Evolution of the human lifespan and diseases of aging: Roles of infection, inflammation, and nutrition

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Humans have evolved much longer lifespans than the great apes, which rarely exceed 50 years. Since 1800, lifespans have doubled again, largely due to improvements in environment, food, and medicine that minimized mortality at earlier ages. Infections cause most mortality in wild chimpanzees and in traditional forager-farmers with limited access to modern medicine. Although we know little of the diseases of aging under premodern conditions, in captivity, chimpanzees present a lower incidence of cancer, ischemic heart disease, and neurodegeneration than current human populations. These major differences in pathology of aging are discussed in terms of genes that mediate infection, inflammation, and nutrition. Apolipoprotein E alleles are proposed as a prototype of pleiotropic genes, which influence immune responses, arterial and Alzheimer's disease, and brain development.

chimpanzee | pathology

Humans have the longest life spans of any primate. Even under the conditions of high mortality experienced by hunter-foragers, the human life expectancy at birth (LE_0) is twice that of wild chimpanzees. This inquiry considers the demographics and pathology of aging in humans and great apes as an approach to understanding how aging processes evolved with longer lifespans. I argue that immune functions and nutrition have been of major importance in the evolution of aging and longevity.

Evolving Demographics of Aging

The human LE_0 has doubled during over an evolutionary span of about 300,000 generations from a great ape ancestor shared with chimpanzees (1, 2). Then during the last 200 years during industrialization and in <10 generations, the LE_0 has doubled again (3, 4), allowing major increases in older ages. The lifespans of intermediate species during human evolution cannot be known, because the spotty skeletal evidence at hand allows only general estimates of age classes. According to tooth wear, early modern *H. sapiens* and *H. neanderthalensis* had a larger proportion of older adults than prior *Homo* species and *Australopithecus* (5).

Turning from the huge gap before historical times, we may model earlier *H. sapiens* demographics by preindustrial populations for which there is good demographic data: Sweden from 1751 (3, 4) and 20th-century hunter-foragers (6–8). Both lived under unhygienic conditions with high burdens of infection and limited access to effective medicine. Their high mortality at early ages of 10%–30% restricted the LE_0 to 30–40 years. Despite low survival, half of those reaching age 20 reached 60 (LE_{20} of 40 years). Thus, most hunter-gatherers survive beyond menopause, unlike wild chimpanzees (7–9). The greater survival to later ages allowed the evolution of stable multigenerational support of the young, a uniquely human trait among primates (7–9).

Mortality across the lifespan forms a J-shaped curve in most mammalian populations: the high early age mortality declines to a minimum (q_{min}) at the approach of adulthood, followed at midlife by exponential accelerations of mortality in association with increased chronic degenerative disease and dysfunctions that collectively define senescence (2, 10). Humans differ from wild chimpanzees by their lower mortality in juvenile and adult ages, and by the later onset of mortality rate acceleration (6, 8, 11) (Fig. 1). In healthy populations of humans and lab animals, the acceleration of mortality is preceded by increasing morbidity from chronic degenerative disease (2, 10). For wild chimpanzees, typical early mortality rates are 20% per year in infancy, within the range of hunter-gatherers, then decreasing to a q_{min} of about 3.5% per year in preadult ages. The chimpanzee life expectancy at birth (LE_0) is about 13 years, whereas those reaching adulthood (age 15) have about 15 years of further life expectancy (6, 11) (Table 1). Very few have survived beyond age 50, even in captivity with modern veterinary care (13). In contrast, human mortality after the early years is much greater, with >2-fold longer LE_0 and >3-fold lower q_{min}, even with limited access to medicine (Table 1). Since 1800, the LE_0 in developed nations rose progressively to >70 years. Only recently has survival to >90 been well documented; currently, centenarians are about 0.01%–0.02% in developed nations (14). Two key factors in human life expectancy are the delayed mortality rate acceleration and lower q_{min} (Fig. 1). The q_{min} merits attention in human evolution (10): even in populations with high infectious burdens and neonatal mortality, the human q_{min} is >50% lower than wild chimpanzees (Table 1). As discussed later, this apparent species difference may be due to stronger immune responses. Since 1800, the industrialized countries have further lowered q_{min} by 25-fold (12).

Causes of Mortality. There is frustratingly little information on diseases of aging in wild chimpanzees and in hunter-foragers for comparison with modern populations. The following summary necessarily includes individual observations as well as larger studies.

Infections. The main cause of mortality throughout human evolution until the 20th century must have been infections, as observed in wild chimpanzees and 20th-century hunter-foragers. Longitudinal studies of the Gombe chimpanzees (Tanzania) since 1960 by Goodall and colleagues identified infections in the majority of deaths (67%) for all ages (Table 2) (15). The oldest individuals frequently had prolonged diarrhea (16, p 104). Infected wounds from accidents or fighting were also a common secondary cause of death (see note to Table 2). The accelerating mortality rates of chimpanzees soon after age 20 (Fig. 1) implies decreasing resistance to infections with aging, as well as synergies of infections with other myocardial damage, discussed below.

The Gombe chimpanzees cannot be considered a pristine population because of their exposure to pathogens from local humans and domestic animals (e.g., mange, polio, and tuberculosis). A recent SIVcpz infection (chimpanzee-derived simian immunodeficiency virus) has been transmitted vertically and horizontally, with >10-fold higher mortality in carriers and lower fertility and

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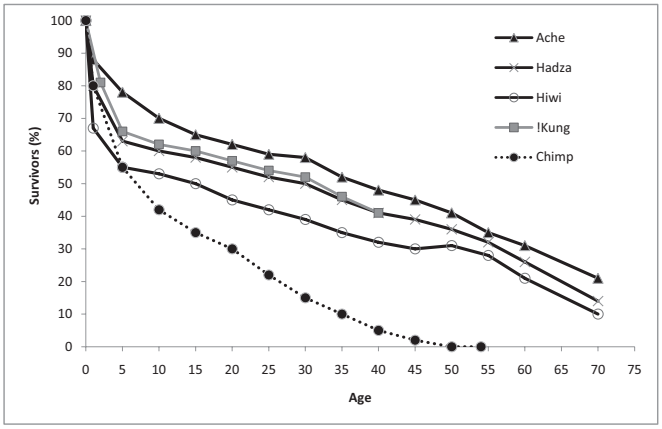

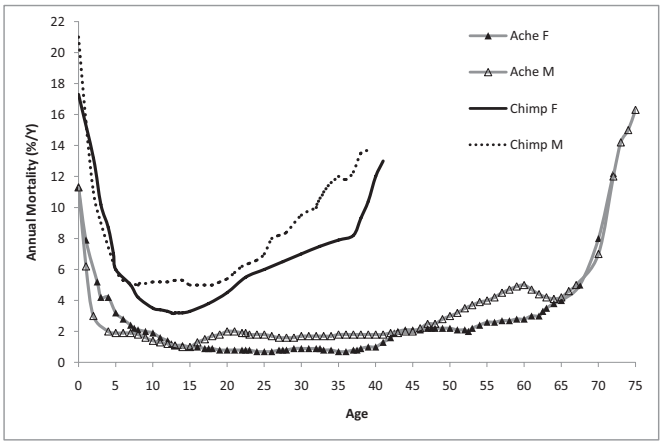

Fig. 1. Demographic comparisons of wild chimpanzees with human populations living under poor hygiene and with little access to medicine. [Reproduced with permission from ref. 6 (Copyright 2000, John Wiley & Sons).] (*A*) Survival curves. (*B*) Age-specific mortality. At all ages after infancy, chimpanzees have higher mortality than the Ache and show acceleration of mortality at least 20 years earlier.

infant survival (17). End stages had depletion of $CD4^+$ T cells and secondary infections, like human HIV. There may be no remaining truly isolated chimpanzee population in which to evaluate pathogen loads and mortality causes, because of increased commercial activity and warfare. There is no detailed profile of native infectious agents in any wild primate population (18)

Human forager-farmers traditionalists with limited access to modern medicine also show infections as a main cause of death (72%) (Table 1) (7, 19). These human populations, although relatively isolated, also had tuberculosis and other pathogenic infections (7) that are unlikely to have been indigenous (20). Notably unlike chimpanzees, a definitive proportion of elderly forager-farmers age 60 or older died from nonspecific senescent causes.

Before the 18th century, there are no national or regional statistical data on mortality rates by age group or causes of death. In the ancient Greco-Roman world, demographic reconstructions agree on short LE_0 ranging 20–35 years (21, 22). These calculations are based on tombstone epitaphs and graveyard samples, which are notoriously unrepresentative (21–23). It may be concluded that few in this era lived longer than 90 years, which is the upper age limit validated in hunter-gatherer-foragers (6, 7). Contagious infections and septic wounds are likely to have been the major causes of death in ancient populations living under unsanitary conditions (2, 21, 22).

The high incidence of infectious causes of death among 20th-century hunter-gathers resembles pre-20th-century populations, where infections, directly or indirectly, were major causes of adult deaths. In national data for England and Wales of 1861, for example, infections caused 25% of female deaths before age 40 (24). Almost all deaths before age 5 were due to infections (9, 24, 25). The much lower q_{min} for humans than chimpanzees (Table 1) suggests corresponding differences of immunological functions, as described later. Data on cause of death for juvenile ages are needed to evaluate the contribution to mortality from transmissible infections, septic wounds from in-group aggression and accidents, and from predation to which subadults are more vulnerable by smaller size and lack of experience.

Exposure to chronic infections and inflammation has major ramifications for aging processes through 2 main fronts: immunosenescence and synergies with chronic diseases that have inflammatory components. In brief, immunosenescence involves depletion of the limited pool of naïve T cells acquired during maturation. During antigenic exposure across life, the pool of memory T cell ($CD8^+$ $CD28^-$ T cells) increases progressively, at least in part from antigenic stimulation by common infections e.g., CMV, HSV, influenza (2, 26–28). A subgroup of elderly with the "immune risk" phenotype for higher mortality have relative depletion of $CD28^+$ T cells and memory T cells with telomere erosion, increased cytokine expression, and other markers of cellular immunosenescence. Because HIV is associated with accelerated memory T-cell accumulation and frailty (29), it is predicted that immunosenescence will be accelerated in the hunter-gatherers with high infectious loads (Table 2).

The associations of high early mortality and shorter life expectancy in historical populations give important clues to early human evolution in highly infectious environments. Crimmins and I examined Sweden and several other 19th-century European populations that had high early age mortality from infections. The correlations of mortality before age 5 with mortality at age 70 were much stronger for birth cohorts than for the periods (5, 25). We proposed a "cohort morbidity hypothesis" in which survivors of early infections carried higher inflammatory loads, which promote chronic diseases with inflammatory components, such as cardiovascular disease. Atherosclerosis, for example, begins before birth, with accumulating lipids, monocytes, and local oxidative damage; "fetal programming" from maternal diet, cholesterol, and stress can influence the later progression of arterial degeneration (2, 30, 31). Higher mortality of elderly to infections could also be involved in cohort effects, e.g., cytomegalovirus (CMV) infections are associated with immunosenescence and cardiovascular disease (2, 32). The progressive reduction of mortality at later ages in birth cohorts with better early survival is likely to involve complex interactions of atherosclerosis and immunity (2).

To further evaluate relationships between infectious exposure and accelerated aging, we examined the 1918 U.S. influenza pandemic for birth cohorts exposed pre- and postnatally (31). Most deaths were secondary to bacterial infections that caused severe pneumonia. This population was considered well-nourished, unlike earlier European cohorts. Specific prenatal influences were found on later aging: the cohort exposed prenatally to the peak pandemic in 1918 had 25% excess ischemic heart disease 60–82 years later, relative to flanking birth quarters. Moreover, the 1919 birth cohort had lower educational achievement and was slightly shorter at WWII enlistment. Because influenza rarely invades the placenta or fetus, these effects may involve stress effects on the fetus with elevations of maternal cortisol and IL-6, and imprinting of the fetal genome (reviewed in ref. 31). Apparently, even brief maternal infections without malnutrition impair postnatal growth and accelerate cardiovascular aging. These findings also extend the Barker theory of developmental origins of adult diseases of aging to effects of stress on the fetus from maternal infections.

Arterial disease. We cannot know the incidence of arterial disease or cancer in pre-20th-century populations because there are no population-based clinical data. Nonetheless, there are indications of arterial diseases in early historical human populations. For

Table 1. Comparative demographics of chimpanzees and humans

	LE_0, years[b]	Infant mortality, %	LE_{adult}, years[b]	q_{min}, % per year[c]	Age, years	Max. lifespan
Chimpanzee (feral) (6)	13	0.20	15	0.035	15	<50
Preindustrial populations						
Forager-horticulturalists (6–8)[a]	33	0.42	40	0.012	11-20	<100
Sweden 1751	35	0.21	40	0.0080	11-20	?[d]
Industrial populations with good nutrition, hygiene, and medicine (12)						
Sweden 1931	64	0.06	49	0.0008	11-20	>100
Sweden 1978	72	0.03	56	0.0003	11-20	
Sweden 2007	79	0.028	61			

[a]Average of 5 nonacculturated groups (6, see table 2); values are rounded, sources in parentheses.

[b]LE_{adult} used age 15 y for chimpanzee and 20 y for human (7, 8). The alleged 75+ age of the Hollywood chimpanzee *Cheeta* was recently discredited (13).

[c]q_{min}, minimum mortality across the lifespan (see Fig. 1).

[d]Rigorous analysis has disproven most claims of longevity >100 years before the later 19th century, when birth records gave more certain identification (14). Sweden in 1751–1760 recorded 24 centenarians per million, which is considered erroneous because of poor records, although it is less than 20th-century norms of 100 centenarians per million; the number declined to 1 per million by 1851, which is still considered uncertain, despite improving records. The accepted record lifespan is 122 of Jeanne Calment, 1875–1997, although there are still skeptics.

arterial disease, the oldest case is the Tyrolean iceman from 5,300 years ago, who died accidentally at about age 45; CT imaging showed calcification of both carotid arteries and portions of aorta and iliac artery (33). Arterial disease was also described for Egyptian mummies from 3,500 years ago (18th Dynasty; $n = 24$) (34, 35): 67% of large arteries were atherosclerotic; of these, 50% were calcified. In modern populations, arterial calcification is a high risk marker for vascular fatal events, with 4-fold more mortality in the following decade (36, 37). Coronary atherosclerosis was also found in mummies from dynastic Egypt (34, 38), China (1150 BCE), and Alaskan Inuit (430 CE) (39). Though these scattered samples cannot inform about the prevalence of atherosclerosis in historical populations or its contribution to mortality, they suggest that advanced atherosclerosis is not a modern condition.

For chimpanzees, the only histopathological data are from captives, which in earlier decades were exposed to varying conditions of husbandry and diet, including dairy products, which are not normal for wild chimpanzees. Up thru 1980, arterial fatty degeneration and sudden death from heart attack or stroke were widely noted as comparable to humans, as represented in these examples from a scattered literature (1). In one U.S. colony, on Yerkes' natural diet, all adults had cerebral arterial lesions, but no coronary lesions (40), whereas the majority of another colony had coronary lesions (41). Premature sudden death from myocardial infarcts was observed elsewhere in 2 young females, an 8-year-old on an unspecified diet (42), and a 10-year-old female with extreme hypercholesterolemia (≥600 mg/dL serum) from a fatty diet (43). More generally, on typical primate diets before 1980, 80% of chimpanzees had elevated cholesterol (*ca*. 200–300 mg/dL serum) (1, table 3*A*). These levels would be considered high risk for cardiovascular events in humans.

Subsequent well-maintained colonies on more standardized diets are puzzlingly divergent for blood lipids: chimpanzees at Yerkes were hypercholesterolemic (44), whereas those at Phoenix had normal cholesterol (45). The Phoenix colony also reported changes in LDL and HDL subfractions that were offsetting in risk by clinical criteria. Other cardiovascular risk indicators included elevated fibrinogen, insulin, and Lp(a); the latter is a species difference, due to increased transcription of the *Lp(a)* gene (46). Markers of oxidation in blood-cell DNA and lipids were higher, though some antioxidants were lower relative to healthy young men. Despite these risk indicators, ischemic coronary artery disease has *not* been identified as the main cause of death in 3 other modern colonies, where most sudden deaths were attributed to congestive heart failure from fibrillation in association with myocardial fibrosis: Yerkes (44), Almagordo (47), and Southwest Foundation (48). Ischemic arterial disease was considered minor in most sudden deaths in these well-maintained colonies, in contrast to the earlier reports. However, myocardial fibrosis was also common in early colonies (40, 41).

Cancer. Chimpanzees and other primates in captivity appear to develop much less neoplasia than humans, as noted in earlier reviews (49–51) and supported by recent studies. To a first approximation, neoplasia was detected in <3% of adults up through older ages. Female chimpanzees from Yerkes and Southwest Foundation had more neoplasia than males, with notable prevalence of uterine leiomyomas (52). The leiomyomas and most other tumors were benign and arose after age 25. Remarkably, no spontaneous mammary carcinoma has been reported in the great apes. In males 25 years and older, benign prostatic hyperplasia is common, and associated with clinical-grade blood prostate-specific

Table 2. Cause of death in feral chimpanzees and hunter-gatherers

	Chimpanzees, %[a]	Traditional humans, %[b]
Infections	67 (TB, polio, mange)	73
Violence/accidents	32	17
Senescence	1	10

[a]Feral chimpanzees (Kasekela community of Gombe, Western Tanzania), studied by Jane Goodall and colleagues, 1960–2006, with 73 deaths across all ages (15, 16). This table excludes deaths from poaching and predation; deaths of dependent offspring from maternal death or disability; and from unknown causes. "Illness" represents the largest cause of death and includes polio, mange, and wasting, and respiratory conditions (epidemic and nonepidemic of 48%). Wasting is described as "a conglomerate of enteric diseases, parasitic infections, or perhaps cancer or AIDS-like disease"; some were positive for streptococci and nematode parasites. The life history of the oldest individuals is known in detail (15, 16). Two elderly males aged 41 (Evered and Huxley) died of infected wounds, which I represented as infections. The oldest death (Flo, aged 43) is described as "wasting ... likely secondary to senescence" (15).

[b]Hunter-gatherers and forager-farmers with limited access to modern medicine (8); 7 groups in the 20th century. Senescent deaths were scored for those >60 y, which may have included infections.

antigen and urinary retention (53). Though prostate neoplasia was not reported (52, 54), later ages need study.

Other primate species also present a low incidence of neoplasia. Adult baboons and monkeys had <3% prevalence at necropsy of >10,000 animals from 3 colonies that included older ages (55–59). Prosimian neoplasia is similar, 1%–3% of adults (60). In view of the absence of mammary carcinoma in chimpanzees, the documentation of mammary carcinoma in prosimians and monkeys (references in ref. 60) give a mandate for continuing surveillance of aging chimpanzees. Provisionally, primate colonies have lower prevalence of malignancy than most modern human populations, e.g., the U.S. lifetime cancer risk was about 40% in 2007 (61). However, the above studies did not present data on the population at risk by age, needed for comparison with human populations. The surviving aging great apes are a vanishing resource because active breeding has been stopped in U.S. colonies. The absence of pregnancy also eliminates a protective factor for breast cancer in humans. There may be no way to obtain autopsy data on wild populations without supporting the bushmeat trade.

The paleopathology of neoplasia may only be approached in bone tumors, which persist in graveyard and fossil skeletons (62). In a large sample of adult bone (>3,500) specimens from pre-Roman Egypt and medieval Germany, about 0.5% of individuals at both sites had macroscopic tumors (>3,500 specimens), similar to that of England in 1900 (63). For comparison, 4,000 baboon autopsies yielded 1 osteoma and 1 osteosarcoma, suggesting a prevalence of <0.1% (55), again consistent with a lower incidence of other types of malignancies in primates than humans. I have not found reports on pathologically confirmed bone tumors in prehistoric human fossils.

Neurodegeneration. The neuropathology of aging in great apes is also surprising. Detailed studies of brains from chimpanzee, gorilla, and orangutan of 40 years or older concur on the rarity of Alzheimer-like neurodegenerative changes of neuronal loss, neuritic plaques (dense amyloid plaques with neuritic degeneration), and neurofibrillary degeneration with tau immunoreactivity (1, 64, 65). In contrast to the great apes, aging monkeys and a prosimian have shown more neurodegenerative changes with varying degrees of neurocytoskeletal abnormalities and amyloid deposits (1, 64–66) and cerebral atrophy (67, 68). Nonetheless, it was recent reported that a 41-year-old chimpanzee died after a stroke with the classic tau-positive neurofibrillary tangles with paired helical filaments (69). This individual also had obesity and chronic hypercholesterolemia. Despite the neurofibrillary tangles, other brain changes were mild: the diffuse amyloid deposits and the absence of major neuronal loss and neuritic plaques do not meet neuropathological criteria for Alzheimer's disease.

Possibly, hypercholesterolemia may promote a subset of Alzheimer-like changes in chimpanzees under some circumstances. In humans, the epidemiological and clinical links of obesity and blood cholesterol to Alzheimer's disease are complex and controversial. Variations of trace elements could be a factor. In rodent and rabbit models of Alzheimer's disease on cholesterol-rich diets, trace iron intake may be a critical variable (70). Lead can also promote later formation of amyloid deposits in monkeys (71). However, none of the rodent or primate models has shown the extensive neuronal loss characteristic of human Alzheimer's disease by early clinical stages. Thus, Alzheimer's disease may be a uniquely human neurodegenerative pathway of aging.

Other age-related changes. Wild chimpanzees of 25 years have increasingly frequent decrepit appearances from bone fractures, skin wounds, tooth loss, weight loss, and difficulty climbing (16, p 104). Degenerative osteoarthitic changes are indicated in some samples. In adult skeletons from Kibale, 75% had some degenerative joint disease, most severe in older females; 65% showed traumatic bone injury from fractures and bite punctures (72). Similarly, an early 20th-century sample from West Africa had prevalent erosive osteoarthritis (73). A Gombe sample, however, had minimal spinal osteoarthritis (74). The uncertain ages and small samples preclude comparisons with humans.

Female reproductive senescence with follicular depletion (menopause) occurs by 50 in chimpanzees in natural populations and in captivity (9, 75–78). Nonetheless, wild females are fertile up through at least 42 years (16). Thus, few if any female chimpanzees survive to reproductive senescence in natural populations. By contrast, most hunter-gatherer females reaching adulthood survive beyond menopause (6, 8, 9). The extended postmenopausal phase also uniquely exposes humans to osteoporotic fractures from low estrogen that are not reported for great apes.

Male reproductive aging is undefined: besides benign prostatic hyperplasia (53), there is no report on how male age influences spermatogenesis or sperm quality. The social hierarchies that determine access to females are dominated by prime-age adult males typically in the late teens to late twenties (16, fig. 15.2); the upper ages overlap the onset of benign prostatic hyperplasia in captive males (53).

Summary on Aging in Chimpanzees. The indications of faster aging in chimpanzees than in humans by the earlier acceleration of mortality require corroboration by age-specific changes in pathology and organ function. Because menopause occurs at about the same age, 50, reproductive declines may be relatively delayed in female chimpanzees. The emerging profile of pathology in aging captive chimpanzees suggests the importance of environmental and husbandry variables for myocardial and brain aging, in which blood cholesterol and trace metals could be important. The low prevalence of ischemic heart disease in modern colonies may represent improvements of husbandry, but the scattered data from earlier colonies do not allow firm conclusions. However, for cancer and myocardial pathology, age-specific rate data are needed for comparison with human aging. Measures of cardiopulmonary function and immunosenescence in captive colonies will also be informative. Ongoing studies of the relict hunter-foragers with limited access to modern medicine (6–8) may be our best basis for comparison with wild chimpanzees. The rarity of malignancy and myocardial infarction, and the absence of Alzheimer's disease, in chimpanzees may prove to be real species differences. Conversely, it is important to know whether the diffuse interstitial fibrosis of aging chimpanzees also occurs in some human populations.

Diet. During human evolution, the diet has shifted to increased consumption of animal tissues, although plant-based foods have always been important (1, 2, 79). The advantages of meat-rich diets include higher density caloric content (reducing efforts in foraging and digestion), and concentrated micronutrients (trace metals and polyunsaturated fatty acids required for optimum development of the musculature and nervous system). However, increased trace metals and fat ingestion could also interact with pathogensis, as noted previously. The greater meat consumption of longer-lived humans than great ape ancestors presents a paradox because in many animal models of human disease and longevity, greater fat and caloric intake is associated with accelerated pathogenesis and shortened lifespan (1, 2). For example, caloric restriction of Alzheimer's transgenic mice attenuated the deposition of brain amyloid and glial reactions (78). Similarly, caloric restriction attenuates atherosclerosis, diabetes, and neoplasia in animal models (2). Moreover, in rodents, caloric restriction slows most aging changes and extends lifespan in proportion to lower intake, over a range of 10%–40%. Conversely, higher fat intake can exacerbate disease in models of atherogenesis, Alzheimer's disease, and neoplasia.

Changes in diet also increased exposure to pathogens and toxins. Uncooked meat, particularly from scavenged old carcasses, would have increased exposure to infectious pathogens. Though cooking can kill most pathogens and increases the digestibility of meat and fibrous plant material (79), cooking also

accelerates nonenzymatic glyco-oxidation to form advanced glycation endproducts (AGEs) that are diabetogenic and proatherosclerotic in animal models and in clinical studies (80, 81). How did humans evolve increased longevity despite the greater fat intake and exposure to pathogens? Finch and Stanford (1) proposed that the diet and longevity shifts during the evolution were supported by meat-adaptive genes, with tradeoffs of mortality and for ingestion of fat and toxins, and pathogen exposure.

Genetic Changes. Before considering specific genes, it is notable that a small part of the DNA difference between humans and chimpanzees shows evidence of positive selection. Though there is 4% DNA sequence divergence, most (*ca.* 3%), represents insertion-deletions (90 Mb difference between species) (82–84). The genome-wide single nucleotide (nt) differences are 1.23%, of which approximately 18% is within-species polymorphisms; thus, the fixed divergence at the species level for proteins is about 1% (82). Genes undergoing positive selection based on the ratio of nonsynonymous:synonymous mutations are overrepresented for immunity and host defense, diet, and brain (85). Moreover, genes associated with immunity and brain have variation clusters of highly localized groups of changes in coding regions (86).

de Magalhães and Church (87) examined human and chimpanzee genomes for longevity gene orthologs from short-lived animal models. Surprisingly, the aging-associated genes had less variation than the average, implying slower evolutionary change in the human lineage, e.g., of *IGF1* and its receptor *IGFR1*, in which loss-of-function mutations increase mouse lifespan (2). Greater coding sequence divergence was observed in *WRN* (Werner's progeroid syndrome), but not other progeria genes, and genes associated with responses to pest/pathogens/parasites (Gene Ontology database accession no. GO:0009613).

The high incidence of neoplasia in humans is not explained so far by DNA sequences. Of 333 cancer-associated genes, the majority are almost identical in chimpanzees (88, 89). The human *BRCA1* has an unusual number of *Alu* repeats that cause gene instability, whereas the chimpanzee *BRCA1* has an 8-kb deletion that truncates the coregulated *NBR2* gene. The breast cancer oncogenes *BRCA2* and *ERBB2* have multiple alleles, whereas chimpanzees have only the lower-cancer-risk human alleles. *BRCA1* also shows evidence for positive selection at the coding level and Hardy-Weinburg disequilibrium in human populations. Influences of *BRCA1* and *-2* alleles on early growth imply tradeoffs for growth and DNA repair relevant to the uniquely human pattern of early breast development with antagonist pleiotropy of later neoplasia (89).

Host defense system genes show evidence for positive selection, as noted. The most details may be available for the major histocompatibility complex (MHC) and sialic acid-binding Ig-like lectins (Siglecs). The MHC system is fundamental to innate and adaptive immunity: its >1,000 genes on CH6 are the most polymorphic of any gene system, particularly for variations in the peptide binding sites that determine host resistance. A major species difference is the loss of polymorphisms in class I*A* and *B* genes. Because the remaining MHC classes had equivalent variety, this class-specific loss of variation suggests a selective sweep (90). An MHC class I peptide that presents a SIV gag peptide to cytotoxic T lymphocytes in macaques (91) could be a target of selection in the ongoing SIVcpz infections noted earlier. There is no easy test of the adaptiveness of the numerous allele differences.

Differences in the Siglec lectin family of proteins (Ig superfamily) cell-surface glycoproteins have specific implications for host-defense evolution in studies from Varki and coworkers (92, 93). Siglecs bind the sialic acids on cell surfaces of macrophages and other immune-related cells. Siglec genes appear to have evolved very rapidly, because there is a much smaller divergence between mice and rats, which had a more distant common ancestor. Human-specific changes arose in at least 10 genes of the 50+ genes involved in sialobiology. Human $CD4^+$ T cells have low expression of Siglecs relative to chimpanzees (93). Siglec-5 manipulation switched the species-type response to T-cell receptor (TCR) stimulation. This species difference may be a factor in T-cell-mediated diseases, including the much milder chimpanzee disease from HIV-1 and hepatitis B or C (94), and the apparent lack of spontaneous rheumatoid arthritis and bronchial asthma. These differences in immunoreactivity could involve the weaker expression of CD33rSiglecs of humans, relative to great apes (93). Siglecs also modulate *Streptococcus* invasiveness (GBS) (95). Direct species comparisons are needed of immune cell responses to specific pathogens and of transcriptomes and kinomes.

Humans also differ by the absence of *N*-glycolylneuraminic acid (Neu5Gc), a major sialic acid of chimpanzees and other great apes (92, 95). A mutation that occurred early in the genus *Homo*, at least before 0.5 M, inactivated the CMAH enzyme that produces Neu5Gc from its precursor Neu5Ac, with implications of Neu5Ac targeting human-specific pathogens. For example, the chimpanzee malarial parasite has a protein that binds preferentially to Neu5Gc during erythrocyte invasion, whereas that of the human parasite *P. falciparum* binds Neu5Ac. The extant *P. falciparum* is likely to have arisen from a single chimpanzee-to-human transfer event (96). The evolving human diet could also have had a role in these complex immunological scenarios, because normal tissues have traces of Neu5Gc, which may be acquired from ingestion of red meat and milk; this could stimulate chronic inflammation induced by anti-Neu5Gc antibodies and also facilitate metastasis (97).

Lastly, I consider the apolipoprotein E (*ApoE*) alleles, which modulate chronic inflammation and many aspects of aging in brain and arteries and which Sapolsky, Stanford, and I (1, 2, 98) have proposed as a meat-adaptive candidate gene in the increases of the human lifespan. Blood apoE mediates the clearance of triglyceride-rich lipoprotein components, and brain apoE transports cholesterol to neurons (100). *ApoE4*, the minor allele in all human populations (<1%–45%), is considered ancestral in the genus *Homo* (99, 101). The uniquely human *apoE3* allele spread about 0.226 million years ago (MYA), range 0.18–0.58 MYA (101). These dates precede the emigration of modern *H. sapiens* from Africa and overlap with the increased organized hunting of large animals and the use of fire (102).

In general, the *apoE4* allele shortens lifespan by several years and accelerates degenerative changes in arteries and brain (2, 99, 100, 103, 104). *ApoE4* carriers have modestly higher total blood cholesterol, more oxidized blood lipids, and greater risk of coronary heart disease (*ca.* 40%) and Alzheimer's disease (depending on the population, *E4*/*E4* homozygotes have >10-fold excess risk).

Table 3. Apolipoprotein E polymorphisms in humans and species differences

ApoE residue (mature peptide)	61[a]	112	158
Human apoE3	R	C	R
ApoE4	R	R	R
Chimpanzee	T	R	R
Gorilla	T	R	R
Orangutan	T	R	R
Mouse	T	R	R

[a]Residue 61 determines apoE protein structure by domain interactions that influence lipid binding by the C terminus (1, 100, 108). Though chimpanzees, other primates, and many mammals have the R112 and R158 that define apoE4, these species differ from human apoE at residue 61. Genetically engineering the mouse apoE with R61T changed lipid-binding affinity to resemble human apoE4 (108). Thus, chimpanzee apoE is predicted to have lipid binding like apoE3 (1). Nonetheless, other amino acid differences from the chimpanzee may be important, because 4 of the 8 residues that showed evidence of positive selection in the human lineage are seated in the lipid-binding C terminus (109).

ApoE4 carriers also have worse outcomes in traumatic brain injury and some neurological conditions. One mechanism may involve heightened inflammatory responses. In transgenic mice with targeted gene (TR) replacement of human apoE alleles, the TR-*apoE4* mice have monocyte reactivity (IL-6, IFN, NO, TNFα) and greater bystander damage to neurons (105). On a fatty diet, TR-*apoE4* mice had larger adipocytes and impaired glucose tolerance (106); however, obesity and diabetes have not shown consistent *apoE* allele associations. Subcellularly, apoE4 causes more lysosomal leakage than apoE3, due to greater membrane disruption from peptide chain unfolding at lysosomal pH ("molten globule") (107); this biophysical feature of apoE4 is unique to humans and is implicated in the greater neurotoxicity of β-amyloid in *apoE4* transgenic models of Alzheimer's disease (100).

Though the chimpanzee apoE has 2 amino acids like apoE4, it is predicted to function like the human apoE3 isoform because of a further coding difference that influences peptide folding (108, 109) (Table 3). The putative apoE3-like function could contribute to the low levels of Alzheimer's and ischemic heart disease in chimpanzees noted previously. Although chimpanzee apoE has not shown allelic variation in small samples (101), serum cholesterol had considerable heritability in a former breeding colony (110).

Besides influencing brain aging, *apoE* alleles also affect brain development. Cortical neurons of young TR-*apoE4* mice have less dendritic complexity (111), which may be a factor in their impaired spatial memory (112). ApoE alleles are increasingly included in studies of human development. In MRI studies of healthy juveniles, the *apoE4* carriers had a thinner entorhinal cortex (113). This regional growth difference is relevant to Alzheimer's disease, which causes early damage in the entorhinal cortex. In sum, the *apoE* alleles are remarkable for the range of pleiotropies on blood cholesterol, immune responses, brain development, and arterial and Alzheimer's disease. As a hedge against overinterpretations of these broad effects, it may be reassuring that apoE alleles have not shown consistent associations with fertility or neoplasia (2).

Given these adverse effects of *apoE4*, at least in modern environments, the persistence of the allele has been proposed as the result of balancing selection, as in malarial protection by heterozygotes of hemoglobinopathies (1, 98). Two examples are under discussion, for which the evidence must be considered as preliminary. In hepatitis C infections, *apoE4* carriers incurred less fibrotic damage by allele dose (114, 115), whereas Brazilian slum children carrying *apoE4* showed less diarrhea and associated impairments of cognitive development (116, 117).

The hyperreactivity of human T cells noted previously, and the inflammatory responses in apoE4 carriers, may be part of an evolved group of heightened immune defenses relative to great apes that decreased baseline mortality represented in the q_{min}, as discussed earlier. However, the heightened immune responses could then have delayed adverse effects in cardiovascular disease and other chronic conditions of aging that involve inflammation (2) and that became more prevalent in the 20th century. This suggestion extends the antagonistic pleiotropy theory of aging in which genes selected for early advantages can have delayed adverse effects that are under weaker selection. The unique human social system of multigenerational support in child nurture has been argued as a key factor in the selection for delayed disability and increased life expectancy at later ages (1, 2, 7–9, 98).

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