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Nutrigenetics in the Light of Human Evolution[1]

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Abstract
Bio-cultural adaptations to new foods played a key role in human evolution. The fossil record and sequence differences between human and chimpanzee genes point to a major dietary shift at the stem of human evolution. The earliest representatives of the human lineage diverged from the ancestors of chimpanzees because of their better adaptation to hard and abrasive foods. Bipedalism and modifications of the hand, which allowed tool manufacture and use, impacted on dietary flexibility, facilitating access to foods of animal origin. This promoted major anatomic, physiologic and metabolic adaptations. Encephalization, which requires high-quality diet, characterizes the evolutionary sequence that, through the *Homo ergaster/erectus* stages, led to our species, *Homo sapiens*, which originated in Africa about 200,000 years ago. At the end of the Ice Age, climatic changes and human impact determined a major food crisis, which triggered the agricultural revolution. This affected nutrition and health, with rapid evolutionary adaptations through the selection of genetic variants that allowed better utilization of new foods, different in relation to geography and culture. Today population growth, globalization and economic pressure powerfully affect diets worldwide. We must take into account our evolutionary past to meet the present nutritional challenges.

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Diet and Human Evolution

To quote the title of a commentary by Theodosius Dobzhansky: 'Nothing in biology makes sense except in the light of evolution' [1, 2]. Evolutionary success depends on the ability to adapt to environmental change. As explained by Darwin in *On the Origin of Species* (1859): 'It is not the strongest of the species that survive, nor the most intelligent, but the one most responsive to change' [3, 4]. Food is crucial to survival. Thus the ability to meet nutritional requirements by adapting to new foods plays a crucial role in the origin and evolution of species. Darwin's 'finches' (Geospizinae) on the Galapagos islands provide a classic model for this concept, as the diversification between related species of these passerine birds is readily evident

[1] Dedicated to the bicentennial of Charles Robert Darwin.

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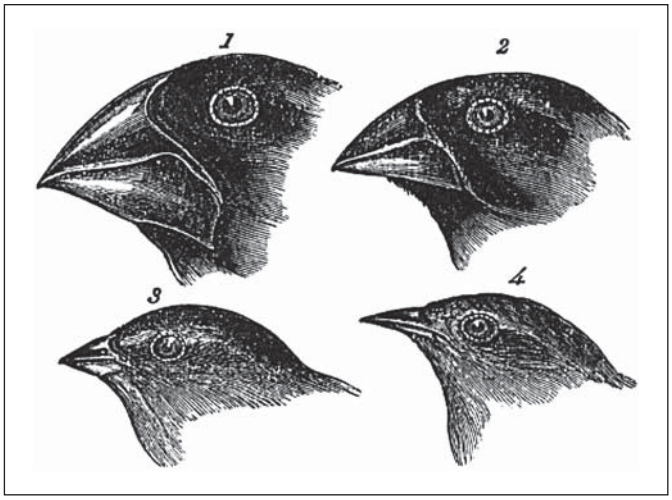

Fig. 1. Darwin's 'finches' (also known as the Galápagos Finches or Geospizinae), a classic example of diversification by natural selection, from the original illustration published in the 1859 and subsequent editions of *On the Origin of Species* [3]. These Passerine birds include a number of related species, mostly classified within the genus *Geospiza*, which are connected to American tanagers in the family Emberizidae rather than to the European finches. (1) *Geospiza magnirostris*. (2) *Geospiza fortis*. (3) *Geospiza parvula*. (4) *Certhidea olivacea*. *G. magnirostris* and *G. fortis* have broad, deep beaks useful for crushing seeds; *G. parvula* has a small symmetrical beak, suitable to more generalist ground feeding, while *C. olivacea,* the 'warbler' finch, has an elongated beak useful for capturing insects. In September 1839, when HMS Beagle reached the Galápagos islands, these and other 'finches' struck Darwin's mind, later highlighting the concept that exploitation of different food resources leads to evolutionary divergence. It has been recently shown that beak diversification in *Geospiza* and other bird species is determined by heterochronic and heterotopic gene regulation during craniofacial development.

from beak morphologies, which manifest different nutritional adaptations (fig. 1) [3]. Today we know that in bird species, beak diversification is determined by the heterochronic and heterotopic expression of genes differentially modulated during craniofacial morphogenesis, particularly BMP4 (implicated in the well-known signaling pathway of bone morphogenetic proteins) and calmodulin (a mediator of calcium signaling) [5–7]. Notably, a recent study conducted on a population of common Mediterranean lizards *(Podarcis sicula)*, which had been experimentally introduced into a novel insular environment, demonstrated that exploitation of a different dietary resource may trigger surprisingly rapid large-scale evolutionary divergence in morphology and physiology [8].

The fossil record points to a major dietary shift at or near the stem of human evolution. Genetic and paleoanthropological data indicate that between 5 and 10 million years ago (mya), the lineage of our extinct bipedal ancestors diverged from the most closely related ape lineage, that led to the two extant chimpanzees, *Pan troglodytes*, the common chimpanzee, and *Pan paniscus*, the 'bonobo' [9]. This critical split of the common hominoid root followed climatic and geological events that, in east Africa, led to an expansion of dryer, sparsely wooded savannahs at the expense of primary rainforest [10]. This must have resulted in increased availability of potential new foods that had previously been scarcely exploited, such as hard seeds, insects and abrasive roots and grasses, with comparatively reduced availability of fruits and soft leaves. The hominoid species ancestral to both humans and chimpanzees, which occupied these progressively fragmented forest environments and was most probably partially adapted to terrestrial life, must have been subjected to a strong selective pressure for new nutritional adaptations. In fact, the earliest known fossils ascribed to close relatives or direct ancestors of humans, broadly dated between 7 and 3 mya, had chimpanzee-sized brains and may have been still imperfectly bipedal, but already displayed notable and typical morphological and structural changes in the dentition (decreased size of canines, large molars and, particularly, increased thickness and different microstructure of enamel) [11, 12]. These dental changes allowed a functional shift from ape-like slicing and cutting, suited to relatively soft but tough foods and dependent on shearing crests forming on molars at wear-exposed enamel-dentine junctions, to human puncture-crushing and grinding, better adapted to process hard, brittle foods and affording better protection, and thus prolonged tooth life, in the presence of an abrasive diet. This provided a critical selective advantage since, under natural conditions, the health and lifespan of mammals is primarily dependent on the status of the dentition, which must allow adequate food processing and protection from infection [13]. Genome-wide protein sequence evolution data support the view that dietary shifts played a major role in the divergence between the ancestors of humans and chimpanzees. In fact, based on the comparison of 7,645 human-chimp-mouse gene trios, the most significant functional gene categories showing positive selection include those involved in amino acid metabolism, in addition to those implicated in skeletal regulation, olfaction and sound perception [14]. Furthermore, the promoter sequences and the amino acid sequences of diet-related genes carry more differences between humans and chimpanzees than do random genes [15].

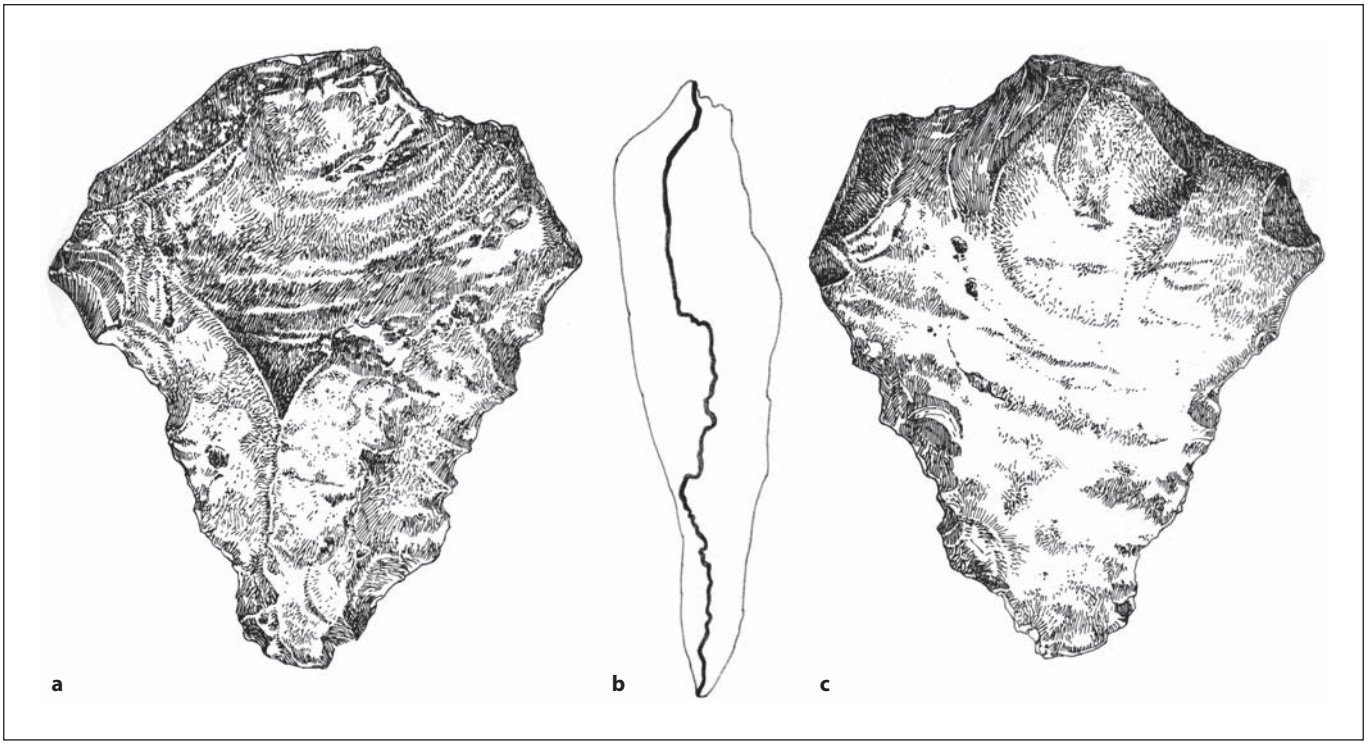

Fig. 2. Lower Paleolithic flake tool from the Saharan desert, representative of stone industries associated with *Homo erectus*. This flake was struck with a stone hammer from a nucleus of chert, which like other cryptocrystalline stones used by our ancestors, breaks with sharp edges. **a** Dorsal (upper) face of the flake. **b** Sharp edges suitable for cutting and slicing meat and skin. **c** Ventral (or underside) face, with the characteristic percussion bulb starting from the striking platform.

Biocultural Factors and Dietary Adaptations in Earliest Human Ancestors

In the human lineage, technology was soon to become a major motor for new nutritional adaptations. Several species of extant Old and New World primates may use stone anvils and hammers to process hard foods, such as nuts, but in general the upper limbs of non-human primates are anatomically unsuited to manufacture and use tools with sufficient precision [16]. Instead, in the early representatives of our lineage, the extensive anatomical remodeling of the hand made possible by the progressive acquisition of bipedalism, perfected the acquisition of the two fundamental human handgrips – the 'power' and 'precision' grips – which serve for finely controlled crushing, for the related ability to manufacture sharply-edged stone tools (fig. 2), and for the use of such tools in cutting and slicing [17]. These critical abilities decisively facilitated access to foods of animal origin, in the absence of the specific dental adaptations usually associated with mammalian carnivorism [18–20]. Animal carcasses, particularly defleshed marrowbones and heads containing brains, abandoned by carnivores, as well as placentas, which are shed in numbers during delivery seasons, must have been readily available on the ancient African savannahs densely populated by large herding ungulates [21]. The bipedal gait also freed hands and arms from their function in locomotion, allowing their full use to hold excess food, which could then be carried away in quantity to safe hiding places (fig. 3). This must have significantly improved the scavenging strategies of our early ancestors, since carrion in open savannahs rapidly attracts dangerous competitors and thus cannot be consumed on site [22].

Abundant archaeological evidence supports the view that the use of stone tools allowed dietary flexibility and a more systematic reliance on animal foods in the specific lineage of early bipedal apes that gave rise to the genus *Homo* [23]. The first evidence of stone tools use for bone defleshing and crushing, from a site in Gona in the Afar region of Ethiopia, is dated at 2.6 mya [24]. The increased dietary quality due to tool use may have deter-

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Fig. 3. Several extant chimpanzee populations live in environments that may approach that of the ancient common ancestor of humans and chimpanzees. **a** A band of common chimpanzees *(Pan troglodytes)* feeding at the edge of a forested area in Uganda. When food is abundant and not specifically concentrated, the feeding behavior is relaxed and animals use only the 4-legged gait. However, when a cache of food is concentrated in a limited open area, the ability to walk upright, using both arms and hands, in addition to the mouth, to carry away potential food items for later consumption under cover, provides a distinct advantage. The young male (**b**), a member of the band in **a**, exemplifies this type of behavior, which must have been useful to our earliest ancestors in competing with other scavengers for placentas or partial animal carcasses. Images: R. Mariani-Costantini (2005).

mined rapid large-scale evolutionary divergences in morphology, physiology, social behavior and ecology. In particular, it resulted in larger body size, and may have promoted the acquisition of a set of diet-related anatomic, physiologic and metabolic characteristics which distinguish humans from the extant great apes. These include encephalization, decrease in gastrointestinal tract length, better adaptations to diets high in fat and cholesterol and related changes in gut microbiota [25–27].

Meat, Stones, Fire and the Spread of the *Homo ergaster/erectus* Lineage

Progressive incorporation of more meat into the diet of our early ancestors depended on progress in active hunting in addition to scavenging, in both cases made possible by improvements in tool technology and social organization (fig. 4). Ecologically, carnivores, particularly those of large size which are more mobile and can adapt to different temperatures, tend to have a wide geographic dispersal, as meat can be naturally found in a large variety of climates and habitats [28]. Thus, increased carnivorism may lie at the basis of the first wave of the early human 'out of Africa' migration, which appears to have coincided with the emergence of the large-sized *Homo ergaster/erectus* lineage in east Africa around 1.9 mya, and soon after in Eurasia. The first non-African fossils, dated between 1.8 and 1.0 mya, are found in a broad southern Eurasian belt comprising sites as distant as Dmanisi in Georgia, Sangiran in Java and Atapuerca in Spain [29, 30].

Significantly, the spread of *H. ergaster/erectus* coincided with the extinction of the robust Australopithecines, African bipedal apes representing a side-branch of the human lineage that did not develop stone tool technology and that may have subsisted mainly on vegetable savannah foods (fig. 4) [9, 12].

Archaeological evidence at most *H. erectus* sites, both in Africa and in Eurasia, strongly suggests that this hominin species was capable of hunting large mammals or, at least, successfully competing with large carnivores for the appropriation of carrion [30]. The consistent evidence of cannibalism associated with the Eurasian forms derived from *H. erectus* along the extinct *antecessor/heidelbergensis/neanderthalesis* lineage and also, later, along our own lineage, *H. sapiens*, suggests that dependence on meat was driven by ecological necessity [31–37].

As stated above, human evolution provides a fascinatingly complex model for the study of the evolutionary relevance of biocultural interactions. Control of fire was a cultural adaptation that impacted on dietary quality, and hence on biology [38]. Data from extant apes suggest an innate preference for cooked food in hominoids [39]. The earliest evidence of fire use, probably due to *H. ergaster/erectus*, comes from archaeological sites in eastern

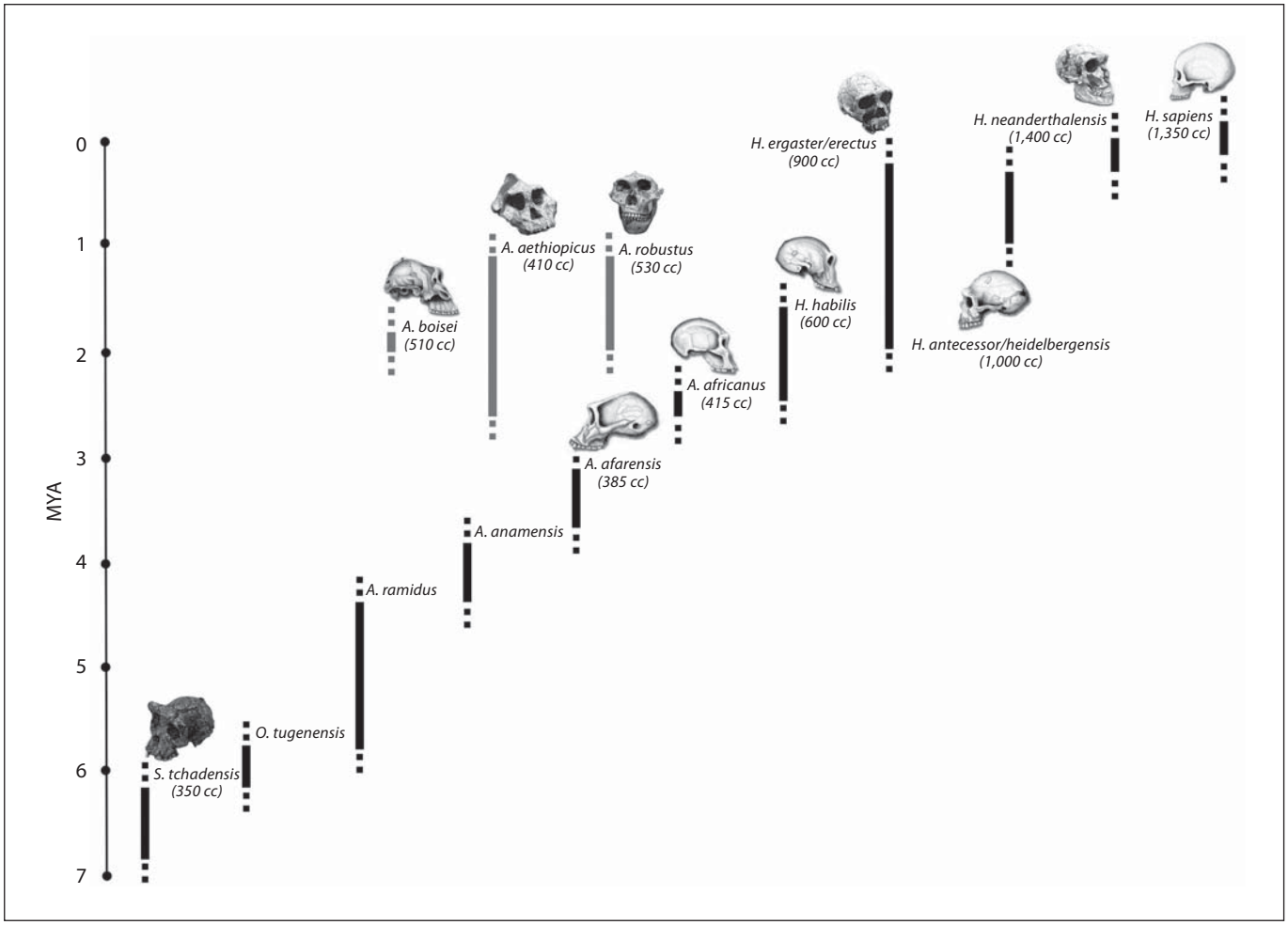

Fig. 4. Evolutionary timetable of fossil hominins and brain sizes. The first fossil species, *Sahelanthropus tchadensis*, represented by a unique well-preserved skull dated to about 7 mya, was probably very close to the common ancestor of humans and chimpanzees, had a cranial capacity of about 350 cm^3 (that of chimpanzees), but dental features supporting its relation with the human lineage. *Orrorin tugenensis*, *Ardipithecus ramidus* and *Australopithecus anamensis*, dated between about 6.5 and 4 mya, had dental adaptations typical of the human lineage and postcranial anatomy indicating imperfect bipedalism. Brain size was most probably in the chimpanzee range, although informative fossils are lacking. In *Australopithecus afarensis*, a later bipedal ape dated at about 3 mya, and represented by the famous partial skeleton known as 'Lucy', we have evidence of a cranial capacity still nearing that of chimpanzees. With *Australopithecus africanus*, and particularly with *Homo habilis,* there is a definite increase in brain size. The available documentation suggests that these species tended to consume animal foods, possibly by scavenging, although tool use is not clearly documented. Notably, the robust australopithecines, representing a side branch of the human tree which includes bipedal ape species dated between 3 and 1 mya, such as *Australopithecus robustus*, *Australopithecus boisei* and *Australopithecus aethiopicus*, did not develop particularly large brains. These extinct close relatives of humans did not develop a distinct stone tool technology and appear to have relied on a diet of grubs and plants. Returning to the human lineage, about 2 mya, with the emergence of *Homo ergaster/erectus*, probably from *Homo habilis* or related forms, there is a rapid increase in absolute and relative brain size, associated with strong evidence of tool manufacture and use. *H. ergaster/erectus* butchered, and probably hunted, large animals. Reliance on meat increased environmental adaptability, allowing spread to Eurasia, where local evolution took place along the *antecessor/heidelbergensis/neanderthalensis* lineage. These ancient Eurasian hominids, which appear to have been later entirely replaced by *Homo sapiens*, certainly relied on meat and more or less consistently used fire. *H. sapiens,* our species, emerged about 200,000 years ago from an advanced African *H. ergaster/erectus* population. The brain of *H. sapiens*, although on average smaller than that of Neanderthals, shows major structural differences, particularly expansion of the frontoparietal regions.

and southern Africa, such as Lake Baringo, Koobi Fora and Olorgesailie (Kenya) and Swartkrans (South Africa), dated between 1.5 and 1.4 mya [40]. At these early times fire use was most likely occasional, depending on fire collected from natural sources, and may have not significantly impacted on food processing. However, exploitation of fire for cooking was to become quite systematic later in human evolution. Cooking gelatinizes animal connective tissues, allowing easier chewing and digestion, facilitates the digestion of complex carbohydrates in vegetables and permits the consumption of plant foods inedible or toxic when raw [38, 41]. Thus fire taming, which like tool use is a cultural trait, contributed to dietary flexibility and quality, and through this, to biological evolution.

Metabolic and Dietary Constraints on Brain Size

The striking absolute and relative increase in brain size along the evolutionary sequence that, through the *H. ergaster/erectus* stage, led to our species, *H. sapiens*, occurred through genetic processes that largely remain to be clarified. Primary microcephaly, a rare genetic disorder due to deficient neurogenesis in which the brain is severely reduced in size but architecturally normal, may provide clues to such processes [42]. Evolutionary studies of two of the known primary microcephaly-causing genes, microcephalin (MCPH1) and abnormal spindle-like microcephaly associated (ASPM), which encode proteins that influence neurogenic mitosis, reveal clear evidence for positive selection in the human lineage [43–46].

Nonetheless, a diet including energy-dense foods that provided the full complement of nutrients must have been a prerequisite for the selection of the genetic variation that allowed encephalization (fig. 4) [47]. The brain has much greater energy demands per unit weight than muscle and, unlike muscle, its metabolism cannot be down-regulated to conserve energy [48]. The brain accounts for about 20–25% of the resting metabolic rate in adult humans, compared to about 8–10% in other extant primates and 3–5% in most non-primate mammals. These figures are much higher in newborns, where over 80% of the basal metabolic rate may be due to the brain alone, and in children, where, at about 5 years of age, the brain may account for over 40% of the resting energy demand [49]. Thus, the striking expansion of the cerebral hemispheres in the *Homo* lineage necessitated a higher quality diet, particularly in pregnant or breast-feeding females, and in children. Adaptations in body composition that distinguish humans from other primates were most likely required to meet the metabolic needs of brain expansion. This is consistent with the fact that humans have the highest body fat level at birth among mammalian species [50]. In fact, due to the anatomical constrains of the bipedal female pelvis, human newborns have a relatively small and immature brain, which rapidly develops postnatally, with major energetic demands [51]. Fat is less metabolically expensive than muscle, produces agents that regulate physiological processes directly related to carbohydrate and fat metabolism and provides a supply of stored energy usable in response to food deprivation [52, 53]. Thus the expansion of the cerebral hemispheres may have promoted increased body fatness and reduced muscle mass in the human lineage compared to other primates.

Origin and Spread of *H. sapiens,* the Perfected Hunter-Gatherer

The analysis of mtDNA and Y chromosome variation of modern human populations, supplemented by data on other nuclear DNA variation and by phylogenetic studies of human-specific pathogens, supports the view that our own species, *H. sapiens*, originated quite suddenly in Africa less than 200,000 years ago (200 kya), from an advanced *ergaster/erectus* population [54–57]. This is in good agreement with the fossil evidence [58, 59]. In fact, the earliest isotopically well dated fossils attributed to our species, from the Kibish Formation of the Omo River and from Herto, Middle Awash, both in southern Ethiopia, have suggested estimated ages of 200–190 kya and 160–154 kya respectively. These are quite consistent with the timeframe independently inferred from the above-mentioned genetic studies. *H. sapiens* spread from Africa to southern Eurasia by approximately 100 kya, and by about 50–30 kya appears to have replaced, apparently with no interbreeding, all the continental Eurasian human variants that had evolved from the earlier dispersal of *H. erectus*, such as the well-known Neanderthals in Europe. However, the spread of *H. sapiens* was not limited to Eurasia, as its mobility and technology very soon allowed colonization of Australia, and, later, near the end of the last glaciation, of the Americas [60]. Nonetheless, because of our relatively recent origin, the genetic legacy of our species is African, and the highest diversity of the human genome is still to be found in Africa, where variation accumulated and was selected over a much longer period of

time [57]. This is certainly relevant to the genetic variation that affects nutrition and metabolism, which underlines the need to include African populations in studies of nutrigenomics and nutrigenetics [61].

The advantage that permitted the rapid spread of *H. sapiens*, to the detriment of other human forms, appears to lie in the ability to develop better technology, symbolic conceptualization and more complex social structures, which must have allowed more efficient hunting and better adaptation to environmental, seasonal and geographic variables [60]. The ability to exploit the large mammalian faunas of the Ice Ages is widely documented at several archaeological sites, most strikingly in the Franco-Cantabric region of Europe, where symbolic Ice Age art (fig. 5) developed to its highest level [62].

The optimal foraging theory states that energy from foods should be superior to the energy expended in food procurement. The food choices of the ancient *H. sapiens* hunter-gatherers living in cold northern climates during the last glaciation must have been prioritized relative to energy return rates, so that whenever and wherever ecologically possible, animal food – particularly the fattiest parts – would have been preferred, and larger game animals to smaller [63]. Nonetheless, given its spread and adaptability, *H. sapiens* remained a flexible eater, with a combination of cultural and genetic traits that allowed quick dietary shifts in relation to geography, seasons, climatic change and social factors [60].

Fig. 5. A dramatic hunting scene painted by a Magdalenian artist about 17,000 years ago. It is located at the bottom of the shaft in the heart of the cave sanctuary of Lascaux – the 'Sistine Chapel' of prehistory – in the Périgord region of France. It shows a wounded bison *(Bison priscus)* with a barbed spear in its belly, entrails hanging out, that attacks and probably kills a naked hunter. The bird nearby has a symbolic significance that escapes our understanding. Overall, this scene exemplifies the challenging life of the hunters of the Ice Ages, our direct predecessors, who relied on the meat of large wild mammals, more or less as the North American Indians of the Great Plains did in the early 19th century.

'Pygmy' Phenotype

Body size is a complex trait influenced by multiple gene-environment interactions, in which nutrition plays a central role. In most animals, given adequate food resources, reproductive performance increases with body size, mediated by higher survival of offspring from larger females and increased mating success of larger males [64]. This may explain the large body sizes documented in specimens of *H. erectus* and ancient *H. sapiens*. However, there is clear evidence that human populations genetically isolated in areas with a combination of complex and still poorly understood environmental factors, most notably hot humid climates in dense continental rainforests or tropical/subtropical islands (fig. 6), can be rapidly selected for small body size: the so-called 'pygmy' phenotype [65]. This phenotype may be partly explained by restrictions on the availability of food, which limits growth, and to selection for climbing trees and/or moving in areas densely covered by vegetation. However, very small body size is also advantageous metabolically, in terms of better heat dispersal, and appears to be linked to faster growth and earlier sexual maturity, which may be a key advantage in populations with high mortality levels in young adults [66–69]. A 'pygmy' phenotype has independently evolved in several African, southeast Asian and South American populations, and is also documented in extinct *H. sapiens* populations from Pacific islands [65, 68]. Furthermore, according to very important recent findings, this adaptive phenotype may not be exclusively linked to our own species, as skeletal remains of a diminutive small-brained hominin found in Late Pleistocene cave deposits strongly suggest that a 'pygmy' human closely related to early *H. erectus* evolved on the island of Flores, Indonesia, surviving up to very recent times [69–72]. The genetic basis of the pygmy phenotype are still unclear, but the GHBP/GHR/IGF1 system appears to play a key role in its determination [73, 74]. Heritable epigenetic modifications could provide a link between the environment and modifications in gene expression control that might contribute to adaptive phenotypes [75, 76].

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Fig. 6. Human populations genetically isolated in hot continental rainforests or in tropical/subtropical islands were evolutionarily selected for small body size, or 'pygmy' phenotype. We see here a Lobe Pygmy village in coastal Cameroon, exemplifying a characteristic type of environment where this particular human adaptation has been developed. Photo courtesy of Ing. P. De Blasio (2009).

Diet-Mediated Evolutionary Impact of the Agricultural Revolution

At the end of the last Ice Age the increase in human populations that were capable of efficient hunting, coupled with the severe biological stress imposed by the glacial maximum and by the marked postglacial climatic changes, determined the decline or extinction of major prey animal species in several areas of the world [60, 77, 78]. This appears to have triggered a global food crisis, which stimulated migrations and the development of the new food sources, made possible by the transition from foraging and hunting to farming and animal husbandry. This major ecological and, hence, nutritional change occurred independently and spread metachronously in several areas of the world, starting first at the Paleolithic-Neolithic transition in the area of the 'fertile crescent' of the Middle East, about 11,000 years ago, then, independently, in the Yangtzi and Yellow River basins of China, about 9,000 years ago, in the New Guinean highlands, about 9,000–6,000 years ago, in Subsaharan Africa, possibly 4,000–5,000 years ago, and in Central, North and South America between 5,000 and 3,000 years ago [79, 80]. The agricultural revolution significantly affected nutrition and health, as it determined rise in population density, marked social stratification and, therefore, differential access to foods, sedentary lifestyle and an increased workload. Overall poorer nutrition – reflecting reduced meat intake, reduced mineral absorption due to cereal-based diets, and seasonal monophagy – resulted in the spread of carential diseases, which, after the Neolithic, are readily evident in the osteoarchaeological record (fig. 7) [81–83]. Significantly, a marked decrease in stature of about 15 cm compared to their paleolithic predecessors also becomes evident in many agricultural populations, a phenomenon which in several areas of the world may have been reversed only by the spread of the affluent Western dietary lifestyles of the 20th century. Furthermore, sedentary life and close contact with domes-

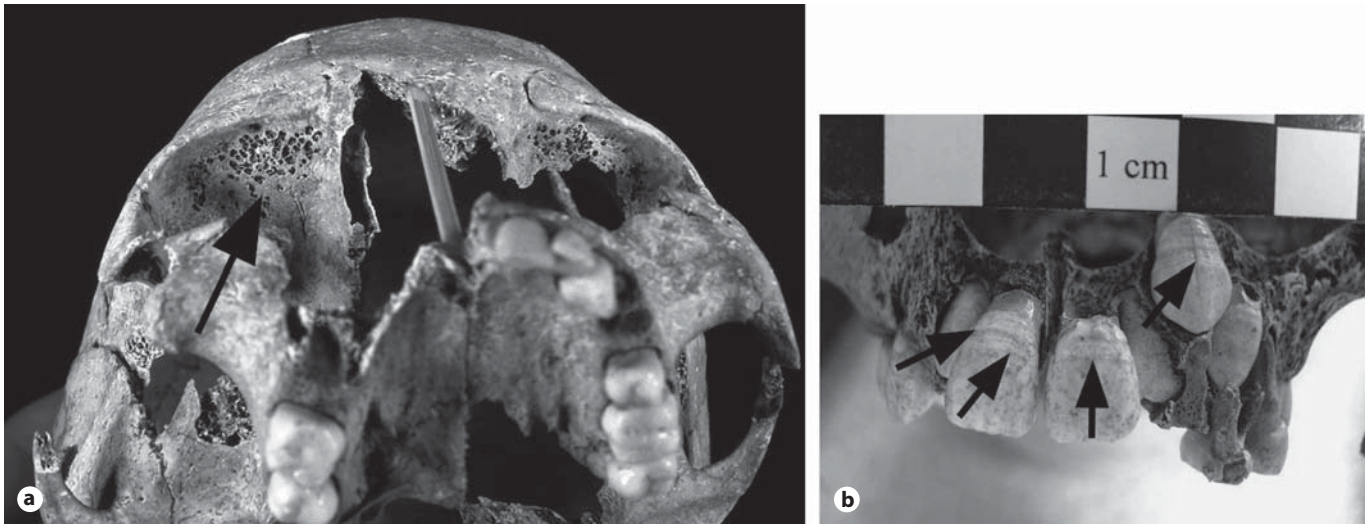

Fig. 7. After the agricultural revolution, evidence of carential diseases becomes common in the osteoarcheological record, as exemplified here by skeletal material from the Iron Age necropolis of Alfedena, Abruzzo, Italy (3rd century BCE). **a** Cranium of a young individual showing cribra orbitalia, a pathological lesion which has been associated with iron deficiency anemia and which is characterized by pitting and porosity of the cortical smooth bone of the roof of the orbit. **b** Teeth of the cranium showing circumferential rings of enamel hypoplasia, which may reflect diet or disease-related stresses during the mineralization of the permanent dentition. Photo courtesy of Dr. R. D'Anastasio (G. d'Annunzio University, Chieti, Italy).

tic animals favored the spread of infectious or parasitic diseases and zoonoses, which until the development of modern medicine (and then mainly only in affluent areas of the world) severely impacted on the economy, quality of life and life expectancy [81–83]. There is evidence that the new agricultural lifestyles determined rapid evolutionary adaptations in *H. sapiens*. In fact, about 700 regions of the human genome appear to have been reshaped within the past 5,000–15,000 years [84–87]. The rapidity of these genetic processes can be explained by strong selective pressure and genetic drift, often mediated by cultural factors. A notable example of the selection of genetic variants that allowed more effective utilization of new staple foods is provided by the ability to tolerate lactose, which, across cultures and geographic regions, is inversely related to the timing of the transition to agriculture and to the domestication of dairy animals [88, 89]. Lactase level is controlled by the enhancer element upstream of the lactase gene, and different lactase-persistence alleles appear to have been independently selected in diverse populations that heavily relied on milk and dairy products in Europe and in Africa [90, 91]. Another remarkable example of genetic adaptation is the ability to better digest starchy foods, which depends on higher mean salivary amylase gene copy number selected in agricultural populations with high-starch diets [92, 93].

Present Challenges

As discussed before, humans evolved and continue to evolve as a result of gene-environment interactions that are strongly modified by culture and mostly mediated through the diet. Today global changes in diet triggered by the industrial revolution and promoted by the introduction of new food technologies, low physical activity patterns and globalization, with the ensuing rapid spread of untested nutritional models, open new avenues and pose new challenges for the evolution of our species [94, 95]. The 'thrifty genotype' and the 'thrifty phenotype' hypotheses, originally advanced in 1962 by J.V. Neel [96], suggest that genetic variants determining complex gene-environment interactions, which enable individuals to deposit fat during periods of food abundance, were advantageous to survival and/or fertility under the conditions of periodic famine that, up to a recent past, impacted on most agricultural societies. In the modern affluent societies, such 'thrifty' alleles would be highly detrimental, being implicated in the pathogenesis of the set of complex degenerative diseases linked to the metabolic syndrome, namely type 2 diabetes, cardiovascular disease and cancer [97–99].

Cultural elaboration and transmission of adaptive diets and of specific food preparation techniques played a

major role in allowing adaptations to diverse food environments in most of the world's pre-industrial societies [100]. Unbalanced population growth, global admixture, loss of cultural roots and strong economic pressures ignore genetic and cultural factors that differentiate human populations with respect to dietary adaptations [101]. An early historical example of the undesirable health consequences of dietary globalization is provided by the appearance of pellagra in Mediterranean Europe, particularly in northern Italy, following the 'post-Columbian' dietary revolution [102]. During the 16th and 17th centuries, porridge (polenta), the central component of the diet of the poor North Italian peasantry, became almost exclusively based on flour obtained from maize, a Central American cereal which was easier to grow and therefore less costly then native Italian cereals. Unfortunately, because of lack of cultural adaptation, maize porridge was prepared without a traditional procedure developed by the native peoples of the New World (nixtamalization), which required treatment of maize with slaked lime or other alkaline products like plant ashes [103]. This alkali treatment makes niacin, biochemically bound in maize, nutritionally available and thus reduces the severity of niacin deficiency, which may cause pellagra in people that consume quasi-monophagic maize-based diets [104]. This led to the development of the terrible scourge of pellagra, that up to the dawn of the 20th century, haunted the countryside of northern Italy [102].

Presently, there is a double threat, related on one side to inadequate access to foods, mostly in the developing world, and on the other, mostly but not only in the developed world, to the epidemic diffusion of complex chronic degenerative diseases, such as atherosclerosis, diabetes and cancer. These diseases often reflect imbalances between genetic/metabolic backgrounds and diet. There is an urgent need to implement intervention policies that effectively contribute to the global diffusion of food security and safety. Such actions require a better understanding of diet-mediated gene-environment interactions. We should take into account the cultural and genetic legacy of our evolutionary past to meet the food-related challenges that our species is presently facing.

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