone regulators and FGF-family growth factors (Appendix and Table 6).

The genome projects are rapidly increasing the number of genes that differ between human and chimpanzee, as known for *apoE, CMAH,* and others cited above. We may anticipate many further gene candidates from comparisons of mRNA levels in different cell types and organs of humans and the great apes. "Transcriptome analysis" of chimpanzee and human tissues indicates many quantitative differences in gene expression in brain (Normile 2001; Enard et al. 2002a) and cultured fibroblasts (Hacia 2001; Karaman et al. 2003). Some differences in growth timing may be sought at the level of gene transcription, as shown above for mutations in the *Lp(a)* gene promoter.

TABLE 6

Other adaptations that support hunting and meat eating and gene candidates

Organ	Difference from Chimpanzee	Gene Candidate
Brain[1]	• Differential enlargement of prefrontal association cortex	*apoE3*
	• Larger spindle neurons	
	• Further microosmia in association with decreased reliance on olfactory clues, relative to visual	Inactivation of olfactory receptor genes (*OR*)
	• Denser myelin and slower myelination	
Gut[2]	Small intestine is twofold longer	
Hair and Skin[3]	• Better heat exchange because of thinner body hair and greater sweating; more pilosebaceous gland secretions	Hair keratin pseudogene (*hHaA)* FGF-network
	• Skin pigmentation	Tropoelastin (*ELN*) melanocortin 1 receptor (*MC1R*)
Growth[4]		
Bone Maturation	• Long bone growth spurt absent in chimpanzee	Fibroblast growth factors (FGF); thyroid hormones and transthyretin
	• Delayed pelvic development	
	• Slower dental development	
Puberty	Delayed	Neuroendocrine

Notes to Table 6

1. The earliest hominids 5 to 6 Mya had ape-sized brains of 350 cm^3. Subsequent brain increases were proportionate to increased body size (Figure 1), e.g., "Lucy," *A. africanus* (450 cm^3, 35 kg). After 1.8 Mya in early *Homo,* brains increased faster than body size, e.g., *H. ergaster* (850 cm^3, 60 kg), with further relative increases during the last 500,000 years (Ruff et al. 1997; Collard and Wood 2000; Elton et al. 2001). There was also a relative increase of the prefrontal association cortex (Area 10), which is a seat of executive function and which has threefold more neurons than in great apes (Semendeferi and Damasio 2000; Semendeferi et al. 2001, 2002). The prefrontal cortex matures later than other brain regions (Huttenlocher and Dabholkar 1997; Sowell et al. 1999, 2001), a schedule consistent with slow maturing executive functions. The spread of *apoE3* in the last 500,000 years (Fullerton et al. 2000) could have supported increases in brain size by the enhancement of neuronal sprouting (Table 4, Note 1c).

   The olfactory receptor genes (*OR*) changes may also fit into a suite of changes that promoted the evolution of language for hunting and other social interactions. Humans may not be as dependent on their sense of smell as the great apes (Gilad et al. 2003), which may have relaxed selection on the huge *OR* gene family, resulting in a threefold higher rate of *OR* gene inactivation than in chimpanzee, gorilla, or orangutan (Gilad et al. 2003). Human populations may differ in functional *OR* (Gilad and Lancet 2003).

   Myelination, which supports the fast electrical conduction required for complex cognition, continues beyond 20 years in humans (Allman and Hasenstaub 1999; Giedd et al. 1999; Sowell et al. 1999, 2001, 2002; Bartzokis et al. 2003).
2. The human small intestine, where meat is largely digested, is twofold longer than in chimpanzees, whereas the colon, where fibrous materials are digested, is 50% smaller (Shipman and Walker 1989; Aiello and Wheeler 1995; Milton 1999a). Chimpanzees fully digest small portions of meat with a GI transit time similar to humans (Milton and Demment 1989), but it is not known if they can digest the larger portions eaten by humans. Aiello and Wheeler (1995) inferred that *H. ergaster*'s gut was like humans, because its rib cage was barrel-shaped and less conical than in australopithecenes and chimpanzees.
3. Human foragers travel tenfold greater daily distances than great apes (Stanford 2001) and burn much more energy for their body weight than other great apes (Leonard and Robertson 1997). The increased hunting in early *Homo* required the evolution of greater heat exchange to support prolonged walking and running, particularly in equatorial zones (Wheeler 1993). Humans have thinner hair than other primates (Montagna and Yun 1963) and sweat more heavily than chimpanzees, particularly on chest and back (Whitford 1976). Pilosebaceous glands are more abundant and secrete lipids that are thought to act as socially important body odors as well as defensins and other antimicrobial peptides (Montagna and Yun 1963; Chronnell et al. 2001).

   The human capacity for extended physical activity in tropical environments is supported by changes in the skin that enhanced heat exchange by convection and evaporative heat loss, as modeled by Wheeler (1984, 1990, 1991, 1992, 1993; also see Newman 1970 and Chaplin et al. 1994). There is also discussion about whether the enlarged human brain required evolution of vascular changes for heat exchange, as proposed by Falk (1990) and challenged by Brangelmann (1990) and Grüsser (1990). These adaptations may account for the absence of panting in humans as a mode of heat exchange found in other primates (Hiley 1976).

   Several genes expressed in skin have evolved in the time frame of interest. We suggest that a set of "heat exchange" genes was part of the meat-adaptive gene suite evolved to support the progressively greater large game hunting. Humans have an inactive (pseudogene) *hHaA* that encodes a hair protein in great apes (Langbein et al. 1999; Winter et al. 2001), which was acquired 0.25 Mya, about when the *apoE3* allele spread (Figure 1). Hair length is regulated by various growth factors impli-

cated in heritable disorders of skin and hair (Hébert et al. 1994; Oro and Scott 1998), which are cogent because these "atavistic mutations" increase body hair (hypertrichosis). The term *gorilla* was first used in reference to a reputed Africa tribe of hairy people according to the *Periplus of Hanno* (450 BC) (Garcia-Cruz et al. 2002). The angora gene (*go*) increases hair length by delaying the cessation of cell proliferation in the follicle (anagen-catagen transition), which precedes shedding of the hair (telogen phase). The *go/go* recessive mutation alters levels of the growth factor FGF-5 in follicles (Hébert et al. 1994). Hypertrichosis also occurs as drug side effects, e.g., to cyclosporine and minoxidil (Vashi et al. 2001; Garcia-Cruz et al. 2002). It would be informative to compare chimpanzees with human hypertrichosis for hair follicle density and structure.

The loss of hair also increased the need for skin pigmentation that protect skin glands from increased solar radiation as early humans left the forest canopy. The melanocortin 1 receptor (MC1R) is a factor in heritable skin color variations (Rana et al. 1999; Makova et al. 2001) and diversified about 1.5 Mya (Makova et al. 2001) during the emergence of *Homo* (Figure 1). The earliest change in an integumentary gene is in tropoelastin *ELN,* in two exons (E34 and E34) were deleted 6 to 8 Mya (Szabó et al. 1999), approximating the chimpanzee-human divergence. The truncated tropoelastin is expressed in human keratinocytes and is induced by solar radiation (Seo et al. 2001).

4. Thyroid hormones, which modulate rates of development, differ intriguingly between chimpanzee and human (Gagneux et al. 2001). Humans have lower plasma free T3 (-60%) and T4 (-30%) than chimpanzees. Transthyretin, a thyroxine binding protein, is twofold higher in chimpanzee plasma and cerebrospinal fluid and may have lower binding affinity. Gagneux et al. (2001) hypothesized that the differences in free T3 and T4 could alter the rates of craniofacial and brain development.

The evolution of quantitative variations in tooth and brain development (Allman and Hasenstaub 1999) might share gene regulatory processes, because tooth formation, like most cranio-facial components, depends on neural crest-derived cells. For example, FGF-signaling networks are implicated in tooth development (e.g., Kettunen et al. 2000), of salivary glands (Jaskoll et al. 2002), and of brain neurons and glia, including myelination (e.g., Mahmood et al. 1995; Faux et al. 2001). However, the larger human calvarium need not have required specific gene evolution because the cranial vault size is largely shaped by the size of the growing brain.

Many changes of postnatal maturation are driven by neural and endocrine pacemakers. The competence of certain target cells to respond to sex steroids by birth or earlier allows rapid evolutionary reprogramming of developmental schedules by genes that act on neuroendocrine pacemakers (Finch and Rose 1995).

Conclusions

The evolution of the extended human life span was achieved through selection operating on many developmental pathways. The chimpanzee taste for meat could have set the stage for the evolution of genes that allowed increased fat consumption without hypercholesterolemia. The evident sensitivity of captive chimpanzees to hypercholesterolemia and ensuing vascular disease, if present in the shared ancestor, required mutations that allowed emerging humans to have a far richer diet and to extend their development schedule. We argued that the evolution of the human *apoE3* and other candidates for meat-adaptive genes enabled the shift from an herbivorous ape diet to the more omnivorous diet of hominids, while also enabling a major increase in life span.

We would, of course, like to know how life spans evolved during these changes. The fossil record, unfortunately, tells little about adult life spans. The schedules of dental development suggest that prolonged postnatal development was relatively recent. Growth patterns in tooth enamel indicate that Neandertal dental development approximated that of modern humans and was slower than in australopithecines and early humans (*H. habilis* and *H. ergaster*) (Dean et al. 2001; Moggi-Cecchi 2001). On this basis, Neandertals and anatomically modern prehistoric humans might have had longer postmaturational nurture than early humans or australopithecines, but we can say little about life expectancy.

The chimpanzee genome projects (Cyranoski 2002) are being augmented by functional genomics. As an alternative to in vivo studies on captive chimpanzees that face strong ethical objections (NHGRI 2002), we note that cultured cells (fibroblasts, lymphomas, and blood cells) are available to study human-chimpanzee differences (e.g., Karamen 2003). In vitro models can also be used to study gender-hormone interactions on cell metabolism, which are indicated by the sensitivity of female chimpanzees to obesity (Steinetz et al. 1996). Expression profiling for species differences in response to dietary and stress factors could identify genes that confer protection against chronic diseases, some of which might also facilitate the greater life spans of humans. At the same time, as elegant technology is applied to human evolution, there is a major need to study the natural history of aging in the endangered wild chimpanzees and to identify which aspects of aging are not artifacts of captivity.

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APPENDIX

Supplemental information is listed for each table by footnote

TABLE 1

2. The Jane Goodall website describes the aging of Flo (born ca. 1929, died 1972). After having five children, "[S]he looked very old when the time came to wean young Flint, and she had not fully succeeded in weaning him when she gave birth to Flame . . . [who] died at the age of six months" (Jane Goodall Institute 2001). Flo probably died because "she was too old to travel far or climb trees [to obtain food during the dry season]" (Goodall 1983). The slower movements of older chimpanzees (Goodall 1983, 1986; Craig Stanford, unpublished) suggest neurological impairments and painful joints. Hill et al. (2001) reported, "Old individuals (about 35 years onwards) show thinning of hair (e.g., on shoulders, head or lower back), often with browner or greyer color and less sheen. Teeth are worn and may be broken, movements are slow, and facial skin shows sagging and wrinkling" (p 438), and two "very senile" females were believed to be well over 45.

Appearances can be deceiving about vitality, however. "Flo's teeth were worn almost down to the gum 8 years before her death" (Goodall 1983). In another case, "[A] white-haired and bent old male continued to live another 13 years"; one male (the oldest at Kibale) was described as "past prime" and disappeared while still "looking strong" (Hill et al. 2001). Lastly, Evered, an elderly male >40, despite badly worn teeth was still one of the best hunters of monkeys in his community; his dentition was insufficient to gnaw through soft abdominal skin and the prey was often abandoned (Craig Stanford, unpublished; Table 1, Note 11).

3. Further examples of myocardial degeneration: congestive heart failure in a 26-year-old male chimpanzee was associated with brain damage, "perivascular hemorrhage and . . . severe status spongiosis" (Hansen et al. 1984). An overfed and fat young male chimpanzee died suddenly from heart failure with "moderate atheroma and sclerosis of the great arteries . . . extensive fatty degeneration of the myocardium [which had] thin and flabby walls" (Hamerton 1941). In zoo gorillas, cardiovascular disease (fibrosis) is a major cause of mortality (Lindsay and Chaikoff 1966; Schmidt 1978). Aortic dissection is common (Thomas Meehan and L Munson, personal communication). As noted in our text, these findings on chimpanzees and gorillas may not represent normal outcomes of aging, because husbandry conditions were far from optimal for diet, for exercise and physical activity, and for social interactions.

5. Several criteria are widely used for diagnosis of Alzheimer's disease (AD): (1) Cognitive impairments, particularly in short-term memory, which progress slowly over years, and cortical atrophy; these signs are indicative but not definitive. (2) Postmortem histopathology in the hippocampus and frontal cortex that includes classical neuritic plaques (dense extracellular accumulations of fibrillar Aβ1–42 with abnormal neurites and inflammatory cells), neurofibrillary degeneration (intraneuronal accumulations of hyperphosphorylated tau, Alz-50 immunoreactive), and large neuron atrophy and loss.

Controversy continues on the role of Aβ in neurodegeneration in AD. Chimpanzees and many other vertebrates have an Aβ1–42 sequence identical to that of humans (Finch and Sapolsky 1999) which implies negative pleiotropy. Aβ accumulates in certain brain regions to some degree in a wide range of vertebrate species during aging. Laboratory rodents are an exception because their slightly different Aβ sequence aggregates less readily, which may be why aging laboratory rodents do not normally accumulate brain amyloid deposits during aging, unless made transgenic.

The Aβ deposits in the two chimpanzee brains were immunoreactive for apoE, as found in Alzheimer's disease, but were much sparser than in human

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AD or in aging macaques (Price et al. 1991; reviewed in Finch and Sapolsky 1999). Moreover, the Aβ peptide composition differed: in humans, cerebrovascular Aβ is mainly Aβ1–40 (40 amino acids long), whereas plaque amyloid is mainly Aβ1–42. Chimpanzee plaques had relatively more Aβ1–40 than humans, as judged by the 70% larger ratios of Aβ1–40:Aβ1–42 (Gearing et al. 1996). The additional two amino acids in Aβ1–42 promote aggregation and neurotoxicity (Klein et al. 2001). The presence of diffuse amyloid plaques does not qualify these brains for a postmortem diagnosis of AD by human pathologic criteria.

The absence of neuritic degeneration in the two aging chimpanzee brains is important. Neuritic degeneration with abnormal, hyperphosphorylated tau occurs during aging in the grey mouse lemur (*Microcebus marinus*), rhesus, and some other primates (Finch and Sapolsky 1999; Härtig et al. 2000; Hof et al. 2002). The age progression of these changes in apes is not known. One 45-year-old, terminally ill male chimpanzee had no cerebrovascular amyloid or diffuse amyloid plaques (Suzanne Mirra, personal communication). The Great Ape Aging Project (Hof et al. 2002) is examining a large series of brains by MRI and histological techniques.

In general, neuron loss in adult brains is increasingly regarded as a change due to AD or other specific disease processes that are distinct from normal aging (e.g., West et al. 1994). However, cognitive impairments during aging may arise independently of neuron loss. For example, no neuron loss was found in aging rhesus monkeys aged 24 years, an age when other studies showed extensive neuritic plaques and memory impairments (Merrill et al. 2000).

The attention on fibrillar amyloid is shifting because much recent evidence shows the importance of smaller, soluble aggregates of Aβ (Klein et al. 2001; Hardy and Selkoe 2002). For example, in transgenic mice which carry human AD genes, impaired memory correlated best with the amount of soluble Aβ (Mucke et al. 2000). Soluble Aβ includes neurotoxic oligomers of Aβ1–42, which are designated as ADDLs (amyloid-derived diffusible ligands) (Oda et al. 1995; Lambert et al. 1998, 2001; Klein et al. 2001). ADDLs impair LTP, a neurophysiological function related to memory (Klein et al. 2001). ADDLs are also found in human AD brains (Gong et al. 2003). The presence of ADDLs could be more indicative of cognitive impairments during aging than the amount of neuritic or neurofibrillary degeneration in nonhuman primates. ADDLs and other soluble Aβ forms may not be detected by conventional histology and may have greater importance than the classical fibrillar Aβ to neurodegenerative process. It should be possible to obtain frozen specimens from brains of aging captive pongids who died spontaneously within the 6 to 12 hour postmortem interval which allows detection of ADDLs in human AD brains.

10. Bone lesions are twofold more common in adults than subadults; >98% of adult skeletons from Gombe and other sources showed traumatic lesions, whereas 20% had inflammatory lesions (Woods 1986; Lovell 1990a, 1990b: Table 16).

11. Mastication depended almost entirely on the canine teeth in these elderly. Tooth wear is the result of a lifetime of chewing of abrasive materials and fighting. Impairments in chewing are a likely factor in emaciation (Table 1, Note 2) and osteoporosis (Table 1, Note 9) (Lovell 1990; Zihlman et al. 1990; Morbeck et al. 2002). In elephants, tooth wear is a major factor in frailty at later ages (Finch 1990:197–199).

12. At Gombe, Flo and her daughter Fifi had successful pregnancies after age 40 (Jane Goodall Institute 2001). Flo's age of 40+ is estimated; Fifi's is more certain. Goodall (1983) observed, "In captivity, female chimpanzees usually remain fertile until the end of their lives, whereas Flo . . . showed a gradual spacing out, then cessation of swelling. This may be related to the poorer physical condition of old individuals in the natural habitat (less nutrition, more parasites)." The cessation of sexual swellings strongly implies perimenopause.

Reproductive aging is well characterized in few other primates (reviewed in vom Saal et al. 1994; Finch and Sapolsky 1999). The rhesus has a definitive menopause by 25 to 30 years, about 10 years before the maximum life span. The changes closely resemble human menopause, with full ovarian oocyte depletion, decrease of sex steroids, and hot flushes. The grey mouse lemur may be similar to chimpanzees because females reproduce up to a year before their maximum life span of 12 years (Finch and Sapolsky 1999; Noelle Bons, personal communication).

None of these primate studies, however, has characterized the success rate of fertilization and pregnancy, which sharply declines in humans after 40 (vom Saal et al. 1994; Gosden and Finch 2000). Further data on reproductive aging in captive animals may come from the Great Ape Aging Project (Erwin et al. 2002; Hof et al 2002). Human menopause is clinically characterized by blood hormones (low estrogens and high gonadotropins). Although the ethics of field studies of chimpanzees and bonobos forbids blood sampling, hormones can be assayed in fresh excreta.

13. State-of-the-art clinical criteria were used to evaluate chimpanzees at the White Sands Research Center (Steiner et al. 1999). The ages of 10 to 30+ years included substantial numbers of older animals (N = 17 for 26+ yrs). Serum levels of prostate specific antigen (PSA) increased progressively with aging to

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threefold elevation by 26 to 30+ years. BPH was evaluated by prostate volume (TRUS) and biopsy in 70% of males 30+ years of age. The BPH caused urinary obstruction, as measured by decreased urinary flow rates and increased leak point pressure.

TABLE 3

1. The relative species ranking in the study of Srinivasan et al. 1976 for total cholesterol and LDL are consistent with their prior study of total plasma cholesterol for chimpanzee > rhesus and African green (vervet) > macaque > baboon > patas (Srinivasan et al. 1974). In Srinivasan et al. 1976, cholesterol was added for three weeks in a series of diets containing 0.05, 0.2, 0.5, 1.0, 1.5% cholesterol (g cholesterol/100 g diet), with return to control diet from three weeks before the next increment of cholesterol. The baseline intake was <12 mg cholesterol/day. The 0.05% cholesterol (900 mg/day) increased blood total cholesterol in chimpanzees by 15 mg/dL and by 18 mg/dL in green and rhesus monkeys.

2. We briefly summarize several papers from Simon Stevin Instituut from the Proceedings of the 3rd Conference on Experimental Medical Surgery of Primates, Lyon, 1972, that were difficult to obtain. Blaton et al. 1972: experimental feeding of 10 chimpanzees for up to 8 years on atherogenic diet (2.5% cholesterol; saturated fats), leading to fatty streaks after three years and one death from myocardial infarction. Blood lipid profiles of total cholesterol (elevated), triglycerides (normal), and phospholipids (elevated). Peeters and Blaton 1972: electrophoretic lipid profiles of chimpanzee versus human. Vestesaeger et al. 1972: plasma cholesterol of a female (see Blaton et al. 1972 above) who developed extreme hypercholesterolemia (500–900 mg/dL) and died of myocardial infarction after three years. Figures show arteriography and evidence of prior stroke associated with hemiparesis.

3. The "Jumbo Monkey Diet 5037" named in Steinetz et al. 1996 is the Purina (PMI Feeds Inc.) Monkey Diet No. 5037 ("Jumbo" biscuits) for Old World monkeys. It includes cultivated grains and soybean, whey (milk component presumably from cows), fish meal, and animal fat. The proportions of bulk protein, fats, and carbohydrates may vary within narrow limits (as specified for this Purina product). However, the components of most commercial diets have been known to vary seasonally by bulk availability and market price, e.g., fish meal and animal fat; these variations may be important because trace components can be allergenic. PMI guarantees that Diet 5037 has a crude protein > 15% and crude fat > 5%. In fact, Steinetz et al. 1996 (Table 1) reported 10.9% fat, which is twice the minimum given by PMI. Such large variations in fat content between lots could be a serious confound in comparing studies.

5. Howell et al. (1997), a widely cited meta-analysis, preceded the availability of the *apoE* genotype. In particular, *apoE4* carriers are more responsive than *apoE3* in serum cholesterol responses to dietary cholesterol (Table 4, Note 1). In a unique prospective study, Sarkkinen et al. 1998 fed mildly hyperlipidemic adults (plasma total cholesterol mean 6.5 mmol/L or 260 mg/dL) on three successive diets: (I) normative Finnish diet (baseline), 0–4 weeks; (II) lower fat diet recommended for cardiovascular health (National Cholesterol Education Program, NECP), 4–8 weeks; and (III) NECP diet supplemented with increased cholesterol, 8–16 weeks, reaching 300 mg/d cholesterol (2 egg yolks) in the last 4 weeks. Each *apoE* genotype had N = 15 Ss, balanced by sex, age, and body mass index; subjects did not use cholesterol-lowering drugs. The addition of 300 mg cholesterol (2 egg yolks) to the low fat diet (II) caused modest increases in serum total cholesterol, with important *apoE* allele effects: E4-E4 (+0.57 mmol/L or +22 mg/dL; +10%) > E4-E3 (+3%) > E3-E3 (+2%). These responses of serum cholesterol by *apoE4-E4* was threefold larger than the population average 6.6 mg/dL change predicted by the equation of Howell et al. 1997.

TABLE 4

1a. An example of low genetic associations of *apoE4* with AD comes from a longitudinal study of 5,000 community-dwelling elderly African Americans in Indianapolis and Yoruba in Ibadan, Nigeria (Hendrie et al. 2001). Both communities had identical *apoE4* prevalence and were evaluated with a test designed to detect memory impairments across in cultural diversity and educational levels. Dementia is about 70% lower in the elderly Yoruba than the African Americans. The Yoruba have lower incidence of vascular disease, diabetes, hypertension, and lower blood cholesterol (Hendrie et al. 2001). The typical diet of the Muslim Yoruba in Ibadan is characterized as low in fat and protein, consisting mostly of yam and casava, with some corn and fish (Adeoye 1992; Hugh C Hendrie, personal communication). The low dietary fat and low incidence of AD in the Yoruba are consistent with fat as a risk factor for Alzheimer's disease. Another African population, the Khoi San (Bushman), has a very high frequency of *apoE4* (37%); however, on their low fat diet, *apoE* alleles were not associated with the levels of serum total cholesterol (Sandholzer et al. 1995). This finding indicates that *apoE4* potentiates hyperlipidemias to dietary fat (Bernstein et al. 2002; Kivipelto et al. 2002).

The risk of heart disease is less strongly correlated with *apoE4* than Alzheimer's disease (Eichner et al.

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2002). For example, sudden death in Finnish men strongly correlated with the area of fatty streaks and total atherosclerotic area in coronary arteries, with *E3/E4* 25% to 50% greater than *E3* in men aged 33 to 52 years; in men aged 53 to 70 years, the coronary lesions had progressed to the same level in non- *E4* carriers (Ilveskoski et al. 1999). Similar effects of *E4* were found in the aortas of a younger men, aged 15 to 34, of Caucasian and African backgrounds (Hixson 1991). These findings concur with the higher incidence of silent myocardial ischemia in middle-aged and older *E4* carriers (Katzel et al. 1993; Humphries et al. 2001). The effect of *apoE4* on heart disease diminishes at later ages, as in Alzheimer's disease (Meyer et al. 1998). Similar effects of *E4* were found in the aortas of younger men, aged 15 to 34, of Caucasian and African backgrounds (Hixson 1991). These findings concur with the higher incidence of silent myocardial ischemia in middle-aged and older *E4* carriers (Katzel et al. 1993; Humphries et al. 2001).

1d. The enhancement of inflammatory reactions in *apoE4* genotypes might be adaptive as host defense mechanisms against viruses and other pathogenic organisms. For example, macrophages from normal human *E4* carriers and from *apoE4* knock-in mice produce more free radicals and other inflammatory markers relative to *E3* (Brown et al. 2002). Similarly, *apoE4,* but not *E3* or *E2,* potentiated the activation of complement by Aß (McGeer et al. 1997). Microglia are derived from bone marrow monocyte lineage cells and resemble macrophages in many regards. Because microglia can produce reactive free radicals, their activation is a potential source of the oxidative damage in AD, which may be greater in degenerating brain regions of *apoE4* than *E3* (Montine et al. 1997; Ramassamy et al. 1999). ApoE3 protein, but not apoE4, blocked the activation of brain macrophages (microglia) by the amyloid precursor protein, sAPPα (Barger and Harmon 1997). The evidence for increased inflammatory responses of *apoE4* macrophage-microglia supports a hypothesis of antagonistic pleiotropy in host resistance, e.g., *apoE4* allele might have been adaptive to infections by enhancing responses of macrophages which have a major role in host-defense, despite its longer term adverse associations with brain and heart dysfunctions.

In HIV, *apoE4* is associated with severalfold higher incidence of dementia and peripheral neuropathy (Corder et al. 1998). However, there is no information on *apoE* alleles and the risk of HIV infection. Another mechanism may involve heparin sulfate proteoglycans which bind *apoE,* HIV, and other viruses (Mahley and Rall 2000). Herpes simplex virus 1 (HSV1, cause of cold sores) and HSV2 (herpes zoster, cause of shingles) may also interact with *apoE* receptors at sites resembling the *apoE* binding site for LDL receptors (Becker 1992; Dobson and Itzhaki 1999).

Synovial infections by *Chlamydia pneumoniae* are associated with *E4* (Gérard et al. 2000). No general association of *apoE* alleles and bacterial infections is indicated.

1e. *ApoE4* was associated with Creutzfeldt-Jacob disease (CJD) (Amouyel et al. 1994), whereas *apoE2* was associated with later onset (Pickering-Brown 1995). No *E4* association with CJD was found by Nakagawa et al. 1995, Salvatore et al. 1995, Zerr et al. 1996, or Chapman et al. 1998.

4b. Reactive arthritis can occur after infections by *Shigella, Salmonella, Yerssinia,* or *Campylobacter,* or with urogenital infections of *Chlamydia trichomatis.* One gorilla which developed reactive arthritis after a *Shigella* dysentery had an orthologue of HLA *B27* (Neiffer et al. 2000). In laboratory macaques, the absence of reactive arthritis following *Shigella* dysentery was associated with a different MHC haplotype (Urvater et al. 2000).

8. A prospective study showed a threefold difference in risk of acute myocardial infarction according to the body load of iron, as assayed by the ratio of serum transferrin receptor:ferritin (Tuomainen et al. 1998). One mechanism may be by oxidation of lipids, a factor in vascular disease which is promoted by both iron and copper (Fields 1999; Lee et al. 1999).

In a transgenic mouse model of AD, metal chelation therapy decreased amyloid deposits (Cherny et al. 2001). Copper and zinc bind to the amyloid ß-peptide, although the direction of the effect on the amyloid toxicity depends on the model (Huang et al. 2000; Curtain et al. 2001). Dietary copper and zinc may also interact with *apoE* isoforms, which in turn modulate the neurotoxicity of prion peptides and the Alzheimer Aβ-peptide (Aβ). In the presence of copper or zinc, *apoE4* promotes Aβ aggregation more than *apoE3* (Moir et al. 1999).

Iron can be a limiting micronutrient in bacterial infections (Jurado 1997). Metals in meat may also interact with prion diseases; e.g., copper and zinc enhanced the neurotoxicity of a prion peptide (Jobling et al. 2001). Lowering of blood levels of free iron during the acute phase inflammatory response is mediated in part by the increased production of iron binding proteins. The hepatic production of ferritin, a major iron binding protein, is regulated by red meat consumption as noted above. Although basal plasma transferrin is similar in chimpanzees and humans (Gray-Owen and Schryvers 1993), the inducibility of transferrin and other iron-binding proteins has not been examined in the great apes. Lactoferrin binds iron at sites of inflammation; macrophages induce lactoferrin receptors during acute phase responses; and lactoferrin can be proteolytically cleaved to form the

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antibacterial peptide lactoferricin. Plasma ferritin is regulated by red meat consumption (Yokoi et al. 1994; Rossi et al. 2001).

Increased iron can also promote infections. Because plasma ferritin increases with the frequency of red meat consumption in humans (Yokoi et al. 1994; Rossi et al. 2001), it is of interest to examine the regulation by iron of ferritin, lactoferrin, transferring, and other iron-binding proteins in chimpanzee versus human cells. Chimpanzees and humans have similar basal levels of plasma copper and iron (Planas and Grau 1971). Chimpanzee transferrin binds as effectively as human to three bacterial pathogens (*Neisseria meningitis,* *Moraxella catarrhalis,* and *Haemophilus influenzaei*) (Gray-Owen and Schryvers 1993). Monoclonal antibodies to human transferrin crossreacted equally to human and chimpanzee transferrin on Western blots (Miller et al. 1988; Gray-Owen and Schryvers 1993), with the exception of one antibody (Gray-Owen and Schryvers 1993).