

Reducing Calorie Intake as a Method for Prolonging Life Span

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Abstract

Senescence with age may be inevitable, or programmed. However, there seems to be no one single fundamental explanation for why senescence occurs. Strategies for prolonging human life have been a centre of focus for many researchers. One such suggested strategy is reducing calorie intake. Calorie restriction may lead to increased life expectancy, and maximum life span, and a delayed rate of physiological deterioration. This may be due to a slowing of development by delaying sexual maturation, reduced reproductive effort and a lower metabolic rate. Alternately, decreased metabolism and energy use may result in a reduction in free radical damage and toxin intake, therefore prolonging the life span of cells. Decrease in metabolic rate also reduces metabolites and side products in the blood stream, and heightens the concentration of key enzymes and receptors. The switch from cell building to cell repair also reduces cell energy use, and may therefore prolong life span. It is important to study calorie restriction as a method of prolonging life span in preventing, or delaying age-related disease. However, relatively little progress has been made in understanding the mechanisms underlying the apparently beneficial effects of calorie restriction, and further research is necessary.

'The biology of life span is the science of the mechanisms which determine the life span of organisms' (Gavrilov & Gavrilova 1991). The cells of the body do not die simultaneously, but regenerate at different rates, so something other than time since birth must control life span (Jazwinski 2000). According to current research, senescence, the loss of function with age, may be inevitable, or programmed. However, there is no one single fundamental physiological explanation of how ageing occurs. Ageing may either be under programmed genetic control, or a result of inevitable, mechanistic decay processes over time (Finch 1990). There has been exhaustive study into this area with few rewarding outcomes, but the mechanisms that affect life span are beginning to be understood (Gavrilov & Gavrilova 1991).

There is evidence for gene sequences coding for lifespan (Kanungo 1994). However these may not represent a genetic 'switch', but an inevitability, the time at which death occurs depending on the processes that occur in the individual's lifetime. Three main theories have emerged to explain the ageing process. The first involves free radicals, which steal electrons from lipids, proteins and nucleic acids. Free radicals cause oxidative damage, resulting in physiological side effects such as joint stiffening and wrinkles (Masoro 1996). The second theory of ageing is error accumulation: destructive enzymes that generate errors within the DNA eventually replace normal enzymes. The third theory is programmed deterioration which suggests that at a certain point in biological time, hormones in the body switch cells from a regenerative to a degradation phase (Ricklefs & Finch 1995).

However although these theories do have substantial support, differences in life span between individuals within a species have sparked the idea that the environment plays an important role

in determining longevity. Environmental variations may therefore affect the ageing process. Substantial research has focussed on strategies for prolonging human life through environmental manipulation. One widely researched strategy for retarding the aging process, at least in mammals, is calorie restriction. Despite considerable research, the mechanisms by which life extension takes place are not understood completely (Weindruch et al. 2001). Many metabolic processes are simultaneously affected in response to calorie restriction. Only a small proportion of these have an impact on life span (Jazwinski 2000); however, what is now certain is that the reduction of food/calorie intake does lead to an increase in life expectancy and maximum life span (Culter 1981). Furthermore, there is a delay in the rate of physiological deterioration, and the appearance of a wide range of age-related diseases such as kidney disease and cancer (McCarter & McGee 1989; Stern, Gades, Wheelton & Borchers 2001; Masoro 1996). For example, rats are often used in these studies – the majority of which occur as semi-domesticated animals living in cities (Rose 1991). In rats, calorie restriction leads to an increase of 30-50% of the maximum life span, and a delay in, or prevention of age-associated pathologies (Weindruch et al. 2001).

The most common view of the reason that calorie restriction leads to a prolonged life span is a slow-down in development: that is, reduced calorie intake delays sexual maturation and the 'switching on' of the organism's self-destruction mechanisms (senescence) (Kanungo 1994). It has been suggested by a number of researchers that dietary restriction increases life span by physiological enhancement, mainly through reduced reproductive effort, and decreased metabolic rate (Rose 1991; Masoro 1996). It is possible that ageing persists because of pleiotropic genes that have positive effects during the reproductive cycle, therefore are selected for, despite later detrimental effects (Futuyma 1998). This theory fits in well with the programmed life span hypothesis which states that that all sexually mature organisms are programmed to live for a certain, heritable, amount of biological time before degenerating (Rose 1991; Masoro 1996). However, it has also become clear that prolonged life span may also be achieved when calorie intake is restricted *after* sexual maturation, which does not support this theory (Masoro 1988; Holehan & Merry 1986). Another problem with this theory is that life extension through calorie restriction may be linked to an inability to reproduce under 'lean' conditions, therefore trading off energy needed for reproduction against that needed for survival (Rose 1991), as there is evidence that reproduction incurs a lifetime cost (Futuyma 1998).

Although the mechanisms by which calorie restriction influences the ageing process are unknown, investigators such as Harman (1981) have suggested a connection between how quickly animals burn calories and how long they live. For animals such as nematodes, with a short lifespan, the connection between oxidative damage through an aging metabolism, and a limited life span is well established (Finkel & Holbrook 2000; Sreekumar, Unnikrishnan & Fu 2002). Therefore it has been suggested that decreased metabolism and energy use results in prolonged life span of the cells involved. Through a decrease in free radical damage from this decline in metabolic activity, the life span of the organism should be lengthened (Yu, Langanieri & Kim 1988; Ortmeyer 2001). Birds, however, appear to provide evidence against this theory. Birds live much longer lives and age more slowly than similar sized mammals, despite having a higher body temperature and higher metabolic rate (Austad 1997). This phenomenon has led scientists to suggest that birds would be ideal species in which to study the possibility of protective mechanisms against free oxygen radicals (Austad 1997).

The theory of decreased free radical damage fits with the "wear-and-tear" hypothesis, that cells can only make a certain number of divisions until they 'burn out' (Ricklefs & Finch 1995). However, it has been found that when calorie intake is restricted, metabolic activity may be reduced initially, but the reduction in metabolic activity is observed only in the initial stage as the organism adapts to the new low-calorie diet. When the organism's total body weight and



cell mass are reduced to new stable levels, the energy use evens out, presumably because the animal decreases physical activity to compensate for the reduced energy available to it (McCarter & McGee 1989).

Reduction of calorie content of the diet should also lead to a reduction in the metabolic load on a number of systems and organs, and in the organism's intake of a variety of toxins and xenobiotics contained in its food (Holehan & Merry 1986). This theory also agrees with the "wear and tear" hypothesis, as life spans are determined by the number of somatic cell generations that follow after each other in the course of an individual life (Ricklefs & Finch 1995). The "wear and tear" in the cell is caused by random, uncontrolled degeneration and mutation throughout the lifetime of individuals (Ricklefs 1998). It has been suggested that this number, like the lifespan of each generation of cells, is already determined in the embryonic cell (Weismann 1892; Cutler 1981). As the body ages, replication of these cells slows and eventually ceases. Because of everyday wear and tear, cells become less organised, and certain enzymes may not be able to be manufactured further. The death of irreplaceable cells means more pressure on the other cells, while collagen damage can affect cell functioning and prevent diffusion of substances between cells. Accurate replication of cells is essential for individual survival, and so the gradual deterioration of the body throughout time results in senescence (Medina 1996). This process is associated with the accumulation of dead cells due to shortened telomeres (on the end of DNA) and dysfunctional helicases (Ricklefs & Finch 1995).

However, many researchers disagree with the simplicity of this model (Gavrilov & Gavrilova 1991; Rose 1991). An alternative hypothesis is that the extension of lifespan which occurs with a restricted calorie intake is brought about by the animal's reversion to a natural feeding regime and the evolutionary shift from cell building to cell repair while waiting for food to be available again (Furlow & Armijo-Prewit 1999). The basis of this theory is shortening life through overeating of 'controlled' animals rather than extension through overeating (Culter 1981; Masoro 1988). This is a plausible theory, but it does not solve the problem of mechanisms underlying the strong inverse relationship between life span and calorie content, rather than the type of food the animal eats. Furthermore, there is no appropriate way of ascertaining what 'normal' eating patterns would be, and whether these differ depending on the animal being studied.

Gavrilov and Gavrilova (1991) developed another physiological theory, suggesting that restricted calorie intake leads to increased life span through the same mechanism as hypothermia: increasing the signal-to-noise-ratio, that is, the ratio between the rates of controlled enzyme reactions and the rates of harmful non-enzymatic side processes. In hypothermia, this ratio increases because of a difference in the activation energies of enzymatic and non-enzymatic process. In calorie restriction studies, the same ratio changes are achieved through a reduction in the concentration of metabolites and their side products. Therefore, at the same time, metabolic activity can remain unaltered by heightened concentration of key enzymes and receptors (Gavrilov & Gavrilova 1991). Calorie restriction has also been suggested to produce altered pathways for nutrient disposal, which may involve plasma glucose, and the hormones insulin and leptin (Hansen 2001). In studies of weight reduced individuals, energy efficiency was increased, that is, fewer calories per lean body mass were required to maintain stable weight. This mechanism could be the reason for increased life span.

Unfortunately, there is evidence that life long diet restriction does not retard cognitive ageing, but merely physiological ageing. Therefore from the human perspective, it is likely that despite living longer, quality of life may not be assured (Markowska 1999). Despite this, it is important to study calorie restriction as an environmental phenomenon that can theoretically 'change the destiny' of predisposed cells, or at least slow the process of ageing. The power of calorie restriction to delay or prevent the development of age-related disease, despite the prevalence of underlying

metabolic defects, points to the need for further study into calorie restriction and mimetic approaches to slow or halt the consequences of ageing.

The prospect of prolonging human life is an important, yet complex, line of study. However, concrete research in the area is presently underway (Gavrilov & Gavrilova 1991; Furlow & Armijo-Prewit 1999; Ortmeyer 2001). The mechanisms for life extension by calorie restriction have some experimental support, but must be further studied. There has been a great deal of progress in describing the genetic and physiological processes that are altered by calorie restriction; however, relatively little progress has been made in understanding the underlying mechanisms controlling the beneficial effects of calorie restriction (Austad 2000). Theories of ageing may prove helpful when seeking to explain the mechanism behind prolonging life span through caloric restriction. However, when exploring the topic of life spans, factors such as stress and the phylogenetic differences between animal species must be taken into account (Austad 1997). Perhaps in the not-so-distant future, further study will reveal the mysteries of calorie restriction and its effects on the ageing process.

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