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The shrinking human gut microbiome

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Mammals harbor complex assemblages of gut bacteria that are deeply integrated with their hosts' digestive, immune, and neuroendocrine systems. Recent work has revealed that there has been a substantial loss of gut bacterial diversity from humans since the divergence of humans and chimpanzees. This bacterial depauperation began in humanity's ancient evolutionary past and has accelerated in recent years with the advent of modern lifestyles. Today, humans living in industrialized societies harbor the lowest levels of gut bacterial diversity of any primate for which metagenomic data are available, a condition that may increase risk of infections, autoimmune disorders, and metabolic syndrome. Some missing gut bacteria may remain within under-sampled human populations, whereas others may be globally extinct and unrecoverable.

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Introduction

A typical human harbors on the order of 10^{13} bacterial cells in the large intestine [1]. This gut microbiota, which can contain over a thousand species, is deeply integrated with virtually every tissue and organ system in the body. Gut bacteria process difficult to digest components of the diet, promote angiogenesis in the intestine [2], train the immune system [3], regulate metabolism [4], and even influence moods and behaviors [5].

Humans' intimate relationships with gut bacteria likely reflect a long history of coevolution, wherein host and symbiont lineages have acted as selective forces on one another over millions of years. Recent work has shown that some of the most prevalent bacteria in the human gut are descended from ancestral symbionts that have persisted within the human lineage since before the divergence of humans and gorillas [6•]. The maintenance of gut bacterial lineages within host lineages over evolutionary timescales is consistent with the possibility that these symbioses have been conserved by selection. Under this view, disruption of the gut microbiota is expected to negatively impact human health.

Here, I summarize current understanding of the changes in the composition of the gut microbiota that occurred over the course of human evolution. In particular, I review recent evidence that humans have experienced a massive loss of gut bacterial diversity since diverging from chimpanzees. I discuss the timeline of this gut bacterial depauperation, the hypothesized causes, and the potential consequences for human health.

Ancient losses of gut bacterial diversity

Humans diverged from chimpanzees over six million years ago and have since undergone myriad phenotypic changes. One transition that came to distinguish Homo from Pan was increased consumption of animals by ancestral hominins. Evidence of persistent hominin carnivory has been reported from archaeological remains dating back to the first half of the Pleistocene ~2 million years ago [7]. Over the course of human evolution, the dietary shift away from plant-based foods and towards animal fat and protein has led to a reorganization of gut morphology as well as substantial changes in the bacterial composition of the gut microbiota.

Decreased reliance on dietary fiber and increased intake of animal fats and proteins during human evolution led to a reduction in the size of the large intestine. In the Great Apes, the large intestine composes over half of the total intestinal volume while the small intestine constitutes approximately one fourth [8]. In humans, these proportions are inverted, with the large intestine composing one fifth of the total intestinal volume and the small intestine constituting approximately 60% [8]. Across mammals, the ratio of small and large intestinal volumes differentiates carnivores and herbivores, with carnivore guts consisting of relatively larger small intestines and relatively smaller large intestines compared to herbivores [8]. Together, these observations suggest that the morphology of the human gut has become adapted to a meat-based diet since the divergence of humans and chimpanzees.

Coincident with a reduction in the volume of the colon, humans have experienced a substantial reduction in bacterial richness (*i.e.*, alpha diversity) within the gut microbiota since diverging from chimpanzees.

Comparisons of the gut microbiotas of humans and the African apes, enabled by high-throughput sequencing of 16S rRNA genes present in fecal samples, have revealed that individual humans, on average, harbor fewer phyla, classes, orders, families, genera, and species of gut bacteria than do individual chimpanzees, bonobos, or gorillas [9•]. This trend is recapitulated across a diversity of human populations representing a range of lifestyles, including Amerindians of the Amazon rainforest in Venezuela, rural Malawians, and urban Americans [9•].

The ancestral decreases in gut bacterial diversity within the human lineage are consistent with the reductions in dietary fiber and increases in the intake of animal fats and proteins that occurred during human evolution. Across mammals, carnivores tend to house the lowest levels of gut bacterial species richness per host, whereas herbivores harbor the highest [10]. Moreover, many of the bacteria that have decreased in relative abundance within the human gut microbiota are known to digest complex plant polysaccharides. For example, the relative abundance of *Fibrobacter*, a genus named for its fibrolytic activity, is over fivefold lower within the gut microbiotas of humans, regardless of lifestyle, relative to within the gut microbiotas of African apes [9•]. Conversely, the few bacteria taxa whose relative abundances have increased within human gut microbiotas include genera that are positively associated with the degree of meat-eating within human populations (*e.g.*, *Bacteroides*) [9•,11].

Modern lifestyles dwindle gut microbiomes

The dietary transition toward carnivory in the early evolutionary history of hominins has been hypothesized to have contributed to the evolution of larger brains and improved cognition [12]. Subsequent to these neurological enhancements, some of the most conspicuous differences between humans and other apes have arisen as a consequence of human culture. Approximately 12 000 years ago, at the dawn of the Holocene, multiple human populations around the world simultaneously shifted from hunter–gatherer lifestyles to settled, agricultural societies [13]. This Neolithic Revolution began a prolonged period of rapid cultural evolution that has accelerated within industrial and post-industrial societies over the last ~300 years. Extant variation in lifestyle practices of human populations around the world afford an opportunity to evaluate how these cultural transitions have impacted the composition of the human gut microbiota.

Available data suggest that transitions from hunter–gatherer to agricultural lifestyles have led to shifts in the relative abundances of gut bacterial taxa but little or no change in gut bacterial richness. Gomez *et al.* [14••] compared the gut microbiotas of two coexisting human populations residing within the Central African Republic: the BaAka, who maintain a hunter–gatherer lifestyle, and the Bantu, who have adopted an agricultural lifestyle. Consistent with the dietary differences between these populations, the BaAka hunter–gatherers harbored higher levels of bacteria capable of amino-acid and vitamin metabolism, whereas the Bantu agriculturalists harbored higher levels of bacteria capable of carbohydrate and xenobitotic metabolism. However, the authors detected no significant differences in per-host bacterial species richness between the gut microbiotas of the two populations. Similarly, Obregon-Tito *et al.* [15] and Morton *et al.* [16•] compared the gut microbiotas of hunter–gatherer and traditional agriculturalist populations in Peru and Cameroon, revealing compositional differences between the gut microbiotas of host populations consistent with dietary differences, but no differences in per-host bacterial species richness.

In contrast to hunter–gatherer to agricultural transitions, adoptions of industrial and post-industrial lifestyles have led to massive reductions in bacterial richness within human gut microbiotas. Individuals living in urban centers in the United States harbor fewer gut bacterial species on average than do individuals living more traditional lifestyles in Malawi [17], Venezuela [17,18], Peru [15], and Papua New Guinea [19]; the gut microbiotas of urban Nicobarese people are less species-rich than are the gut microbiotas of Nicobarese living more traditional lifestyles [20]; the gut microbiotas of urban Italians are less species-rich than are the gut microbiotas of Hadza hunter gatherers [21] and display altered functional and resistome profiles [22]; the gut microbiotas of children living in urban Italy are less species-rich than are the gut microbiotas of children living more traditional lifestyles in Burkina Faso [23]; gut bacterial loads are higher in rural Africans relative to African Americans [24]; the gut microbiotas of urban Russians appear to be missing functional pathways associated with Gram-positive Firmicutes relative to the gut microbiotas of rural Russians [25]; and the gut microbiotas of Han Chinese are less diverse than are the gut microbiotas of Tibetans and Mongolians living traditional lifestyles [26,27]. High-throughput sequencing of fecal samples retrieved from archaeological contexts (*i.e.*, coprolites) dating between 1400 to 8000 years before present further corroborate the view that the gut microbiotas of industrialized populations have deviated substantially from the ancestral state [28]. The compositional profiles of the bacterial communities preserved within these ancient fecal samples more closely resemble the gut microbiotas of extant populations following traditional lifestyles than they do the gut microbiotas of extant industrialized populations [28].

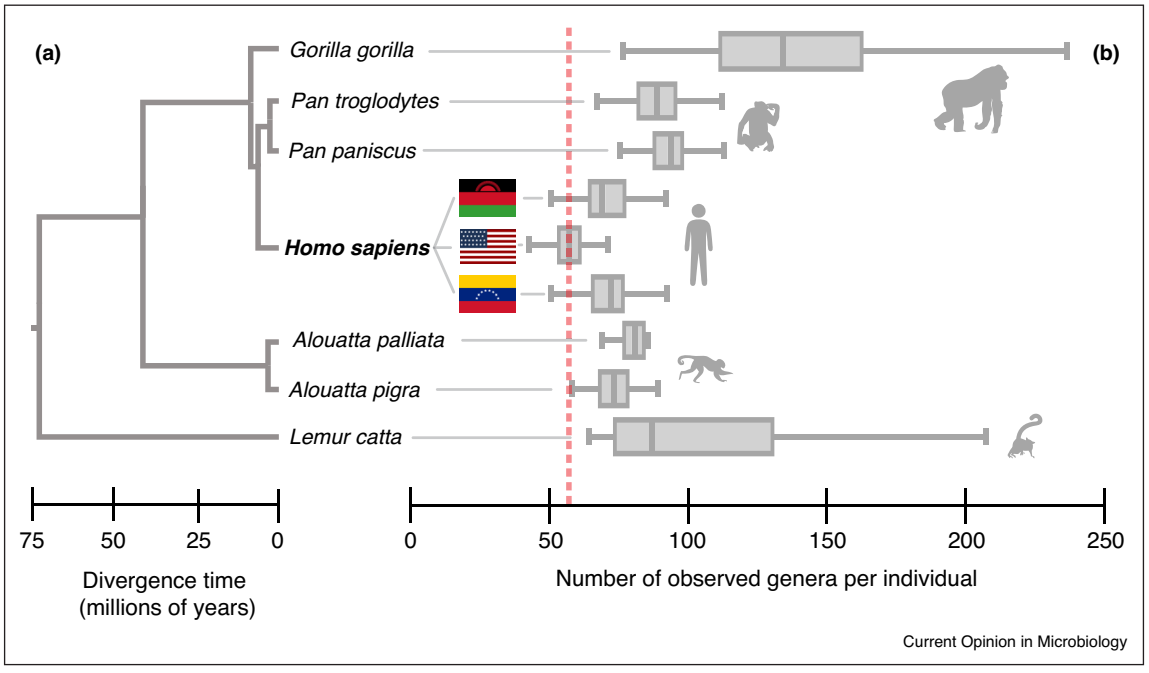
Industrialized and traditional lifestyles differ in many respects, confounding the identification of the specific practices that have led to decreases in gut bacterial diversity within industrialized societies. One potential cause is the rise of food processing and the corresponding reductions in the intake of dietary fiber in favor of simple

sugars. Recently, studies in model systems have indicated that long-term reductions in dietary fiber can lead to the extirpation of gut bacterial taxa from host lineages. Sonnenburg *et al.* [29••] showed that removing fiber from the diets of mice precluded the transmission of certain gut bacterial taxa to offspring. Similarly, Clayton *et al.* [30•] found that lack of dietary fiber was the primary factor associated with the loss of gut bacterial diversity from captive primates. In mice, changes in the gut microbiota induced by lack of dietary fiber can alter intestinal short-chain fatty acid profiles, leading to a rewiring of the transcriptional landscape across an array of host tissues [31]. Thus, the recent diet-induced changes in the gut microbiotas of industrialized human populations may have wide-reaching effects on host phenotypes.

Other potential causes of reduced gut bacterial diversity within industrialized human populations include certain modern medical practices. For example, longitudinal studies in humans have shown that levels of gut bacterial diversity decrease drastically after antibiotic use [32,33]. Although bacterial richness may recover after treatment is completed, the timeline and extent of the restoration is highly subject-dependent [34]. The consequences of antibiotic use on gut bacterial diversity may be most severe when treatment is administered during the early years of life, before the adult microbiota has fully formed [35]. Similarly, Caesarean section has also been associated with lower levels of gut bacterial diversity within infants throughout the first two years of life relative to vaginal delivery [36]. However, a recent study based on a larger sample of individuals found no evidence of an effect of Caesarean section on infant gut bacterial diversity [37].

Lifestyle practices in industrialized societies drive reductions in gut bacterial diversity within individual humans, but bacterial transmission through social contacts may enable the maintenance of gut bacterial diversity within human populations at large [38,39]. A current challenge is to determine which, if any, gut bacterial lineages have gone extinct from entire human populations. Moeller *et al.* [6•] sequenced *gyrB* amplicons derived from Bacteroidaceae, Bifidobacteriaceae, and Lachnospiraceae residing within the gut microbiotas of humans living in the United States and wild populations of chimpanzees, bonobos, and gorillas. Phylogenetic analyses of these data revealed several gut bacterial lineages that have codiversified with hominids over the last ~15 million years. However, two Bacteroidaceae lineages that have codiversified with and been maintained within African apes were not recovered from any humans in the United States, suggesting that these ancient gut bacterial symbionts

Figure 1



Humans in industrialized societies harbor the fewest gut bacterial genera of any primate.
(a) Time calibrated phylogeny of primate species for which comparable 16S rDNA gut-microbiome datasets are available [9•,17,49,50]. **(b)** Box and whisker plots show the mean number of bacterial and archaeal genera detected within individual gut microbiomes of each primate species. Datasets were merged and analyzed in QIIME [51] following the methods of [9•]. Humans from the United States, Malawi, and Venezuela were sampled from urban centers, rural communities, and traditional Amazonian villages, respectively [17]. Dashed red line highlights the mean bacterial richness within individuals from the United States.

have been lost from the United States population. One of the Bacteroidaceae lineages that appears to be missing from humans in the United States was detected within individuals living in rural Malawi, indicating that the loss of this lineage from humans in the United States occurred after the divergence of these human populations. These results highlight how evolutionary analyses of gut microbiotas of humans and non-human primates can reveal ancestral constituents of the hominid gut microbiota as well as specific gut bacterial extinction events that have occurred within human populations.

The depauperate gut microbiota and modern diseases

Industrialized lifestyles have led to greatly reduced levels of gut bacterial diversity, such that humans living in industrialized societies harbor the fewest gut bacterial genera per host of any primate for which metagenomic data are available (Figure 1). This observation suggests that the depauperate state of the gut microbiota in industrialized human populations is unprecedented in the history of primate evolution. That humans in industrialized populations may be missing gut bacterial taxa and functions that have been conserved across primates demands investigation of the consequences of reduced gut bacterial richness on human health.

A complete summary of the links between richness of the gut microbiota and human health is outside the scope of this review; however, recent prospective studies and experiments in gnotobiotic organisms have indicated that lack of diversity in the gut microbiota may cause or contribute to a range of modern diseases. Obese individuals harbor lower levels of gut bacterial diversity than do lean individuals [40,41], and microbiota-transplant experiments in germ-free mice have shown that this obese-associated microbiota is sufficient to cause obesity and its associated neurobehavioral changes [42,43]. The severity of symptoms of irritable bowel syndrome is negatively associated with gut bacterial species richness [44]. Lack of gut bacterial diversity contributes to *Clostridium difficile* infection: transplantation of gut bacterial diversity from healthy individuals into infected individuals cures ~90% of antibiotic-resistant cases [45,46]. Practices that reduce post-natal gut bacterial diversity are associated with an increased incidence of asthma later in life [47,48]. Although it is becoming clear that variation in gut bacterial richness among individuals within industrialized human populations can influence disease risk, the effects on host health of variation in gut bacterial richness among populations of humans and non-human primates remain unknown.

Conclusions

Every mammal harbors a gut microbiota that profoundly influences the health of its host. Humans have lost a substantial fraction of our ancestral gut microbiota since diverging from chimpanzees. The shrinking of the human gut microbiota began early in human evolution with the transition to meat-based diets and has accelerated dramatically within industrialized societies. Evidence is accumulating that this gut bacterial depauperation may predispose humans to a range of diseases. Comparative surveys of humans and nonhuman primates hold the keys to identifying the specific lineages of gut bacteria that have been lost from humans, and experiments in gnotobiotic model systems have the power to reveal what, if any, beneficial functions these missing symbionts confer to hosts. Together, these approaches may pave the way for therapies to restore the gut microbiotas of at-risk individuals and populations.

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