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Starvation in humans: Evolutionary background and contemporary implications

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Abstract

Although there is extensive evidence that caloric restriction (CR) extends lifespan in several species the evidence base for humans is weak. We are still at the stage of applying inductive reasoning and of framing hypotheses to be tested. It is known that a genetic background contributes about 25% to the variation in human longevity, but thought unlikely that any genes conferring longer lifespan have been positively selected to do so. It is more likely that any such benefits are unintended consequences arising from other adaptations. If there is an association between CR and longevity in humans it may have been selected by previous exposures to famine. This paper briefly reviews the historical evidence on the extent and frequency of famines in human history. It is concluded that starvation has been one of the major selective pressures on the human genome and has left abundant evidence of adaptive survival traits. Many of these are mediated through effects on reproduction. However, interpretation of the possible links between these energy-sparing mechanisms and any association between CR and ageing is handicapped by an absence of data on the latter and will remain a matter of debate for many years to come.
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1. Introduction

Evidence from several species studied under rigorous laboratory conditions confirms that caloric restriction (CR) can extend lifespan by a substantial amount (reviewed by Longo and Finch, 2003). As summarised in other papers from this symposium the mechanisms of these effects are still vigorously debated and the possibility of their extrapolation to primates is based, so far, on insubstantial evidence. The exploration of the topic from a human perspective must therefore rely, for the time being, on inductive reasoning, which it is hoped can direct the research agenda. Prominent amongst this reasoning are questions related to the evolution of genetic variants and pathways that might influence the rate of ageing. The current debate generally considers three leading explanatory paradigms for ageing from among the scores that have been suggested (Hughes and Reynolds, 2005; Kirkwood and Austad, 2000): mutation accumulation (an accumulation of late-acting deleterious mutations with the germ line) (e.g. Medawar, 1952); antagonistic pleiotropy (the trade-off between benefit at an early age and harm at later ages) (Williams, 1957); the disposable soma theory (the concept that lifetime-limited somatic resources must be traded between investment in growth, maintenance and reproduction) (Kirkwood, 1977, 1996). These, and other possible paradigms, are not necessarily mutually exclusive.

A key question is whether these are evolved mechanisms or serendipitous effects arising as unintended consequences. Genes are certainly involved in determining the rate of ageing (Cournil and Kirkwood, 2001) and recent molecular studies are starting to reveal some of the possible mechanisms including genes influencing DNA repair and stress damage (Kirkwood, 2003). This does not, however, imply that such genes have been under positive selection pressure that favours longevity beyond the age of natural reproduction; indeed, because longevity traits display their

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benefits after periods of peak reproductive capacity (and may actually compete with fecundity traits) and because in wild animals extrinsic hazards such as predation and infections prevent most animals from ageing, it is highly unlikely that such genes would have been selected except by accidental association with other survival traits. Variations to this general reasoning may possibly occur in a few species, including humans, in which elderly family members might aid survival of their grandchildren (Sear et al., 2002).

A supplementary question is whether any genetic effects on ageing have been selected in relation to caloric restriction and might explain the association between CR and longevity. It is pertinent to consider the evolutionary forces that may have moulded the selection of any such associations and the purpose of this paper is to provide the historical and evolutionary background against which to judge the emerging experimental evidence and to frame new hypotheses.

1.1. Caloric restriction: definition of the term in humans

A large part of the human race is currently over-nourished. The extent of this is sufficiently powerful to overcome natural body weight regulatory mechanisms leading to gradual weight gain and obesity (Prentice, 1997). The excess adipose tissue and its macrophage infiltrate are sources of chronic inflammatory mediators that drive a range of pathological outcomes including dislipidaemia, insulin resistance and hypertension. Diabetes, heart disease and cancers are among the many serious co-morbidities that are associated with obesity (World Health Organisation, 1998).

These disease outcomes have been estimated to shorten the lifespan of an obese person by between 8 and 13 years depending on the age of onset of the obesity (Fontaine et al., 2003). Successful weight loss can reduce the incidence of diabetes and other co-morbidities, cause remission of existing symptoms and reduce all-cause mortality (World Health Organisation, 1998). Thus, there is no doubt that caloric restriction of an *overweight* human will, on average, be associated with a degree of reversal of what would otherwise be an accelerated mortality. In the current paper, it is assumed that this self-evident truism is not the central issue in the debate, but that the question relates to the natural biology of any possible impact on lifespan of CR in non-overweight humans.

This caveat is also worth considering when interpreting the experimental data from small animals and primates kept in captivity (Longo and Finch, 2003). It is likely that these are also in a state of energy excess under most laboratory conditions, as evidenced by gradual fat accumulation and their levels of physical activity are certainly lower than normal. CR paradigms under such conditions might therefore simply be recreating a more natural and healthy body composition in terms of lean:fat ratios.

1.2. Timescales of hunger

Modern humans are meal eaters and generally display highly characteristic temporal eating patterns according to their culture. The poorest people may consume only a single meal each day, but two or three meals and additional episodes of snacking are generally the norm. In healthy people, finely tuned hormonal mechanisms orchestrate the inter-meal adaptations in fuel selection that maintain the organism in an appropriate metabolic state for survival. In evolutionary time, the maintenance of vigilance and fight-and-flight responses, together with reproductive functions would have been the dominant selective drivers. In adult humans, these states are readily maintained for periods of up to 18 h or so after a meal. After these 18 h have elapsed, hepatic glycogen stores are severely depleted and the metabolically expensive process of gluconeogenesis is required to maintain optimal cranial function. The status of glycogen stores in muscle will depend on the extent to which they have been exercised and may range from completely depleted to almost fully repleted if the person has been inactive since the last meal. So in general, and based upon the extent to which hepatic glycogen can maintain glucose homeostasis between meals, intervals longer than 18 h can be considered as the onset of caloric restriction. In the special case of pregnancy, a phenomenon described as ‘accelerated starvation’ (Prentice et al., 1983) reduces this interval to something less than 18 h.

During the next 48–96 h, the organism initiates a number of self-protective adaptations designed to maximise the use of its fuel resources, protect protein mass and minimise the loss of essential micronutrients. Primary amongst these are the induction of enzymes that allow the brain to utilise ketone bodies in place of glucose. This reduces the need for gluconeogenesis and hence the rate of protein breakdown. Other adaptations include a reduction in metabolic rate mediated by a T3/T4 shunt in thyroid metabolism (Prentice et al., 1991).

After these first 4 or 5 days of fasting, the system reaches a state of relative stability in the rate at which it loses vital resources though there is a series of further behavioural adaptations that come into play when survival is seriously threatened by famine (Prentice, 2001). The time over which any individual can survive severe or total caloric restriction may range from a little over a month in thin individuals to a year or more in obese ones.

2. Starvation in humans: from short-term hunger to fatal famine

Food shortages, starvation and famine have probably been among the strongest of any external evolutionary pressures that have moulded human adaptive responses. The current consensus is that hunter-gatherer populations would have repeatedly suffered food shortages of a day or two, but

would rarely have faced outright famine (Diamond, 1993). This is because they lived in small groups, had adopted a highly omnivorous and variable diet and were sufficiently mobile to move to fresh hunting grounds if food supplies dwindled in their original habitat. Thus, the adaptive metabolic responses most useful to our distant ancestors would have been the relatively short-term ones described above. Modern pastoralists might still be experiencing similar conditions.

The dawn of the agricultural era changed this situation radically (McCance, 1975). At first the subsistence farmers continued to live a precarious existence in which farming was only a partial contribution to their diet. Then as agricultural technology progressed populations were able to produce an excess of staple foods, to trade foodstuffs and to create contingency stores to buffer any future shortages. It became possible for towns and cities to develop since they could be supported by the surrounding agriculture. In each of the ecological regions of the world different crops were grown and different farming systems employed enabling population growth far in excess of anything seen previously (Diamond, 1993).

However, it is this very success that created vulnerability (McCance, 1975). The system relies on relatively constant and predictable weather patterns, stable government and an absence of major conflict. When any of these conditions fails then large populations can be plunged into catastrophic famine. Fagan has argued that el nino variations in weather patterns are likely explanations for the disappearance of many past civilisations (Fagan, 2000). Summarised below is just a small fraction of the documentary evidence supporting the view that, even since the dawn of recorded history, famines have been a widespread selective pressure on human metabolic development.

3. Historical evidence of starvation in human populations

Elsewhere we have described in greater detail a selection of the mass of historical evidence that records the influence of widespread catastrophic famine on the human race (Prentice, 2001). These records document extreme privation accompanied by mass mortality. The frequent references to cannibalism as a means of survival, even by parents of their own children, provide a terrible validation of the extent of human suffering. A small selection of some of the best known historical references to human famine is summarised in Table 1.

Readers are referred to a previous paper (Prentice, 2001) or to the two-volume work on '*The Biology of Human Starvation*' by Keys et al. (1950), for greater detail about the effects of starvation. Excellent summaries of individual famines are also available (see for instance Jordan, 1996). Here, the discussion is confined to outlining the key points, namely:

Table 1
Selected historical references to famine

'I am mourning on my high throne for the vast misfortune, because the Nile flood in my time has not come for seven years. Light is the grain; there is a lack of crops and of all kinds of food. Each man has become a thief to his neighbour. They desire to hasten and cannot walk. The counsel of the great ones in the court is but emptiness. Torn open are the chests of provisions, but instead of contents there is air. Everything is exhausted.'
The Stella of Famine. Chiselled into Egyptian rock in the time of Tcheser c 2000BC.

'All of Upper Egypt was dying of hunger, to such a degree that everyone had come to eating his children ... the entire country had become like a starved grasshopper ...'
The Sepulchers of Ankhtifi 2180-60BC

'If there be a cutting down of the food offerings of the gods, then a million men perish among mortals, covetousness is practiced, the entire land is in a fury, and great and small are on the execution block.'
Middle Kingdom Hymn to the Nile

'And there was famine in the land: And Abram went down into Egypt to sojourn there: For the famine was grievous in all the land'
Abram's journey into Egypt, Genesis 12

'... in the city we are exchanging our children and eating them ...'
China 594BC, The Siege of the Chong Capital

'One could scarcely see the water in the Vistasa, entirely covered as the river was with corpses soaked and swollen by the water in which they had long been lying. The land became densely covered with bones in all directions until it was like one great burial ground, causing terror to all beings.'
Kashmir in the years 917-8AD as related in Kalhana's 'Rajatarangini'

'Parents killed their children and children killed parents, and the bodies of executed criminals were eagerly snatched from the gallows.'
Contemporary report from Flanders at the beginning of the Great Famine 1319

'The region has been visited by the exterminating angel. Every scourge has been unloosed. Everywhere I have found men dead of cold and hunger.'
Mirabeau's report from a visit to Provence immediately prior to the French Revolution

(a) There is widespread evidence that starvation and famines must have exerted a strong selection effect on the human genome. This would have occurred both through suppression of fertility as well as through actual mortality.
(b) These famines should not be viewed as occurrences remote in either time or place. Even the most secure and affluent populations of today need only trace their history back a short distance to find evidence of famines that would have impinged on their forebears. Keys et al. (1950) estimate that there have been over 190 documented famines in Britain alone since the Roman invasions 2000 years ago. Many of the forebears of Irish Americans were survivors of the Great Famine of the 1840s, and only one-fifth of the original Mayflower

pilgrims have left descendants since many were carried away by famine (the relief from which is celebrated to this day at Thanksgiving). These examples provide only a glimpse of the likely wider influence of famine on genetic selection.

(c) Whilst in many respects the human genome has remained very stable over the 12,000 years since the dawn of agriculture, we contend that the 600 or so generations during this time will have been sufficient to permit significant selection of 'thrifty genes' especially if mediated through effects on reproductive capacity (see Prentice et al., 2005).

In summary, we concur with Darwin himself in placing famine among the major drivers of natural selection. In the concluding remarks to *The Origin of Species* he noted that '*The evolution of higher animals directly follows . . . from the war of nature, from famine and death. . .*' (Darwin, 1989).

4. Contemporary implications of biological adaptations for surviving famine

Table 2 briefly lists the areas of human function through which energy can be stored in readiness for possible famine, or spared in times of actual famine. These have been discussed in greater detail elsewhere (Prentice, 2001; Prentice et al., 2005). In the current context it is only pertinent to consider which, if any, may have possible direct or indirect effects on the rate of ageing and hence might explain the putative link between CR and longevity. Although behavioural adaptations may influence lifespan (for instance, a reduction in physical activity could reduce exposure to predation, infection or other damaging events that may ultimately contribute to an earlier death among more active people), we will concentrate our attention here on the metabolic issues. These can usefully be separated into non-reproductive and reproductive. It is worth stressing that in each of these areas the field remains far from reaching any consensus.

4.1. Non-reproductive metabolic adaptations

As indicated above and discussed extensively elsewhere (Dulloo and Jacquet, 2001), metabolic rate can be modestly down-regulated in times of caloric restriction. In their seminal studies on starvation Keys et al. (1950) showed that this was partly caused by a reduction in active tissue mass (lean body mass) and partly by a reduction in the specific metabolic rate per unit of the active tissue mass. This has been repeatedly demonstrated in studies of weight loss in obese people and can be shown to depend on the extent and duration of the energy restriction. Except in the most severe conditions, when significant mass has been lost from the musculature and vital organs, metabolic rate does not decline more than about 25% in total (Prentice et al., 1991). In passing, it can be noted that if individuals are interested in extending lifespan by CR then it will be almost impossible to exceed a 25% restriction against their habitual intake at weight equilibrium without showing continued weight loss. Even restriction at 15–20% will undoubtedly cause loss of active tissue unless accompanied by significant reduction in physical activity.

The precise nature of the metabolic changes that spare energy remain surprisingly poorly understood. This is largely because the processes that make up the total cost of basal metabolism are also imprecisely known. In humans, it is generally stated that basal metabolic rate is composed of: protein turnover; energy-requiring membrane pumping necessary for the maintenance of ionic homeostasis; cell turnover and repair; the muscular work of respiration and circulation; the costs of nutrient handling. Under most conditions, it is assumed that the waste heat occurring as a by-product of these reactions is sufficient for the maintenance of thermoregulation in humans given their large body size (and hence low surface-area-to-volume ratio) and their ability to adjust their micro-climate through clothing and heating. The work of Brand (2000) would indicate that the costs of quenching the reactive oxygen species (ROS) that arise from mitochondrial metabolism may also represent a significant proportion of total basal metabolism with possible implications for CR and ageing.

Reductions in basal metabolism as a response to CR might act in either a positive or a negative direction with respect to optimal cellular maintenance and hence longevity. On the one hand, and according to the 'rate of living' theory of lifespan (Weinert and Timiras, 2003), reductions in metabolic activity should be associated with increased longevity mediated by a reduction in the rate of cell damage, especially oxidative damage originating from mitochondrial metabolism. On the other hand, if DNA and protein repair processes are down-regulated, then there may be a greater

Table 2
Biological strategies for surviving famine

Metabolic rate	'Energy sparing' super-efficient metabolism
Physiological compensation	Ability to switch-off non-essential processes
Reproduction	Down-regulation of the reproductive axis in both males and females
Food intake	Gluttony: tendency to gorge when food is available
Physical activity	Slothfulness: tendency to conserve energy through inactivity
Behavioural mechanisms	Hoarding, meanness, theft, etc.

accumulation of damage and hence reduced longevity. To our knowledge it has not been successfully predicted which of these effects would dominate in CR and any such prediction is likely to remain difficult in the absence of empirical data, which in themselves are going to be difficult to obtain in humans. There may also be some counter-intuitive surprises. For instance in rodents CR has been shown to *increase* protein turnover in the liver (reviewed in Longo and Finch, 2003) and in humans it increases the activity of uncoupling protein 3 (UCP3) which may help reduce oxidant stress (Dulloo and Samec, 2001). An analogous conundrum can be found in the field of calcium metabolism in which an adverse outcome on bone health (osteoporosis) can be associated with either an elevated or a suppressed rate of bone turnover (Compston, 1993) emphasising how difficult it will be to predict the outcome for suppressed energy metabolism in the absence of solid data.

There are other components of the overall metabolic process in which reductions may be induced by CR and which could be predicted to have beneficial effects on survival. Much interest has focussed on the glucose/insulin/IGFl axis in mammals and similar pathways in lower animals (e.g. the *daf* genes in *C elegans*) (Gems and Partridge, 2001) and it has been argued that modest reductions in glucose, insulin and IGF1 could benefit survival. These and other possible changes have been reviewed in some detail by Longo and Finch (2003) who cite numerous examples of beneficial responses to CR. However, these authors also stress the fact that, as argued above, the benefits may only occur against the background of over-nutrition and inactivity inherent in most animal models used.

4.2. Reproductive metabolic adaptations

Under the natural conditions of our evolutionary past in which parents generally sought to maximise family size, the lifetime costs of reproduction for women were very considerable. For instance, in our studies of very high parity mothers in rural Gambia we can calculate that during their lactations alone they will have transferred to their offspring around 30 kg of protein, 90 kg of fat and over 200 kg of lactose together with substantial quantities of calcium and micronutrients (unpublished calculations). The nutrient costs of pregnancies should be added to these values together with the necessary increase in metabolic rate for the maintenance of the fetus. In total, these energetic and nutrient costs of reproduction borne by the female of the species are considerable. However, it should also be noted that primates in general and humans in particular, have adopted a parsimonious reproductive strategy in which a small number of very slow-growing offspring are produced and each is nurtured with care. This means that the total costs of reproduction are actually smaller (as a proportion of maternal metabolic body size) than in any other mammals (Prentice and Whitehead, 1987). Over an entire reproductive cycle of a 9-month pregnancy and a 24-month lactation the additional energy costs to the human mother will average an increment of about 15–20% of her daily energy turnover (Poppitt et al., 1994). The equivalent reproductive costs borne by rodent dams with large fast-growing litters are a 100% increment during pregnancy and as much as a 300% increment or greater in lactation (Prentice and Whitehead, 1987). As a result of these differences it would probably be invalid to make any extrapolation to humans from experimental rodent data designed to test effects of CR on ageing with respect, for instance, to the disposable soma theory that envisages resource competition between reproduction and maintenance.

Human reproduction is predictably sensitive to maternal energy supply in a number of ways. First, as originally argued by Rose Frisch's hypothesis (Frisch, 1982), nutritionally mediated variations in the hypothalamic–pituitary–ovarian axis and FSH secretion switch-off reproduction when maternal body fat stores reach critically low levels. This phenomenon can still be clearly seen in contemporary agricultural populations undergoing seasonal food shortages such as in The Gambia and Bangladesh in which conception rates can vary by as much as two fold between hungry and harvest seasons (Prentice et al., 2005). Second, there is an energy-sensitive variation in the amount of energy that mothers allocate to support fetal growth; in undernourished women the metabolic costs of maintaining the products of conception and the amount of fat deposited in pregnancy are much lower than in well-nourished women (Prentice et al., 1996). We have shown that this metabolic plasticity is a particularly prominent feature of human pregnancy that is not readily observed in other species (Prentice and Whitehead, 1987). We argue that this results from the fact that, due to the low marginal costs of human reproduction, energy-sparing adaptations would create a significant margin of survival for the offspring and hence would have been under evolutionary selection pressure.

These observations on the energetics of human reproduction leave plenty of room for divergent interpretations in respect of their implications for CR and ageing. At first sight women might be assumed to bear greater additional nutrient and energy costs than their male counterparts. In respect of the disposable soma theory of ageing this would imply that women should have shorter lifespans than men, which is almost universally untrue. On the other hand, it could be argued that the slow reproductive strategy adopted by humans, with its low marginal costs, minimises any such effects. It might also be argued that the energetic adaptations, including a suppression of basal metabolism, adopted by undernourished women in order to protect the growth of their fetus may represent a form of indirect CR and that this might offset the detrimental effects the additional disposal of soma. It can also be argued that male investment in reproduction (by growing bigger, competition for mates, territory defence, etc.) is as large as in females. In short,

inductive reasoning can arrive at virtually any answer given the current state of our knowledge.

A search for observational evidence regarding any possible relationship between reproductive load and longevity does not, as yet, yield an extensive literature. Westendorp and Kirkwood (1998) have presented some evidence that, in women dying beyond the age of 60 years, longevity was negatively correlated with the number of progeny hence supporting the disposable soma concept. Others have found similar evidence that generally supports this thesis (Doblhammer, 2000; Doblhammer and Oeppen, 2003; Korpelainen, 2000; Lycett et al., 2000). As stressed above, any data from other species, except perhaps other primates, should be interpreted with the greatest of scepticism.

5. Conclusions

In conclusion, there is extensive evidence that the human genome has been under pressure by famine, and this has led to the selection of numerous adaptive traits to protect reproductive capacity and aid survival. However, as argued by Kirkwood (2003) it is teleologically unlikely that any of these will have been positively selected to enhance survival beyond the age of childrearing, but that it is quite possible that they may accidentally do so.

There is very little doubt that modest CR would benefit most humans living in affluent societies, and most animals kept in captivity, by reducing the inappropriately high adipose tissue mass and its consequent pathology. Whether CR would have such effects in 'wildtype' animals, including humans, living under the natural ecological conditions of their evolutionary past remains quite another issue and one which will be debated for some time to come. The evidence so far is extremely insubstantial in humans and we caution against extrapolation from other species. Nonetheless, studies of the mechanisms of ageing are likely to yield important benefits to mankind through inferences with regard to other disease processes and they may ultimately allow genetic modification to enhance healthy lifespan.

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