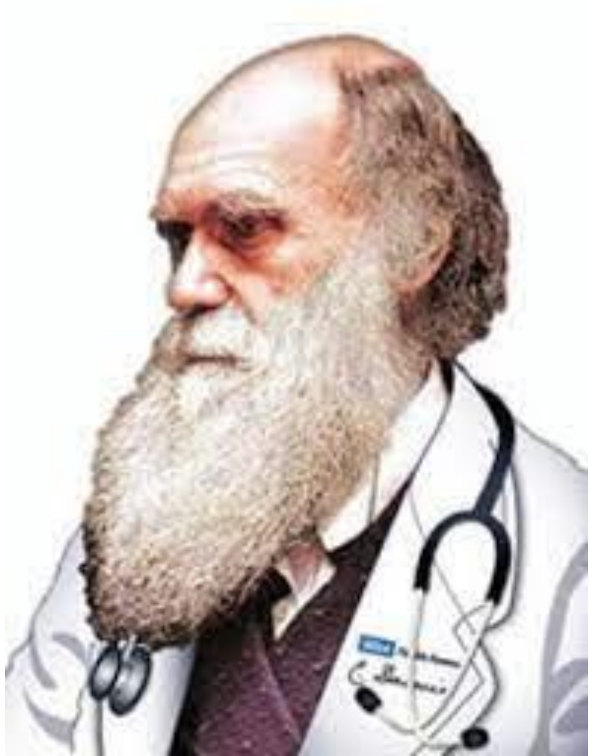
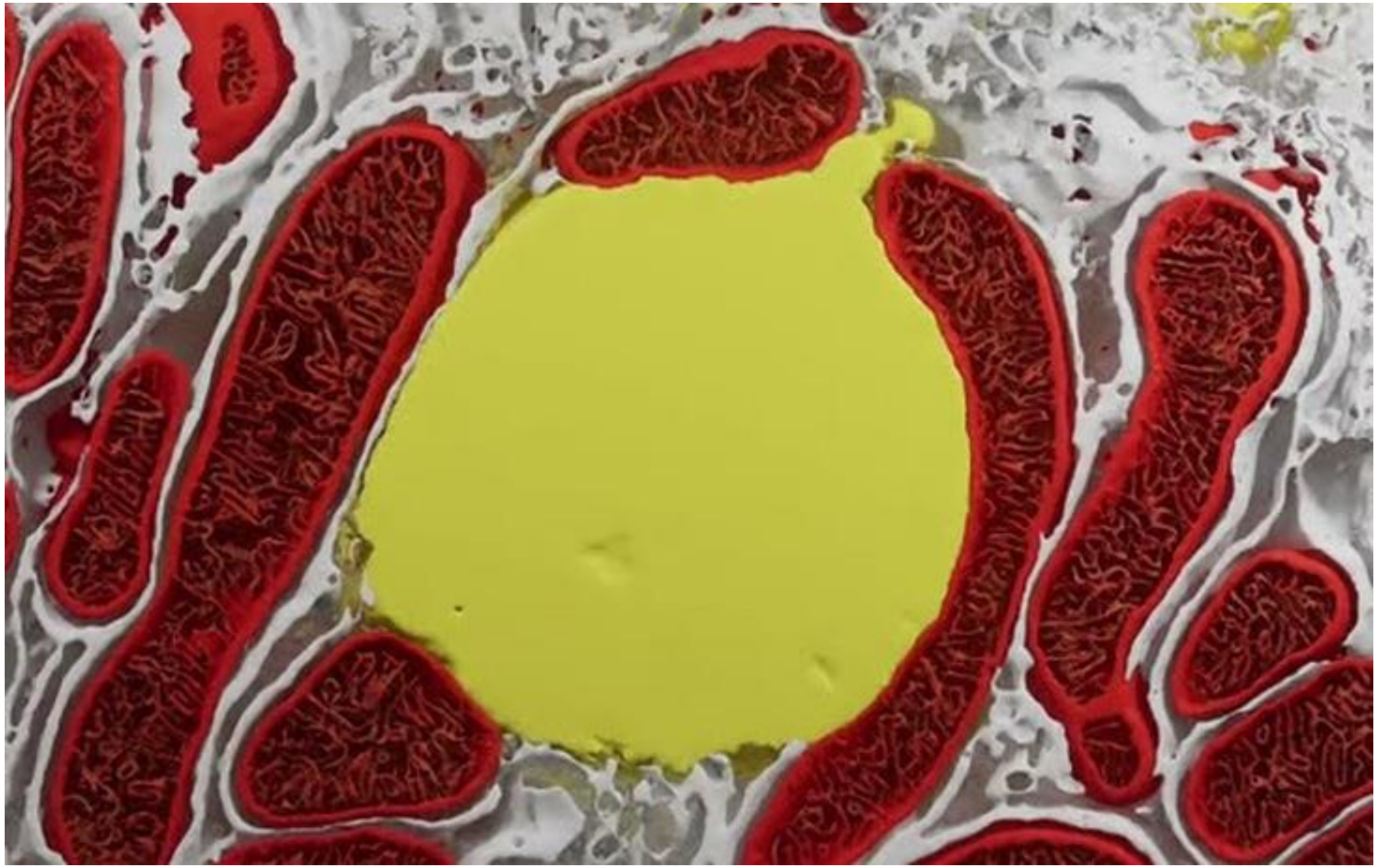
Evolutionary Medicine

Miriam Nývltová Fišáková

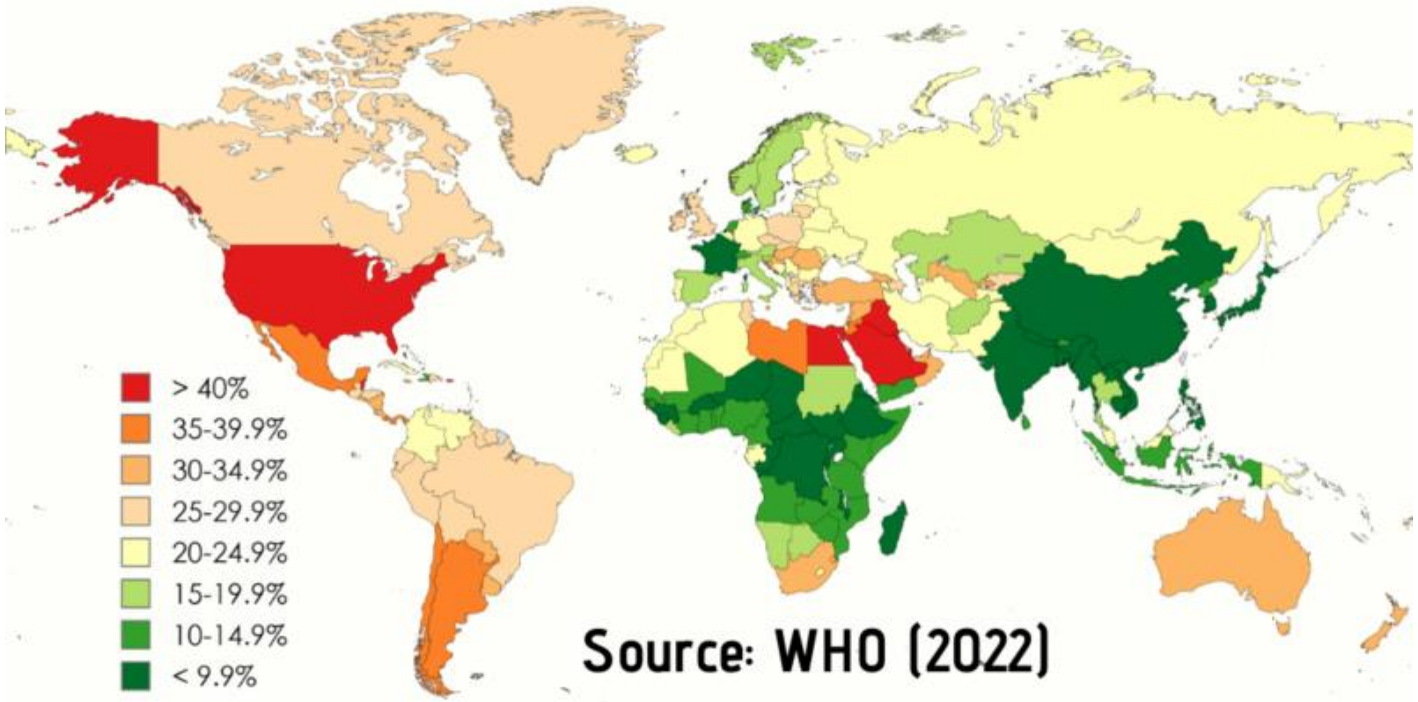
Department of Physiology



Nutritional and Metabolic Adaptation



How an organism adapts physiologically to the available food supplies and adjusts its behavior, metabolism, and energy expenditure accordingly are defining characteristics of a species and major points on which selection has acted. Indeed, life-history theory focuses on how an organism's allocation of finite energy during different phases of its life course, including growth and the reproductive period, is fundamental to its evolved strategy as a species and is thus under strong selective pressure. Humans have evolved as a generalist species able to derive energy from a range of food sources and, uniquely among animals, to use technology to gather food and alter energy expenditure. These characteristics of human evolution are important in understanding how modern environments influence the patterns of health and disease. Obesity and the metabolic disorders associated with it, such as type 2 *diabetes mellitus* and cardiovascular disease, are today often described as a global "epidemic". The epidemic is well established in high-income countries, but is also of rapidly growing importance in low- and middle-income countries. The simple explanation that humans are living longer, and so becoming more susceptible to these diseases as they age, is inadequate given the increasing incidence of obesity and metabolic disorders among younger people. For example, in the UK about 30% of children aged 2–15 are overweight or obese (see Public Health England 2015); childhood obesity is associated with multiple co-morbidities that affect all major organ systems and psychosocial well-being.

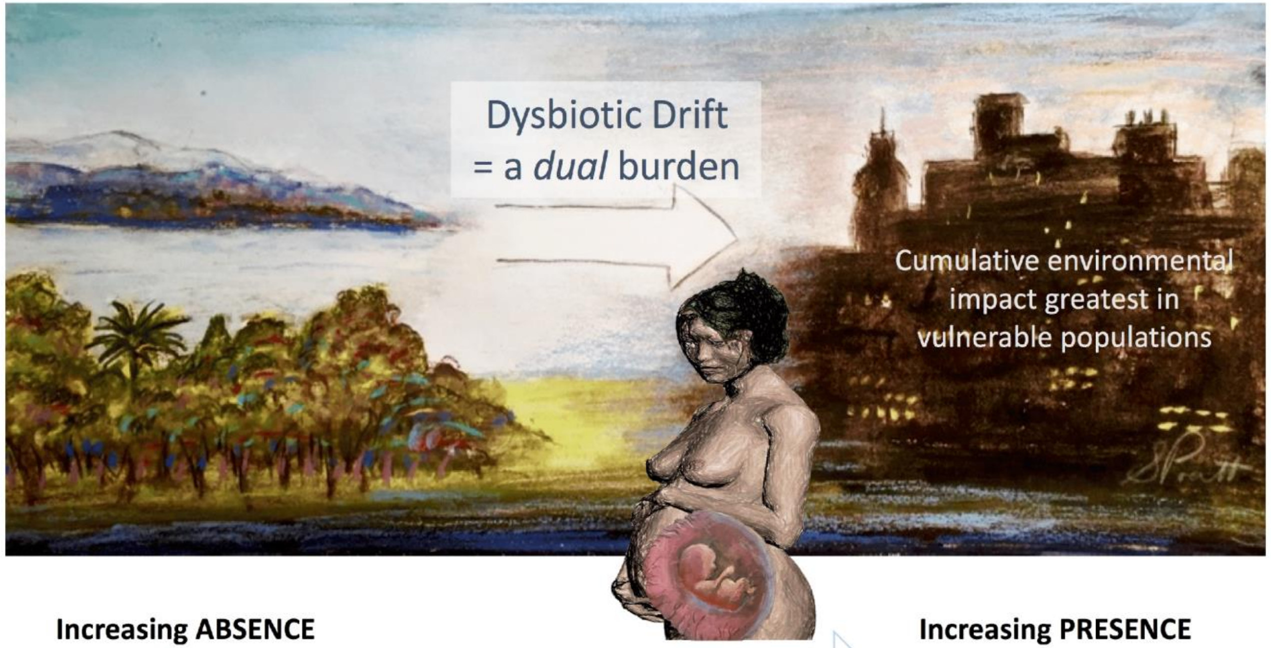


Source: WHO (2022)

The balance between energy consumption and expenditure has changed substantially in modern times. Modern city-dwelling humans consume large amounts of carbohydrates with a high glycemic index and excess amounts of refined sugars, particularly in beverages, as well as fatty foods, but generally have low levels of physical activity. How does this compare with the food and activity patterns of ancestral hominins? The information we have about such aspects of the lives of our ancestors is inevitably limited and somewhat speculative, but it suggests that humans are now in an environment of “evolutionary novelty” that involves exposures beyond the levels previously experienced in our evolution, and that this environment exceeds our evolved capacity to efficiently regulate metabolism, appetite, and food preferences. In other words, human biology, which is the product of evolution over millions of years, is metabolically “mismatched” to the novel and rapidly changing environments that we now inhabit. I will explore evidence that evolution has indeed resulted in a human metabolism that is not equipped for modern environments, and which now contributes to our patterns of susceptibility to non-communicable diseases.

Dealing with a compounding dual burden:

Shift traditional lifestyles to westernization not a zero-sum game

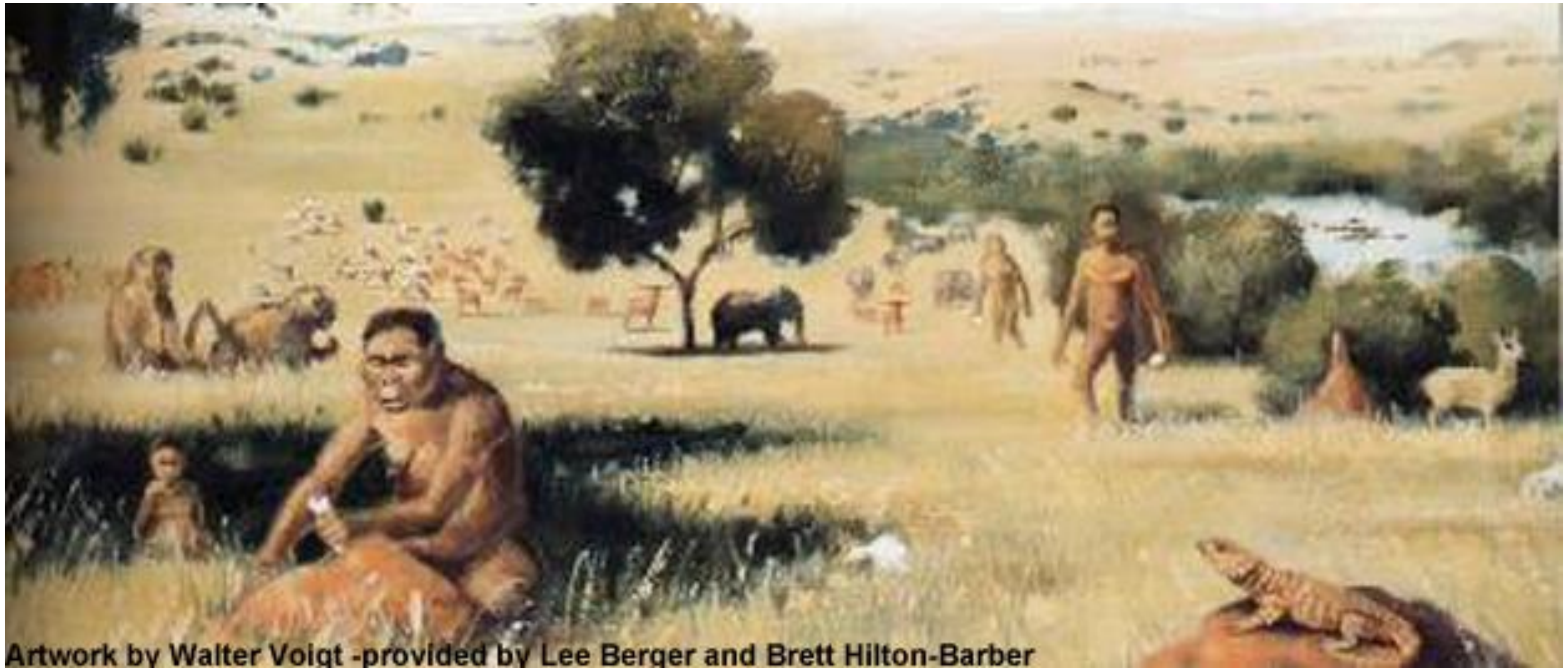


Increasing ABSENCE of traditional lifestyle

Commercial forces and absence of policy drive inequity and dysbiosis by default

Increasing PRESENCE of detrimental exposures

Strategies for Energy Storage



Artwork by Walter Voigt -provided by Lee Berger and Brett Hilton-Barber

The deposition of energy reserves primarily in the form of fat is not simply the passive outcome of excessive consumption of food but is an integral component of the adaptive strategy for many species, from the fat body located in the abdomen of insects to the subcutaneous fat of hibernating mammals such as the grizzly bear. Fat deposits also provide thermal insulation in cold-adapted species such as marine mammals. Fat is the major way in which the body stores excess energy—the net difference between energy intake and that expended in maintenance, growth, reproduction, repair, and physical exercise. Each aspect of this balance is under regulatory control.

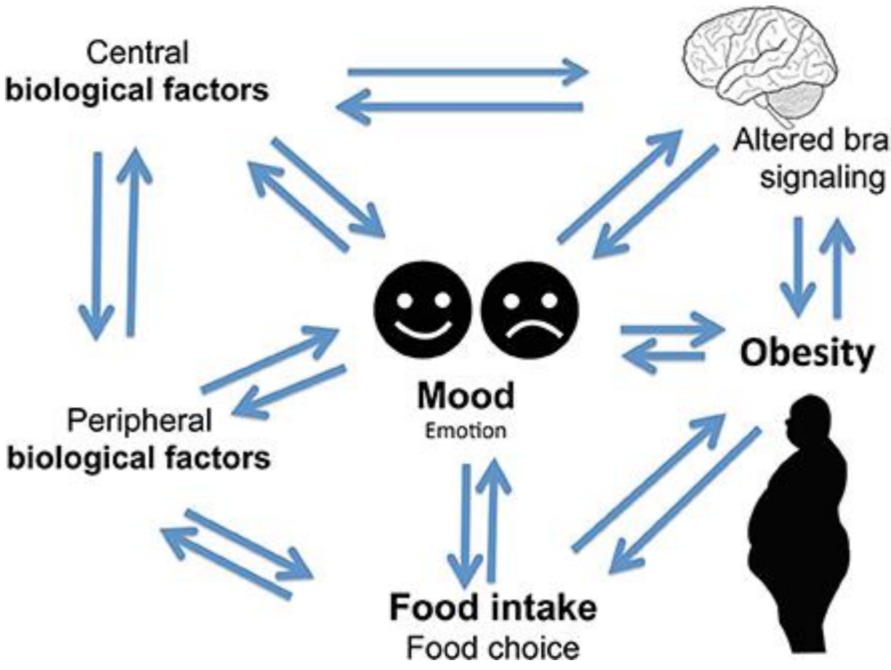
Not all fat stores have the same biology or physiological significance. While excess fat can have adverse consequences in any region of the body, it is increased deposition of ectopic fat in particular, including visceral, hepatic, and intramuscular fat, which is associated with the development of insulin resistance, vascular dysfunction, and eventually diabetes (see Shulman 2014). A significant proportion of the energy consumed by an adult organism is directed to maintenance and repair of its structure. This includes ensuring function of vital organs such as the brain, heart, and kidneys. Indeed, the adult human brain expends of the order of 25% of all calories consumed at normal levels of intake (see Holliday 1986). There is also an essential component expended in non-exercise activities such as standing and fidgeting—this is known as non-exercise activity thermogenesis, or NEAT. Beyond these basal maintenance requirements is the energy required for physical activity—walking and running, hunting and gathering, agriculture or work—and the energetically costly reproductive processes of pregnancy and lactation. In addition, young animals require energy for growth.

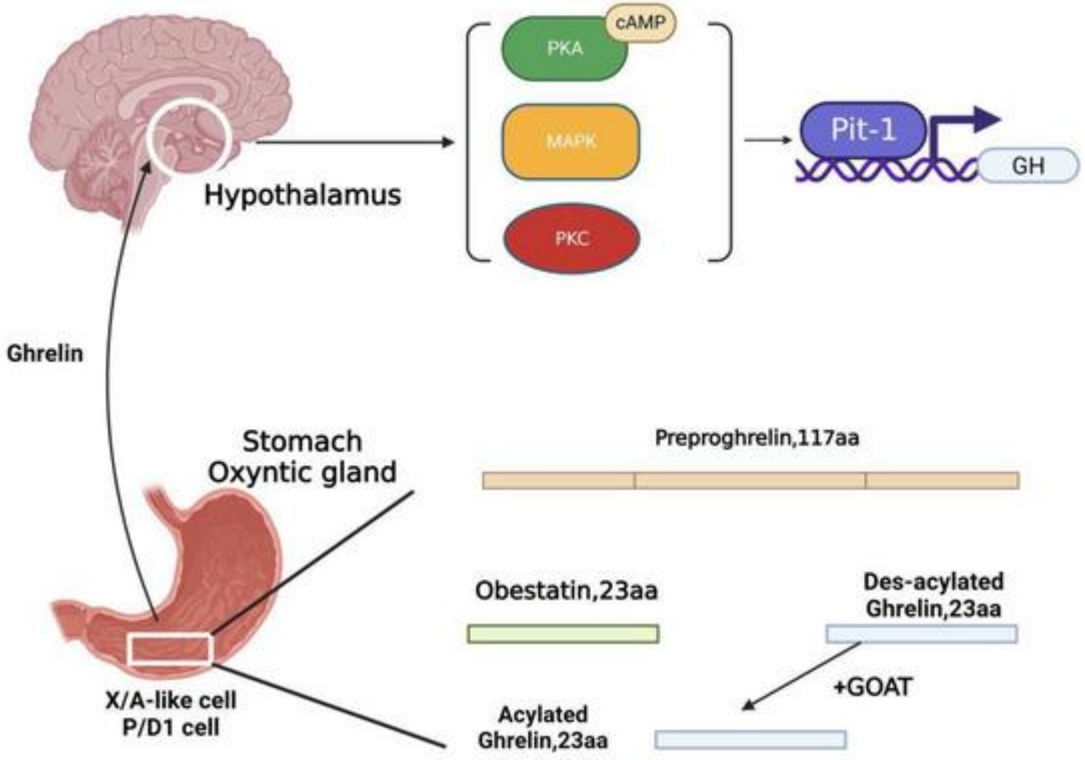
The main sources of energy in the diet are carbohydrates and fats, whereas protein is needed to provide amino acids for growth and support the turnover of tissues. These food constituents of fat, carbohydrate, and protein are referred to as macronutrients. Additionally, mammals require micronutrients in the form of vitamins (that function as co- factors in enzyme reactions, as hormones, and as antioxidants) and minerals (e.g., calcium for bone structure, iodine for thyroid hormone synthesis, and sodium/ potassium to maintain the ionic composition of bodily fluids). Although mammalian intermediary metabolism allows interconversion between macronutrients, certain essential amino acids and fatty acids cannot be synthesized by the body, or only to a limited extent, and must thus be obtained from the diet. It is also important to consider the role of the gastrointestinal microbiota (all the microorganisms within a particular environment), which itself utilizes some nutrients and generates others. What is absorbed from the gut is therefore a function not only of what is eaten
but also of gastrointestinal function and the gut microbiome (i.e., the microbiota, their genomes, and products generated by the host and microbiota). A typical adult human male consumes about 1 million calories each year. If weight is stable, this means that he is also expending 1 million calories, suggesting that humans balance their energy intake and energy expenditure with remarkable accuracy. Only a small imbalance is required to lead to progressive weight gain. So, faced with the choice of foods available to us in a modern diet, how do we choose what and how much to eat in light of the constantly changing demands for energy that we face in our daily lives.

Neuroendocrine mechanisms have evolved to help ensure that energy balance is generally maintained, other than in chronic scarcity or starvation or in disease- induced cachexia. Various inputs from the periphery— signaling blood glucose levels, adiposity, nutrient availability, and filling of the gastrointestinal tract— are integrated centrally in the hypothalamus (Lustig 2010). The long- term control of energy balance involves the adipoinsular axis: as adiposity increases, rising plasma leptin concentrations act on the hypothalamus to decrease food intake and on the pancreatic islet to lower circulating insulin levels, thereby reducing adipogenesis. On the other hand, when adipose stores decrease, falling plasma leptin concentrations increase feeding activity and permit increased insulin production, resulting in the deposition of additional fat (see Kieffer and Habener 2000). Central leptin resistence is a feature of the metabolic syndrome. Other adipokines such as adiponectin also play a role by affecting the sensitivity of the tissues to insulin.

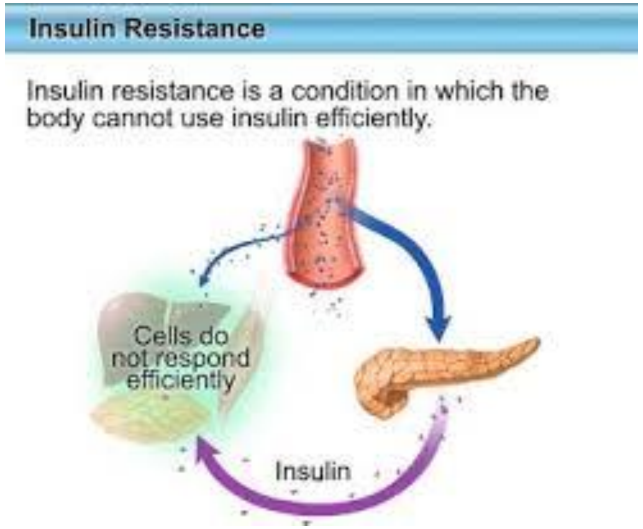
Short-term mechanisms acting on an hour-to-hour basis involve insulin, which itself also acts centrally to decrease food intake, and a variety of gut-related peptides which signal hunger or repletion following a meal. The latter are affected by therapeutic techniques to reduce food consumption, such as gastric bypass surgery, which not only reduces stomach size but also affects the release from the stomach of appetite-controlling hormones such as ghrelin. There are also interactions with emotional states. For example, ghrelin signaling mediates reward-eating behaviors induced by chronic stress/depression (seeChuang et al. 2011). In phylogenetic terms this is perhaps not surprising as predation-related fear and hunger would often coexist in nutritionally limiting circumstances.

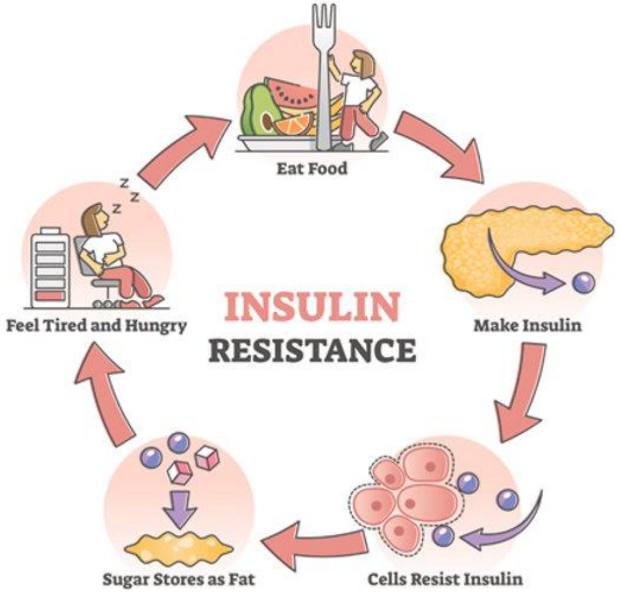
Because hunger and thirst are critical survival mechanisms, it has been suggested that the default position is to favor excess food intake over energy expenditure, and that this is why humans, and indeed other animals in captivity, are so prone to obesity. This argument is perhaps supported by the large number of polymorphisms that have been associated with morbid adiposity, and that generally involve disturbance of appetite control.



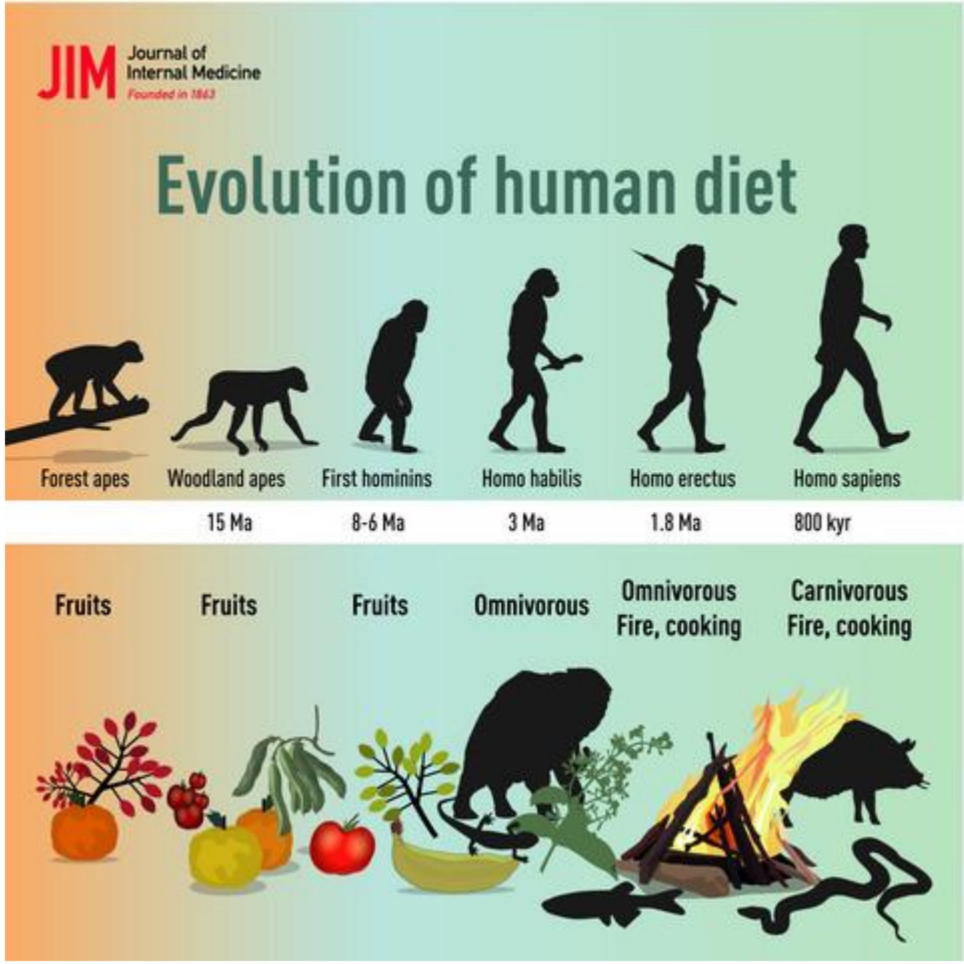


Glucose is the primary metabolic fuel for most tissues, so homeostatic mechanisms have evolved to keep its concentration in the blood reasonably constant despite variations in nutritional supply caused, for example, by overnight fasting. Brain function is adversely affected if blood glucose drops too low, yet excessive levels of blood glucose are toxic, primarily by glycation of many constitutive proteins and glycoproteins, affecting their function. Insulin efficiently promotes the uptake of glucose by tissues after a meal. Some of this glucose is metabolized, some is converted into glycogen, which acts as a short-term energy store in muscle and liver, and some is converted by the liver into triglycerides for longer-term storage as fat in adipose tissue. Conversely, as circulating glucose is depleted in the fasting state, other hormones (e.g., glucagon, growth hormone, glucocorticoids, and catecholamines) mobilize the energy stores for conversion into glucose. For any animal faced with day-to-day or season-to-season variability in food intake the ability to store energy as fat, and to mobilize that energy when required, is a capacity fundamental to its survival. This required the evolution of mechanisms to regulate and promote tissue uptake of glucose from the circulation, as well as maintain readily available storage depots for long-term backup energy reserves in the form of adipose tissue.





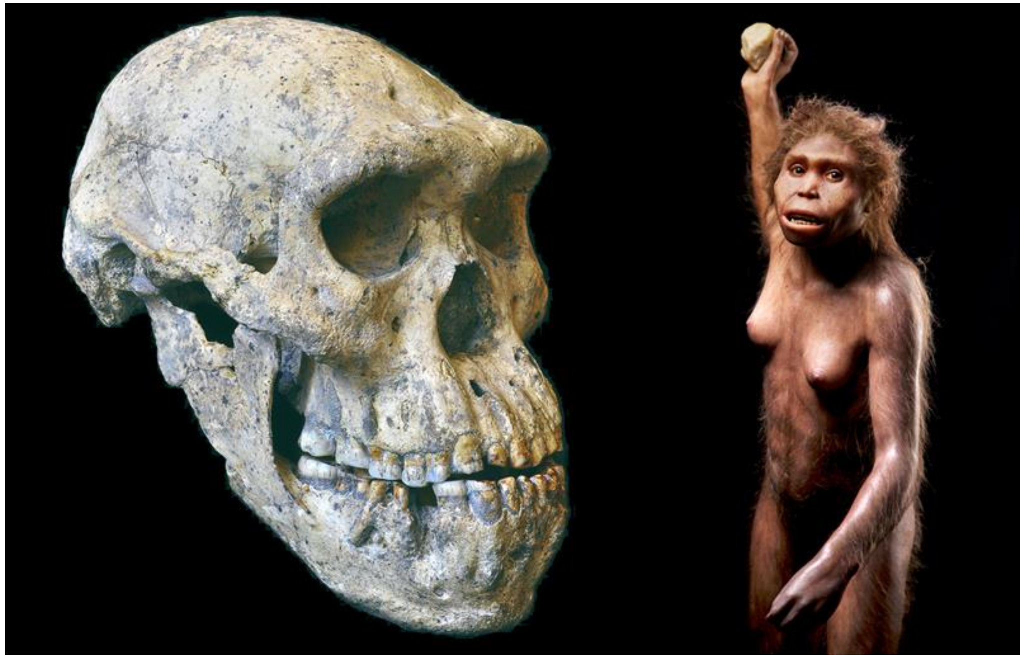
Human Diet: An Evolutionary History



Pre-agricultural Hominins

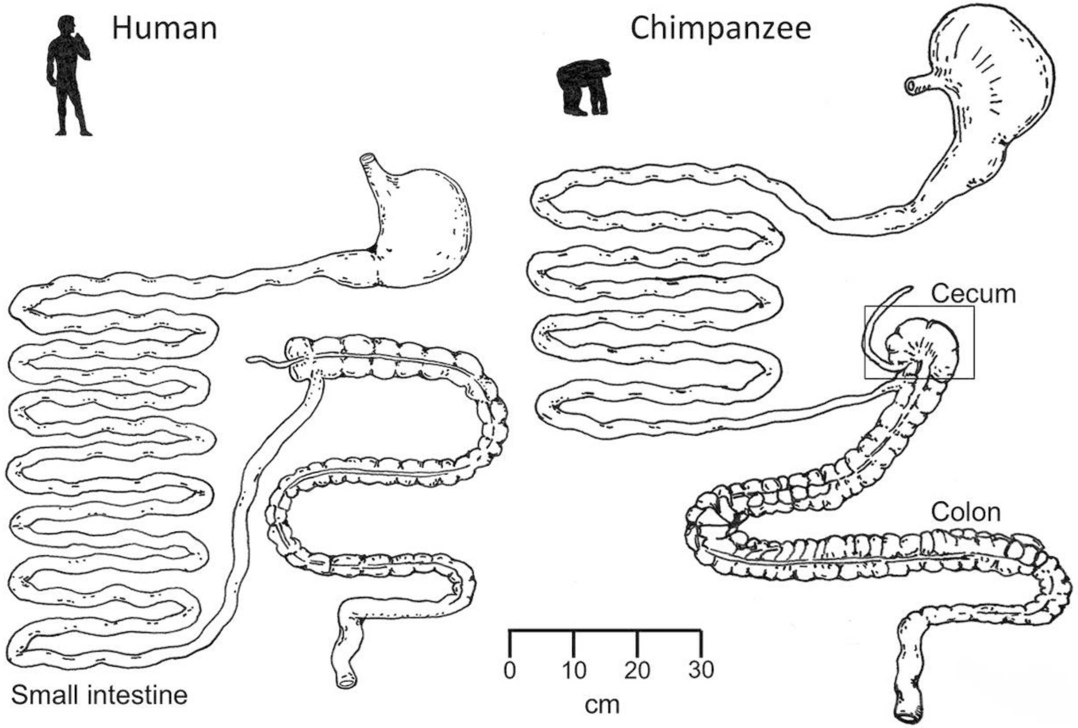
The earliest members of genus *Homo* appeared about 2 million years ago. The first archeological evidence for agriculture, in contrast, dates from a mere 12,000 years ago in the Middle East. Given that humans and our hominin ancestors survived as hunters and foragers for 99% of our existence, it can be argued that selection has driven our biology and metabolism to be better matched to the physical activity and diet that characterized the foraging way of life. From this perspective, the current global epidemic of metabolic disease can be understood, in part, as a result of a mismatch between our “ancient” foraging-adapted genome and our rapidly changing modern diet and lifestyle.

Thus, one way to gain insights into contemporary patterns of disease is to understand how our ancestors lived, and how modern culture might conflict with our biological adaptations to our previous lifestyle (see Gluckman and Hanson 2006). This is no simple task, and the answers to these questions are not straightforward. Indeed despite the hype of marketeers, there is no single “paleo diet,” and in fact what is marketed as a paleo diet bears little relationship to the probable realities of our ancestors’ lives (see Zuk 2013).



Anatomical Evidence for Diet Quality in Early Humans

Clues about the evolution of the human diet come from our anatomy and digestive biology, which differ from that of our closest living relatives, the great apes, in important ways. Most great apes have a gut biology that is well suited to foods that require more extensive processing and digestion, such as leaves and roots. In contrast, gut size is greatly reduced in modern humans, showing that at some point since the split between us and the great ape lineage about 7 Mya the need to maintain a large gut was reduced. The evolution of a shorter gut would have accompanied the adoption of a more digestible diet, which was calorifically dense and with less cellulose bulk.



One likely possibility is that this reduction in gut size accompanied an increased reliance on eating meat (see Stanford and Bunn 2001). Mammalian bones found in association with early *H. habilis* sites, such as Olduvai Gorge, have cut marks and other evidence of butchery. Early *Homo* populations would probably have acquired meat by scavenging remains left by savannah carnivores. Assessment of modern carnivore kill sites shows that carnivores routinely leave the brain, bone marrow, and other scraps of meat. These would have provided a rich source of dietary fat, including essential fatty acids such as docosahexaenoic acid that are required in abundance in humans to support early brain growth. Human requirements for the longer-chain (C20 and C22) fatty acids are similar to those of carnivores, reflecting low metabolic capacity for elongating and desaturating shorter plant-derived (mostly C18) fatty acids and implying a significant contributionof animal-derived lipids to the early hominin diet. Evidence for reliance upon game, whether hunted or scavenged, increases with the appearance of *H. erectus*, and becomes quite prominent with the emergence of fully modern humans around 150,000 years ago. The increase in dietary quality that came with eating meat probably relaxed selection for maintaining a larger gut, leading to the reduction in gut size.

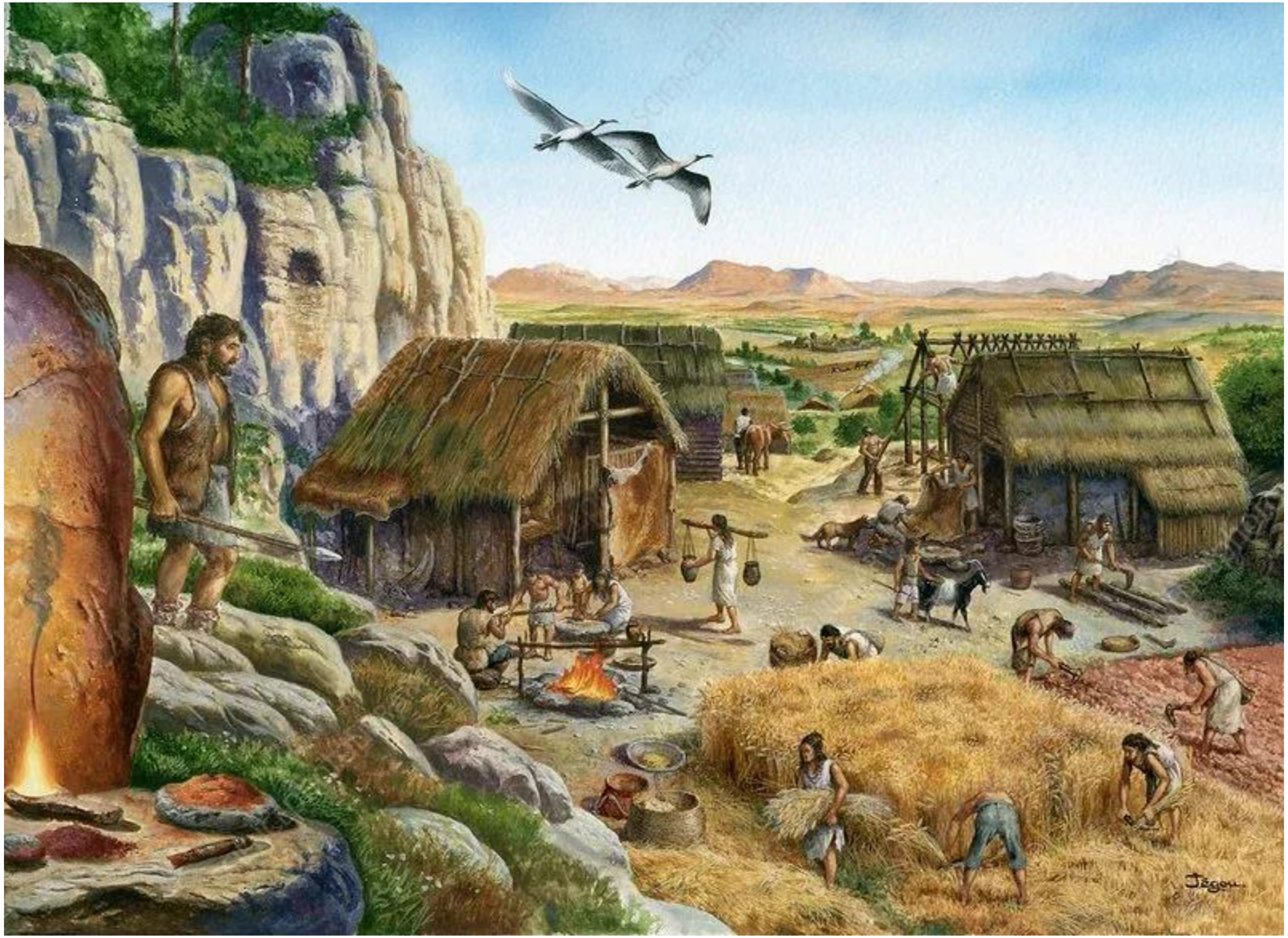
Modern Foraging Populations

One important source of information on ancestral human diets comes from modern or historical human populations who also subsist as foragers (hunter-gatherers- see Jordan 2014). Before considering what we can learn from such modern populations, it is important to bear several points in mind. It would be a mistake to view such populations as carry-overs from an earlier time in human evolution. There are probably no populations today that have not been influenced, either directly or indirectly, by the flow of ideas, technologies, and cultural practices from other societies. The idea of a “lost tribe” roaming the backwoods untouched by the global economic system, or the earlier institutions of colonialism, is little more than a myth. All modern foragers have been shaped by the passage of trade goods, infectious disease, cultural practices, and in myriad other ways that are not always obvious. Although the environments that modern foragers inhabit are remarkably varied, what they share in common is that they tend not to be suitable for more intensive resource-extraction methods such as farming. The most productive environments, which today are the seat of the densest human settlements supported by intensive agriculture, would have been the preferred habitats of our distant foraging ancestors; yet the environments of modern forager societies have been markedly changed. Because of this, we have no record of what foraging diets might have looked like in these once-common settings. In many cases modern foragers live in marginal environments to which they have been displaced by colonizing populations. Indeed, some populations that forage today were not foragers in the past: some are the modern descendants of agriculturalists who were pushed, often by force, into carving out a new living in a marginal environment. For all these reasons and more, we should not view modern foragers as evolutionary relics.

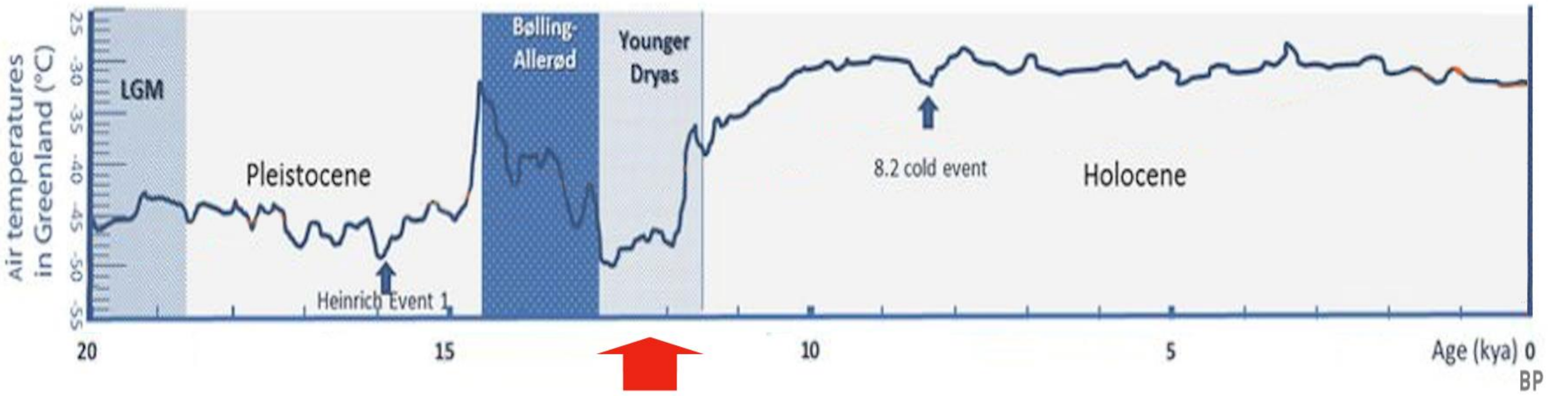
However, despite these caveats, modern foragers *do* provide important insights into the types of diets that our distant ancestors probably consumed. A quick thought experiment illustrates why. Imagine that you and 20 of your closest friends and family were transported to a region far from roads, communication, or human settlement. If your group survived, it would necessarily do so by subsisting on dietary resources that occur naturally in the local environment, such as plants, roots, small prey, berries, and fruits. Through trial and error, you would gradually build up a sophisticated repertoire of knowledge of which resources taste good, which are not digestible, and which are dangerous. You would refine methods for trapping or hunting prey species, and you would develop ways of processing and cooking the meat harvested from them. Within several generations, your group would develop a local knowledge, culture, and technology of food extraction, processing, and preparation that was sustainable within the confines of what was available in your local habitat. In any given ecology or habitat, there are finite ways to subsist by hunting and gathering. For instance, there are likely to be only a handful of important potential sources of calories, a handful of easily captured game species, and so on. As a result, different groups left to survive in the same environment would probably converge on similar strategies and diets, and perhaps even develop similar migratory patterns to follow seasonal gradients of resource availability between food patches. While your hypothetical extended group of friends would clearly not be an evolutionary link with the past, in all likelihood you would settle into a diet and style of living not all that different from what ancestral hominins must have developed when faced with a similar palette of natural resources. For the purposes of this discussion, modern foraging societies can therefore be viewed as the equivalent of this thought experiment: not as evolutionary relics or stepping stones to industrial society, but as a source of insight into the types of strategies that are sustainable by humans living solely, or primarily, from gathered and hunted food sources and without access to a staple crop.

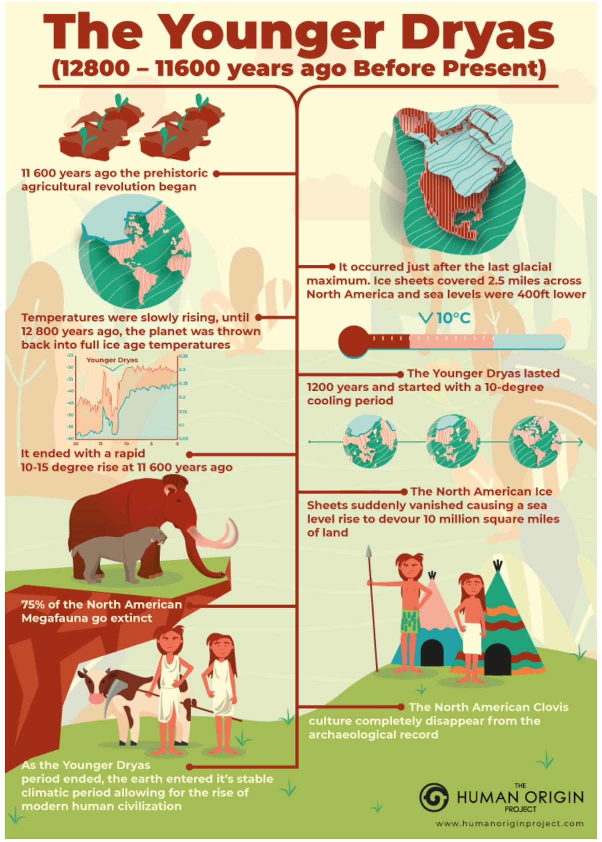
So what do modern foraging populations eat? One defining feature of forager diets is the sheerdiversity in what different populations in different environments consume—this is an important consideration in addressing the naďve belief that Paleolithic societies had a stereotypic way of life. In most, hunting is an important component of the diet, and often contributes half or more of the total calories consumed (see Cordain et al. 2000). Recently, it has also been shown that these populations have very different gut microbiomes from that of industrialized populations, in that they display more complexity and biodiversity (see Obregon-Tito et al. 2015). This highlights the interplay between us, our microbiome, and our environment. However, the proportion of calories derived from meat varies immensely, from 99% among the Arctic-dwelling Inuit to a majority of vegetable calories in groups like the !Kung san (or Khoisan) of Botswana, who have access to a plentiful source of non-animal calories. No known group of foragers lives solely as vegetarians, and meat constitutes at least 25% of the calories consumed by all modern or historical foraging populations for which detailed information is available. Studies of foraging populations show that they also acquire a substantial percentage of their calories from vegetables and fruits that may be gathered in wild settings. Typically, these plant sources would provide high levels of vitamins and fiber compared with the diet of modern urban humans, and their carbohydrate content would have a low glycemic index (a measure of the ability to raise blood glucose levels and therefore promote insulin secretion). Another important difference between a foraging diet and a modern “Western” diet is intake of sodium: modern foragers without access to commercially produced salt consume much less sodium than is found in a modern Western diet, and are generally free from arterial hypertension in consequence. Two more recent subsistence transitions—the Neolithic Revolution and the “nutrition transition”—have radically transformed the human diet and lifestyle. The modern scourge of metabolic disease can be partly understood as a result of these transitions, which have brought our Paleolithic biology into conflict with our modern lifestyle and diet.

„The Neolithic Revolution“



In a process that began around 12,000 years ago in the Middle East, two fundamental changes occurred in the human way of life: first, in some regions the mobility of hunter-gatherer bands was gradually replaced by settled village life; and second, humans began to domesticate and exploit for food the plant and animal species that had become associated with their settlements. At the time of the Neolithic Revolution, the human population of the planet was estimated to be about 5 million. The ice of the Last Glacial Maximum had retreated thousands of years earlier, but it was a time of marked climate change, with the cool and dry period of the Younger Dryas giving way to the warming of the early Holocene a little more than 10,000 years ago. Most explanations for the inception of agriculture include some component of resource or population pressure, whether caused by the extinction by hunting of the large animal populations that survived the Last Glacial Maximum or by the growing human population that had already colonized the most easily exploited regions. Whether sedentism preceded or was followed by agriculture may have been dependent on the region in question (see Rocek 1998). Whatever the cause of sedentism—perhaps protection from other foraging groups, or clustering at a favored site (oasis) in a drier climate—it would by itself lead to population pressure as fecundity increased from the low levels typical of nomadic groups. Nomads are often forced to limit the number of dependent children by ensuring that one child can walk before a subsequent one is born (and can be carried), resulting in inter-birth intervals of children that survive of up to 4 or 5 years.





The Younger Dryas

(12800 – 11600 years ago Before Present)

11 600 years ago the prehistoric agricultural revolution began

It occurred just after the last glacial maximum. Ice sheets covered 2.5 miles across North America and sea levels were 400ft lower

Temperatures were slowly rising, until 12 800 years ago, the planet was thrown back into full ice age temperatures

The Younger Dryas lasted 1200 years and started with a 10-degree cooling period

It ended with a rapid 10-15 degree rise at 11 600 years ago

The North American Ice Sheets suddenly vanished causing a sea level rise to devour 10 million square miles of land

75% of the North American Megafauna go extinct

The North American Clovis culture completely disappear from the archaeological record

As the Younger Dryas period ended, the earth entered it's stable climatic period allowing for the rise of modern human civilization

The early sedentary groups would have exploited a wide range of animal and plant species, and it is easy to imagine how familiarity with, and utilization of, wild cereals would have extended to the deliberate collection and planting of their seeds, and how later association with animals such as sheep and goats led to their domestication. By about 11,500 years ago in the Middle East the crop range, or package, of cereals (barley and wheat) and pulses (lentils and peas) cultivated by settled farmers was well established, and by 9000 years ago the major animal species (sheep, goats, cattle, and pigs) had been added. Export of this package or its components to Europe, North Africa, and western Asia, whether by movement of individual farmers or by acculturation, followed. Farming later arose independently elsewhere in the world, with distinct crop packages, in East Asia (predominantly rice), Central America (maize), South America (potatoes), West Africa (millet and sorghum), and New Guinea (yams), and biogeographical patterns of early farming may have determined later patterns of economic development. Whatever its original stimulus, the increase in population that accompanied agriculture ensured that the process was irreversible. By the time of the Roman Empire 9000 or 10,000 years later, the global population was about 130 million. Was farming a positive development in terms of its effects on a population's food stability and health?

It brings population growth and, importantly, the opportunity for a society to develop specialists—potters, metalworkers, soldiers, philosophers, and so on—which has been so important for the constitution of settlements and modern society. But it also brings less welcome effects: the beginning of a rigid social hierarchy with its attendant stressors, the opportunity for human pathogens and parasites to flourish as their hosts move to crowded communities, the nutritional consequences of reliance on a restricted range of food sources, and the possibility of famine as crops fail because of climate change or infestation (see Cohen 1989). There is evidence from skeletal and dental remains that child growth, adult stature, rates of infection and anemia, and lifespan were all adversely affected by the consequences of the shift from foraging to farming. For example, skeletal remains provide evidence of an increased prevalence of iron-deficiency anemia and infection in sedentary farmers (see Cohen and Armelagos 2013). Famine as a result of crop failure, and often exacerbated by political disputes or conflict, is a recurring theme in recent human history, from the famines of ancient Egypt when the Nile failed to flood, to the Irish famine which started with disease of the potato crop in 1845, to the present crises in the Horn of Africa. The seasonality of agricultural production causes a pre-harvest "hungry season," even among modern subsistence farmers in West Africa. Conversely, as we will discuss later, it is far from certain that famine was a significant factor for human existence prior to the Neolithic Revolution.

TO BE CONTINUED...