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REVIEW

Obesity: evolution of a symptom of affluence.

How food has shaped our existence

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ABSTRACT

This paper delineates the evolutionary background of the unprecedented epidemic of obesity that has evolved over the last century. Some two million years ago, a change of climate in the habitat of our primate ancestors triggered dietary adaptations which allowed our brain to grow. A shift from principally carbohydrate-based to fish- and meat-based eating habits provided sufficient fuel and building blocks to facilitate encephalisation. Insulin resistance may have evolved simultaneously as a means to avert the danger of hypoglycaemia to the brain (in view of the reduction of carbohydrate intake). Ensuing cognitive capacities enabled the control of fire and the manufacturing of tools, which increased energy yield from food even further and eased the defence against predators. The latter development relieved the selective pressure to maintain an upper level of bodyweight (driven by predation of overweight individuals). Since then, random mutations allowing bodyweight to increase spread in the human gene pool by genetic drift. Also, (seasonal) food insecurity in hunter-gatherer societies spurred the evolution of thrifty genes to maximise nutrient intake and energy storage when food was available. The agricultural and industrial revolutions rapidly changed our habitat: virtually unlimited stocks of (refined) foodstuffs and mechanical substitutes of physical efforts push up energy balance, particularly in those of us who are still adapted to former environmental conditions: i.e. who carry thrifty genes and lack (genetic) protection against weight gain. Intrauterine epigenetic mechanisms potentially reinforce the impact of these genes on the propensity to grow obese.

"Thus, from the war of nature, from famine and death, the most exalted object which we are capable of conceiving, namely, the production of the higher animals, directly follows." (Charles Darwin in: On the Origin of Species, 1859)

KEYWORDS

History, insulin resistance, predation release, thrifty genes, type 2 diabetes mellitus

INTRODUCTION

Currently, the World Health Organisation (WHO) estimates more than one billion people worldwide to be overweight, of whom at least 300 million are obese.[1] This is particularly worrisome, because obesity increases the risk of various chronic diseases, i.e. cardiovascular disease, type 2 diabetes mellitus and certain forms of cancer.[1] Therefore, the WHO and other non-governmental organisations have called for global action to prevent further escalation and reduce the number of obese people.[2]

It is of primary importance for the prevention and treatment of any disease to understand its root cause. Although hominid artifacts supposedly depicting obese humans date back as far as 500,000 years,[3] the current epidemic has evolved over the last one hundred. Why is that? Clearly, the industrial revolution plays a major role: motorised labour and transportation, in concert with the availability of virtually unlimited amounts of food in (Western) societies marked by technical and socioeconomic progress, push energy balance upward in many individuals. In fact, given these developments, the appropriate question is not why so many people are obese, but why so many of us appear to escape this physical fate.

This paper delineates the biological and social underpinnings of the obesity epidemic from an evolutionary point of view. Climate change and ensuing dietary adaptations profoundly influenced the development of our brain, which probably permitted two recent events triggering the current epidemic of metabolic disease to occur: the agricultural and industrial revolutions. Although the technical breakthroughs that facilitated

these socioeconomic upheavals doubtlessly contribute to the bodyweight increase of contemporary homo sapiens, it is very important for the development of prevention and treatment strategies to bear in mind that biological features of our species also play their part.

THE EARLY DAYS: EVENTS FACILITATING BRAIN GROWTH

The story begins some four to six million years ago. Our primate ancestors lived in the woods of Eastern Africa (Tanzania, Kenya, Ethiopia). Their diet primarily comprised leaves, roots, fruits and nuts at the time.[4] Thus, the main macronutrient we consumed was carbohydrate. Approximately two million years back, the climate in Eastern Africa changed profoundly (it became dryer and colder), which had a major impact on our habitat. Forests disappeared and were replaced by arid grasslands, inhabited by herbivore game (and large predators).[5] These ecological changes provided an excellent opportunity for our hominin ancestors with sufficient capability to exploit animal resources. Archaeological and anthropological evidence strongly suggests that we ultimately moved to these grasslands and coastlines, attracted by much higher quality food[6,7]: from then on proteins and unsaturated fatty acids (from game and fish) were abundant in our diet, comprising some 50 to 60% of intake on a percentage of total calories basis.[7,8] This dietary change in turn allowed a crucial event in our evolutionary history to occur: the growth of our brain. There are at least two reasons why this particular change of food habits was essential for our brain to be able to grow: first, unsaturated fatty acids are essential building blocks of neural tissue. Approximately 50 to 60% of the human adult brain is made up of lipids,[9] of which nearly one third are polyunsaturated, primarily arachidonic acid and docosahexaenoic acid.[10] Second, our brain is extremely expensive in terms of energy costs: it consumes >20% of total resting expenditure.[11,12] Energy yield from far more nutrient dense fish and meat is much higher than from (structural) plant components (e.g. bark, mature leaves).[13] The growth of our brain was probably essential for our intellectual development. In due course we learned how to control fire (first evidence dates back some 800,000 years.[14] Heating of food improved energy yield even further, as it clearly facilitates digestion.[15]

Notably, these biological and cultural developments merely *allowed* the brain to grow; they do not explain *why* it did. Various theories address the latter issue. For example, it has been proposed that intellectual development increased survival among hominids exploiting the complicated nutritional niche of hunting and gathering. It requires tools, social strategies and memory to effectively catch prey in open grasslands and forage for ripe fruits and nuts in continuously changing seasons and environments. Chance changes in brain morphology, intensifying neuronal number and connectivity (thereby promoting intelligence), may therefore have conferred a survival advantage on our hominin ancestors.[16] In addition, the use of tools and social interactions *per se* may have spurred neural development.[17] One other possibility I would like to put forward here is that we needed our intellect to escape from predators in open grasslands. Our species does not have powerful physical tools at its disposal to ward off life-threatening attacks by predators. Climbing trees or quickly getting away in an underground refuge are alternative means to escape which do not particularly fit with our physique either. Attacks by predators probably posed a major threat to our ancestors until technical (stone tools, fire control) and social (coordinated defence strategies) developments quite significantly facilitated survival.[18,19] Conceivably, growing intellectual capacity, as a function of neural connectivity, was a prerequisite for the emergence of these adaptations which clearly conferred a survival advantage. Therefore, hominids with larger brains harbouring extensive neural networks (i.e. greater intellectual capacity) may have survived more often than those with smaller brains.

TEN THOUSAND YEARS BACK: THE AGRICULTURAL REVOLUTION

Perhaps also as a result of intellectual progress, our ancestors became adventurous and migrated out of Africa for the first time some 1.8 million years ago (the precise timing of this event is hotly debated by the way). The majority of migrants moving away during this first out-of-Africa exodus ended up in Asia. Their offspring finally became extinct only recently (100,000 years back).[20] A second exodus, approximately 800,000 years ago, primarily landed in Europe, bringing forth (among others) the Neanderthal species which died out some 20 to 30 thousand years back.[20] Finally, during the third and last exodus which populated the world as it is today, people accidentally passed by the fertile grounds of the land of the Euphrates and Tigris rivers, including significant territory of modern-day countries such as Egypt, Iraq, Syria, Jordan, Lebanon, Israel, Iran and Turkey. The geophysical and climate characteristics of this region pre-eminently enabled the natural occurrence of the wild progenitors of the Neolithic founder crops (cereals, legumes and flax) and four of the five most important domesticated animals (cows, goats, sheep, and pigs). Because of these favourable environmental conditions, the so-called Fertile Crescent became the birthplace of modern agriculture and stock-breeding some 10,000 years ago.[21] Independent

development of agriculture occurred somewhat later in China, the African Sahel region, New Guinea and several areas in the Americas.[21]

The advent of agriculture profoundly affected the composition of our diet. As outlined above, hunter-gatherers thrived on a mix of carbohydrates, proteins and (unsaturated) fatty acids for millions of years. It is important to note that there has not been one universal diet consumed by all hunter-gatherer communities. Rather, as suggested by studies of contemporary hunter-gatherer tribes[22] and commonsense, the availability of food depended on geographic locale and climate conditions. Humans evolved as veritable omnivores, although it seems likely that >50% of hunter-gatherer subsistence comprised animal food.[8] However, various types of food cannot have been consumed on a regular basis before the advent of agriculture and animal husbandry. Agriculture in essence reintroduced carbohydrate as the principal macronutrient. Agricultural produce primarily contains carbohydrate; it partially supplanted hunter-gatherer protein and (unsaturated) fatty acid in our diet. Moreover, animal husbandry introduced dairy and promotes the consumption of saturated instead of unsaturated fat. The latter is for two reasons. First, cattle meat partially replaced fish in our diet and fish is an important source of unsaturated fatty acids. Second, the dominant fatty acids in *adipocytes* of wild mammals are saturated, whereas *muscle and other tissues* primarily contain polyunsaturated (PUFA) or monounsaturated fatty acids (MUFA).[23] Because subcutaneous and abdominal adipose stores are depleted during most of the year in wild animals, PUFA and MUFA constitute most of their total carcass fat.[23] The advent of animal domestication and stock breeding attenuated the (seasonal) depletion of (saturated) fat stores by year round feeding of stored plant foods. Therefore, cattle harbour much more saturated fat when domesticated than in the wild. Also, it became feasible to slaughter animals at peak body fat percentage.

How did these recent dietary changes affect our health? Almost all evidence indicates that it deteriorated. Average adult height declined substantially after the advent of agriculture.[24] Moreover, studies of bones and teeth show that the advent of agriculture coincides with a higher incidence of osteoporosis, rickets, caries and various other mineral and vitamin-deficiency disorders.[25,26] Finally, undisputed evidence indicates that the size of our brain is currently shrinking for the first time in our evolutionary history (perhaps because of a lack of unsaturated fatty acids for build up and maintenance), albeit in parallel with the decline of bodyweight and height.[27]

So how is it that agriculture turned out to be so successful? Agrarian societies rapidly conquered the world, while hunter-gatherers vanished either by defeat or by voluntary adoption of farming as a way of life.[21] Agriculture enabled us to settle down at a fixed spot: we were no longer dependent on local (un)availability of food forcing us to move on to other areas to hunt and gather. This allows the number of offspring to increase, because mothers are no longer obliged to carry their children around in continuous search of foraging areas (it is feasible to simultaneously carry one or perhaps two children at the very most). Building more robust accommodation and fenced villages facilitated defense against predators and hostile congeners. Predation and violence were major threats in hunter-gatherer times, although earlier social developments had significantly abated the danger of violent death (see above).[18,19] Furthermore, agriculture allowed rapid evolution of knowledge-based societies: only a few members of the community could maintain food security for all, the rest had plenty of time to focus on innovation. In sharp contrast, hunter-gatherers were obliged to collectively forage for food during a considerable part of the day. As communities grew, (political) organisation substantially reinforced their capacity to withstand hostile threats and successfully embark on campaigns to expand territory.[21] Clearly, these social corollaries of agriculture provided powerful benefits which explain its rapid world-wide scattering.

Overweight and obesity were probably exceptional for thousands of years after the advent of agriculture, although famous statuettes of obese individuals such as the Venus of Willendorf date back even further. Also, Hippocrates recognised the dangers of overweight some 2400 years ago: 'It is very injurious to health to take in more food than the constitution will bear, when, at the same time one uses no exercise to carry off this excess.... For as aliment fills, and exercise empties the body, the result of an exact equipoise between them must be to leave the body in the same state they found it, that is, in perfect health.'[28] Obesity predominantly occurred among members of the upper social class, who had continuous access to food and usually performed intellectual duties not requiring physical activity.[28] In this context it is vital to bear in mind that food shortage as a result of failed harvest, particularly affecting the man in the street, was fairly common in pre-industrial societies.[29]

RECENT DEVELOPMENTS: THE INDUSTRIAL REVOLUTION

In the late 18th century, major technological developments in the United Kingdom foreshadowed worldwide socioeconomic and cultural changes which signify a third turning point in human history. Machine-based

manufacturing and farming, enabled by spectacular progress in the field of fuelling, dramatically increased (agricultural) production capacity. Moreover, it became far more feasible to store food safely for longer periods of time. For the first time in history, nutrients were available for all (in those parts of the world profiting from the developments). Also, motorised labour and transport pre-empted physical efforts. Childhood mortality declined significantly (for various reasons). The world's population grew almost sixfold since the early 1800's.[30]

As a corollary of these advancements, the industrial revolution had a major impact on human energy balance equations. Reliable data documenting calorie intake are scarce, in particular for food consumption during the 19th and early 20th century. However, commonsense tells us that average intake must have increased substantially. The Food and Agriculture Organization (FAO) of the United Nations reports a continuing increase of total daily calorie consumption by 20 to 25% across the world since 1960.[31] Data from the US confirm the substantial increase of per capita calorie intake over the last 30 years.[32] Perhaps even more important, dietary composition also changed considerably: cereals were highly refined by mechanised mills; refined sugars were introduced and consumed on an ever-growing scale; sodium intake increased dramatically, whereas potassium intake declined; micronutrient density declined whereas calorie density increased; fibre content fell substantially; and saturated fat replaced (poly)unsaturated (*table 1*) (for an excellent review see Cordain *et al.*[33]).

Table 1. *Major differences in food components of modern-day humans as compared with our hunter-gatherer ancestors*

	Contemporary *vs.* hunter-gatherer
Calorie intake	↑
Physical activity	↓ ↓
Dietary composition	
Total carbohydrates:	↑
refined carbohydrates	↑ ↑
fibres	↓ ↓
Total protein	↓
Total fat:	~
PUFA	↓ ↓
ω-6:ω-3	↑ ↑
SFA	↑ ↑
Micronutrients:	↓
sodium	↑ ↑
potassium	↓

PUFA = polyunsaturated fatty acids
SFA = saturated fatty acids

Concurrently, our environment was deliberately designed to minimise the requirement for physical activity. Although reliable methods to quantify total daily energy expenditure are only just emerging, the secular decline in physical activity is obvious. Motorised labour and transport have profoundly suppressed calorie needs.[34,35] Finally, advancements in heating technology and clothing effectively protect us against the nuisance of cold weather, which substantially diminishes the energy requirements for adaptive thermogenesis.[36,37]

The consequences of these lifestyle changes for our energy balance and health are easy to contain. Indeed, when contemporary hunter-gatherer societies adopt the 'Western' way of life, obesity, diabetes and atherosclerosis become commonplace.[38-40] Conversely, temporary reversal of westernisation (by living as hunter-gatherers in their traditional country for seven weeks) essentially cures type 2 diabetes in obese Australian Aborigines.[41] In fact, the obvious question is why so many people maintain metabolic health in the face of the current environmental 'challenges'. The answer to this question is not entirely clear. I will briefly address four important hypotheses trying to explain this enigma.

THE THRIFTY GENE HYPOTHESIS

In the early 1960s, James Van Gundia Neel, a pioneer in the study of human genetics, launched his 'thrifty gene hypothesis',[42] which still dominates thinking about the biological roots of obesity and diabetes. Neel was one of the first to recognise the important role of genes in the pathogenesis of these ailments. His hypothesis is founded on the basic premise that genes which are part of the (human) gene pool must have had survival benefits in evolutionary history. Neel specifically proposed that a genetically determined excessive insulin response to nutrient ingestion would minimise the loss of precious glucose in harsh times of food scarcity. Hyperinsulinaemia would effectively promote storage of ingested calories. Overalimentation in modern times would result in plasma insulin levels that elicit 'insulin antagonism in plasma' as proposed by Vallance-Owen and colleagues,[43] and thereby cause diabetes. As other laboratories could not confirm the existence of circulating insulin antagonists, the original physiological basis of the hypothesis collapsed, which led Neel to revisit his reasoning in regard to the mechanistic link between the obese diabetic genotype and phenotype. Complex adaptive genetic traits would compile multi-faceted endocrine systems designed to retain calories in times of famine.[44] The genes involved 'are very predominantly fine old genes with, of course, some allelic variation, honed by millennia of selection for harmonious

interactions and appropriate epigenetic relationships, the proper function of which is overwhelmed by extraneously imposed parameters of very recent origin'.[44]

Neel's genetic premise still holds. There is widespread consensus that genes determine the variation in bodyweight and body fat distribution in a given (social) environment for at least 50 to 70%.[45,46] Genes are also involved in the pathogenesis of type 2 diabetes mellitus (DM2), although all single nucleotide polymorphisms (SNP) known to be associated with DM2 to date add only marginally to risk prediction by conventional factors.[46,47] Monogenetic forms of either disease are well known, but complex genetic traits predispose to metabolic disorder in the vast majority of patients.[46] The mechanistic links between genotype and phenotype of both ailments remain largely unknown. However, it is remarkable that all monogenetic defects causing human obesity known to date disrupt hypothalamic circuits that control food intake.[48] Therefore, although it is often assumed that genetic factors underlying obesity affect metabolic rate or selective partitioning of excess calories into fat, current evidence suggests that genetic determinants of satiety and food intake are likely to be at least as important. The precise biological correlates of the majority of DM2 SNPs are not known, but many of them map close to genes expressed in the islets of Langerhans and/or are associated with β-cell dysfunction.[46,49] Inasmuch as the pathophysiology of DM2 is marked by dual defects of insulin secretion and action,[50] it is likely that the genes which predispose to DM2 (given the current affluent conditions) control the extent to which β-cell function can be maintained in the face of (also heritable, see below) insulin resistance.

Thus, the thrifty gene hypothesis proposes that those of us carrying a hereditary taint to efficiently harvest and/or store calories are the ones who run the greatest risk to grow obese in contemporary industrialised living climates. These genes conferred survival advantage in ancient times characterised by (seasonal) food insecurity. There is general consensus that genes play an important role in the pathogenesis of metabolic disease. Various alleles related to obesity are widespread among the population.[51] I also think that most evolutionary biologists still tend to agree with the conceptual underpinning of Neel's hypothesis. In keeping with his revised mechanistic explanation, obesity is caused by the concerted effects of multiple gene products in the vast majority of patients. However, in sharp contrast to Neel's original idea about the pathogenesis of DM2, mutations predisposing to this disease appear to hamper β-cell function. These alleles could probably spread in the gene pool, because there has never been selection pressure on β-cell capacity. Current environmental conditions (i.e. unlimited availability of food, particularly refined sugars) and (obesity associated) insulin resistance challenge β-cell function to an unprecedented extent, leading to failure in those of us with functional capacity in the lower range of the boundaries compatible with life.

THE PREDATION RELEASE HYPOTHESIS

I will just briefly summarise John Speakman's intriguing ideas explaining the epidemic of obesity in modern societies, because he elaborately outlined his novel hypothesis recently in an excellent paper.[19] The interested reader will find all relevant references in this paper. In essence, Speakman argues that there is insufficient evidence to support the notion that our ancestors have been exposed to perils of famine sufficiently severe for thrifty genes to propagate. Moreover, he puts forward that strong selection for thrifty genes would predict hunter-gatherers to grow fat in between epochs of famine, and various studies of contemporary hunter-gatherer societies do not report such weight gain. Finally, he asserts that any postulate involving thrifty genes as a root cause of obesity cannot explain the fact that so many people maintain normal bodyweight in the current environment, as such genes spread widely in the gene pool when given sufficient time to propagate. As an alternative, Speakman suggests that ancient genes controlled bodyweight within narrow limits, with mutations causing obesity selected against by the risk of predation. As mentioned earlier, predation posed a major threat to our hominid ancestors, and obese individuals must have been easy and attractive targets for obvious reasons (i.e. less mobile, more calories to consume). Some one million years ago, humans evolved social strategies to ward off predators. Furthermore, the control of fire and stone tools that could be used as weapons quite significantly facilitated the defence against lethal attacks. These developments relieved the selective pressure to maintain bodyweight below an upper setpoint. Since then, random mutations allowing bodyweight to increase were no longer removed from the gene pool and spread gradually through genetic drift. When food is available in virtually unlimited quantities and physical activity no longer required to meet the necessaries of life, bodyweight can grow unabatedly in those of us afflicted. The fact that the mutations spread through random drift rather than directed selection explains why so many people maintain a normal weight despite current environmental conditions.

FOETAL ORIGINS OF ADULT OBESITY

Barker and colleagues were the first to recognise that intrauterine conditions have a major impact on adult health.[52] Geographical studies demonstrated that contemporary rates of death from coronary heart disease

were closely associated with death rates among newborn babies in the past. Death among newborns was almost invariably attributed to low birth weight. The finding spurred scientific interest in the effects of the intrauterine environment on adult (metabolic) disease. Foetal and neonatal growth are marked by extraordinary plasticity, allowing intrinsic and environmental factors to impact on development so as to optimally adapt the offspring's phenotype to current environmental conditions. A huge body of evidence now supports the view that foetal nutrition shapes its metabolic phenotype through epigenetic modification of gene expression.[53] Intrauterine conditions affect gene expression through histone modification and methylation of DNA, which is heritable but does not bear on mutation of DNA itself (hence the term 'epigenetic').[54] It has now been firmly established that maternal overweight and elevated plasma levels of glucose and triglyceride levels are strongly predictive of foetal and neonatal fatness and body mass index of offspring at 8 years of age.[55] The precise epigenetic mechanisms involved are not known, but may relate to transcriptional modification of metabolic and behavioural gene pathways by in utero exposure to excess maternal lipids.[55] Conversely, and paradoxically, female (but not male) offspring of mothers exposed to famine during gestation in the Dutch 'Hongerwinter' are also obese at middle age.[56] The impact of foetal malnutrition on adult obesity was recently confirmed by a study among children whose mothers were undernourished during the Biafran civil war famine.[57]

The currently available data documenting the epigenetic origins of obesity allow for a model of its pathogenesis assuming the primacy of recent environmental changes. In particular, they imply that both parental obesity and nutritional deficits during gestation inheritably adapt foetal gene expression profiles so as to predispose the offspring to excessive weight gain. In this context, obesity does not necessarily involve genetic predisposition. Rather, environmental cues affecting food intake (e.g. aggressive advertising of foodstuffs) may induce parental metabolic changes, which alter gene expression profiles in their offspring so as to produce an inheritable trait predisposing to weight gain in subsequent generations. However, epigenetic mechanisms may obviously also cooperate with genetic traits to reinforce pathogenetic mechanisms underlying obesity.

THE CARNIVORE CONNECTION: PUTTING INSULIN RESISTANCE IN EVOLUTIONARY PERSPECTIVE

Insulin facilitates glucose and amino acid uptake in muscle and adipose tissue. It also promotes incorporation of fatty acids in adipose triglycerides. Conversely, it inhibits glucose and triglyceride production by the liver.[58,59] Thus, the postprandial rise of circulating insulin levels effectively clears ingested nutrients from the blood. Consequently, insulin resistance hampers postprandial disposal of glucose, (branched-chain) amino acids and fatty acids and promotes (postprandial) hepatic glucose output and triglyceride production. Therefore, insulin resistance is associated with a cluster of metabolic anomalies, including hyperglycaemia, hypertriglyceridaemia, low plasma HDL-cholesterol levels (directly linked with increased circulating VLDL-triglyceride levels), hypertension and abdominal obesity,[60] often referred to as the 'metabolic syndrome'. Essentially, insulin resistance hampers the use of glucose for fuel by peripheral tissues, saving it for the brain to combust. It provides even more glucose to the brain by simultaneous promotion of endogenous glucose production (with circulating amino acids and glycerol as precursors of gluconeogenesis). In sync, it supplies other tissues with fatty acids as an alternative fuel. The pathogenesis of insulin resistance involves complex gene-environment interactions.[61] What evolutionary pressures have pushed the widespread dissipation of the genes involved?

As pointed out earlier, our ancestor's dietary composition switched from primarily carbohydrate based to protein rich some two million years ago in response to a climate change in Eastern Africa.[4,7,62] Our brain chiefly relies on glucose for its energy requirements and cerebral energy consumption at physical rest amounts to a striking 25% of total bodily expenditure.[11,12] Thus, the dietary change simultaneously allowed the brain to grow (by provision of unsaturated fatty acid and energy) and created a direct threat to brain health and survival: glucose deprivation. Seventeen years ago, Jeanette Brand Miller and Stephen Colagiuri proposed that insulin resistance developed to overcome this environmental threat.[62,63] It is quite conceivable that insulin resistance conferred a survival benefit particularly in winter when food was scarce for hunter-gatherers: effective partitioning of precious glucose towards the brain may have been critical for maintenance of brain health. In this context, the seasonal cycling of fat storage (hoarding in summer in preparation for winter time) that marks wild mammals,[33] probably including hominid hunter-gatherers, is of mechanistic interest: adipose tissue plays a major role in the pathogenesis of insulin resistance.[64]

The agricultural revolution reintroduced carbohydrates as the dominant macronutrient in our diet. Subsequent industrialisation made food continuously available to the majority of the population and catapulted the consumption of refined sugars. In these circumstances, insulin resistance is no longer an asset. In contrast, it elevates blood glucose levels and predisposes to DM2.

SUMMARY AND PERSPECTIVE

Three major events in our evolution presaged the current epidemic of obesity and type 2 diabetes. Approximately two million years ago geophysical and climate changes in Eastern Africa triggered dietary adaptations that allowed the growth of our brain. A shift from principally carbohydrate-based to protein- and unsaturated fatty acid-rich food provided sufficient fuel and building blocks to facilitate encephalisation. Insulin resistance may have evolved simultaneously as a means to avert the danger of hypoglycaemia to the brain. Also, thrifty genes maximised food intake and energy storage when available and technical and social progress relieved the selective pressure to maintain an upper level of body weight. Ensuing intellectual capacities enabled two very recent developments that shaped our society of today: the agricultural and industrial revolutions. These socioeconomic landslides changed environmental conditions so quickly that many of us are not yet physically adapted. Reintroduction of carbohydrate as the predominant macronutrient, availability of virtually unlimited stocks of refined foodstuffs and mechanical substitutes of physical efforts render those of us who are genetically designed to survive in harsh circumstances particularly susceptible to obesity and type 2 diabetes mellitus.

It is of critical importance for the design of preventive measures to bear in mind that we have built our society as it is for good reasons: our recent evolutionary history of seasonal food insecurity strongly drives our inclination to maximise food stocks and consume if food is available as well as our tenor to sit still (and spare energy) as soon as the circumstances allow us to do so. These biological assets are obviously meaningless and even hazardous today. Although obesity and insulin resistance diminish human fecundity,[65] it will probably take thousands if not millions of years of genetic drift to deplete the gene pool, inasmuch as evolutionary pressure to eliminate these traits will be relatively insignificant, because the adverse consequences generally arise well into reproductive age. Moreover, modern medical technology can assist obese patients to reproduce. In this respect, the currently evolving epidemic of childhood obesity may have quite different effects.

Darwin's lessons are as meaningful as ever. For any preventive or therapeutic strategy focussing on obesity and diabetes to be truly effective, it is imperative to consider the evolutionary underpinnings of the problem. In particular, we need to understand that our behaviour and metabolism are driven by strong evolutionary roots. In view of the biological power of these roots, I am convinced that simply informing the public about the dangers of our behaviour and the potential solutions will yield only marginal results. Rather, we have to think of reasonable ways to curb our instincts nolens volens, or accept that nature will probably take a very long time to help us overcome the current epidemic.

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REFERENCES

1. WHO Global Strategy on Diet Physical Activity and Health. http://www.who.int/dietphysicalactivity/publications/facts/obesity/en/index.html.
2. WHO. Global Alliance for the Prevention of Obesity and Related Chronic Disease. http://www.preventionalliance.net/.
3. Haslam D, Rigby N. A long look at obesity. Lancet. 2010;376(9735):85-6.
4. Gaulin SJC, Konner M. On the natural diet of primates, including humans. In: Wurtman RJ, Wurtman JJ, editors. Nutrition and the Brain. New York: Raven Press, 1977;1-86.
5. Reed KE. Early hominid evolution and ecological change through the African Plio-Pleistocene. J Hum Evol. 1997; 32(2-3):289-322.
6. Leonard WR, Robertson ML, Snodgrass JJ. Energetics and the evolution of brain size in early *Homo*. In: Roebroeks JWM, editor. Guts and Brains. An integrative approach to the hominin record. Leiden: Leiden University Press, 2007:29-46.
7. Broadhurst CL, Cunnane SC, Crawford MA. Rift Valley lake fish and shellfish provided brain-specific nutrition for early Homo. Br J Nutr. 1998;79(1):3-21.
8. Cordain L, Eaton SB, Miller JB, Mann N, Hill K. The paradoxical nature of hunter-gatherer diets: meat-based, yet non-atherogenic. Eur J Clin Nutr. 2002;56 Suppl 1:S42-S52.
9. Huang M-C, Brenna JT. On the relative efficacy of alinolenic acid and preformed docosahexanoic acid as substrates for tissue docohexanoate during perinatal development. In: Mostofsky DI, Yehuda SJr, editors. Fatty acids: physiological and behavioral functions. Totowa,NJ: Humana Press, 2001:99-113.
10. Carlson BA, Kingston JD. Docosahexaenoic acid, the aquatic diet, and hominin encephalization: difficulties in establishing evolutionary links. Am J Hum Biol. 2007;19(1):132-41.
11. Leonard WR, Snodgrass JJ, Robertson ML. Effects of brain evolution on human nutrition and metabolism. Annu Rev Nutr. 2007;27:311-27.
12. Cunnane SC, Crawford MA. Survival of the fattest: fat babies were the key to evolution of the large human brain. Comp Biochem Physiol A Mol Integr Physiol. 2003;136(1):17-26.
13. Cordain L, Watkins BA, Mann NJ. Fatty acid composition and energy density of foods available to African hominids. Evolutionary implications for human brain development. World Rev Nutr Diet. 2001;90:144-61.
14. Goren-Inbar N, Alperson N, Kislev ME, Simchoni O, Melamed Y, Ben-Nun A, et al. Evidence of hominin control of fire at Gesher Benot Ya'aqov, Israel. Science. 2004;304(5671):725-7.
15. Carmody RN, Wrangham RW. The energetic significance of cooking. J Hum Evol. 2009;57(4):379-91.
16. McDonald K. Ecological hypotheses for human brain evolution: evidence for skill and learning processes in the ethnographic literature on hunting. In: Roebroeks JWM, editor. Guts and Brains. An integrative approach to the hominin record. Leiden: Leiden University Press, 2007:107-32.
17. Coward F, Gamble C. Big brains, small worlds: material culture and the evolution of the mind. Philos Trans R Soc Lond B Biol Sci. 2008;363(1499):1969-79.

18. Guthrie RD. *Haak and Steek*-The tool that allowed hominins to colonize the African savanna and to flourish there. In: Roebroeks JWM, editor. Guts and Brains. An integrative approach to the hominin record. Leiden: Leiden University Press, 2007:133-64.

19. Speakman JR. A nonadaptive scenario explaining the genetic predisposition to obesity: the 'predation release' hypothesis. Cell Metab. 2007;6(1):5-12.

20. Stringer C. Human evolution: Out of Ethiopia. Nature. 2003;423(6941):692-3, 695.

21. Diamond J. Guns Germs and Steel. The fates of human societies. New York: W.W.Norton & Company Ltd, 1999.

22. Cordain L, Miller JB, Eaton SB, Mann N, Holt SH, Speth JD. Plant-animal subsistence ratios and macronutrient energy estimations in worldwide hunter-gatherer diets. Am J Clin Nutr. 2000; 71(3):682-92.

23. Cordain L, Watkins BA, Florant GL, Kelher M, Rogers L, Li Y. Fatty acid analysis of wild ruminant tissues: evolutionary implications for reducing diet-related chronic disease. Eur J Clin Nutr. 2002;56(3):181-91.

24. Cohen MN. Health and the rise of civilisation. New Haven, Conn: Yale University Press, 1989.

25. Cohen MN. The significance of long-term changes in human diet and food economy. In: Harris M, Ross EB, editors. Food and Evolution: Toward a Theory of Human Food Habits. Philadelphia, PA: Temple University Press, 1987: 261-83.

26. Cassidy CM. Nutrition and health in agriculturalists and hunter-gatherers: a case study of two prehistoric populations. In: Jerome NW, Kandel RF, Pelto GH, editors. Nutritional Anthropology: Contemporary Approaches to Diet and Culture. Pleasantville, NY: Redgrave Publishing Co, 1980:117-45.

27. Ruff CB, Trinkaus E, Holliday TW. Body mass and encephalization in Pleistocene Homo. Nature. 1997;387(6629):173-6.

28. Haslam D. Obesity: a medical history. Obes Rev. 2007; 8 Suppl 1:31-6.

29. O'Grada C. Markets and famines in pre-industrial Europe. Journal of Interdisciplinary History. 2005;36:143-66.

30. Maddison A. The World Economy. Historical Statistics. Paris: OECD, 2003.

31. Food and Agricultural Organisation EaSDD. World Agriculture: towards 2015/2030. Summary Report. 2002.

32. Popkin BM, Gordon-Larsen P. The nutrition transition: worldwide obesity dynamics and their determinants. Int J Obes Relat Metab Disord. 2004;28 Suppl 3:S2-S9.

33. Cordain L, Eaton SB, Sebastian A, Mann N, Lindeberg S, Watkins BA, et al. Origins and evolution of the Western diet: health implications for the 21st century. Am J Clin Nutr. 2005;81(2):341-54.

34. O'Keefe JH, Vogel R, Lavie CJ, Cordain L. Achieving Hunter-gatherer Fitness in the 21(st) Century: Back to the Future. Am J Med. 2010;123(12):1082-6.

35. Haslam DW, James WP. Obesity. Lancet. 2005;366(9492):1197-209.

36. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med. 2009;360(15):1500-8.

37. Cypess AM, Lehman S, Williams G, Tal I, Rodman D, Goldfine AB, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med. 2009;360(15):1509-17.

38. Diamond J. The double puzzle of diabetes. Nature. 2003;423(6940):599-602.

39. Daniel M, Rowley KG, McDermott R, Mylvaganam A, O'Dea K. Diabetes incidence in an Australian aboriginal population. An 8-year follow-up study. Diabetes Care. 1999;22(12):1993-8.

40. Ebbesson SO, Schraer CD, Risica PM, Adler AI, Ebbesson L, Mayer AM, et al. Diabetes and impaired glucose tolerance in three Alaskan Eskimo populations. The Alaska-Siberia Project. Diabetes Care. 1998;21(4):563-9.

41. O'Dea K. Marked improvement in carbohydrate and lipid metabolism in diabetic Australian aborigines after temporary reversion to traditional lifestyle. Diabetes. 1984;33(6):596-603.

42. Neel JV. Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress'? Am J Hum Genet. 1962;14:353-62.

43. Vallence-Owen J, Lilley MD. Insulin antagonism in the plasma of obese diabetic and prediabetics. Lancet. 1961;1(7181):806-7.

44. Neel JV, Weder AB, Julius S. Type II diabetes, essential hypertension, and obesity as 'syndromes of impaired genetic homeostasis': the 'thrifty genotype' hypothesis enters the 21st century. Perspect Biol Med. 1998;42(1):44-74.

45. Maes HH, Neale MC, Eaves LJ. Genetic and environmental factors in relative body weight and human adiposity. Behav Genet. 1997;27(4):325-51.

46. O'Rahilly S. Human genetics illuminates the paths to metabolic disease. Nature. 2009;462(7271):307-14.

47. McCarthy MI. Genomics, type 2 diabetes, and obesity. N Engl J Med. 2010;363(24):2339-50.

48. O'Rahilly S, Farooqi IS. Genetics of obesity. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1095-105.

49. Staiger H, Machicao F, Fritsche A, Haring HU. Pathomechanisms of type 2 diabetes genes. Endocr Rev. 2009;30(6):557-85.

50. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. Lancet. 2005;365(9467):1333-46.

51. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. Nat Rev Genet. 2009;10(7):431-42.

52. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. Lancet. 1989;2(8663):577-80.

53. Jackson AA, Burdge GC, Lillycrop KA. Diet, nutrition and modulation of genomic expression in fetal origins of adult disease. World Rev Nutr Diet. 2010;101:56-72.

54. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet. 2003;33 Suppl:245-54.

55. Heerwagen MJ, Miller MR, Barbour LA, Friedman JE. Maternal obesity and fetal metabolic programming: a fertile epigenetic soil. Am J Physiol Regul Integr Comp Physiol. 2010;299(3):R711-R722.

56. Stein AD, Kahn HS, Rundle A, Zybert PA, van der Pal-de Bruin, Lumey LH. Anthropometric measures in middle age after exposure to famine during gestation: evidence from the Dutch famine. Am J Clin Nutr. 2007;85(3):869-76.

57. Hult M, Tornhammar P, Ueda P, Chima C, Bonamy AK, Ozumba B, et al. Hypertension, diabetes and overweight: looming legacies of the Biafran famine. PLoS One. 2010;5(10):e13582.

58. DeFronzo RA. Pathogenesis of type 2 diabetes mellitus. Med Clin North Am. 2004;88(4):787-835, ix.

59. Pereira S, Marliss EB, Morais JA, Chevalier S, Gougeon R. Insulin resistance of protein metabolism in type 2 diabetes. Diabetes. 2008;57(1):56-63.

60. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-45.

61. Lahiry P, Pollex RL, Hegele RA. Uncloaking the genetic determinants of metabolic syndrome. J Nutrigenet Nutrigenomics. 2008;1(3):118-25.

62. Colagiuri S, Brand MJ. The 'carnivore connection'--evolutionary aspects of insulin resistance. Eur J Clin Nutr. 2002;56 Suppl 1:S30-S35.

63. Miller JC, Colagiuri S. The carnivore connection: dietary carbohydrate in the evolution of NIDDM. Diabetologia. 1994;37(12):1280-6.

64. Galic S, Oakhill JS, Steinberg GR. Adipose tissue as an endocrine organ. Mol Cell Endocrinol. 2010;316(2):129-39.

65. Pasquali R, Patton L, Gambineri A. Obesity and infertility. Curr Opin Endocrinol Diabetes Obes. 2007;14(6):482-7.